14 July 2023
EMA/384132/2023
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/0104/G

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

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List of abbreviations

Ab	Antibody
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
AR	Adverse reaction
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
GLSM	geometric least square mean
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
IS	Immunogenicity Set
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
MSD	MesoScale Discovery
nAb	neutralising antibody
PP	Per-Protocol
PPIS	Per-Protocol Immunogenicity Set
PPIS-Neg	Per Protocol Immunogenicity Set – negative
PPIS-Pos	Per Protocol Immunogenicity Set – positive
PsV	pseudotyped virus
PsVNA	pseudovirus neutralisation assay
RNA	ribonucleic acid
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SOC	system organ class
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
US	United States
UTR	untranslated region
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

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 18 April 2023 an application for a group of variations.

The following variations were requested in the group:

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

Grouped variation:

- C.I.6.a: Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection as a two-dose primary vaccination course in children 6 months through 5 years of age, based on data from study mRNA-1273-P306 (NCT05436834), an Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years; as a consequence, sections 2, 4.1, 4.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 6.7 of the RMP has also been submitted.

- C.I.6.a: Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 as a single-dose primary vaccination course against COVID-19 in individuals 6 years of age and older, irrespective of vaccination history, based on epidemiology and clinical data from Study P306 Part 1; as a consequence, sections 2, 4.1, 4.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections throughout the product information.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0152/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0152/2023 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 appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	18 April 2023
Start of procedure:	24 April 2023
CHMP Rapporteur Assessment Report	24 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
PRAC members comments	31 May 2023
Updated PRAC Rapporteur Assessment Report	1 June 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	18 June 2023
Request for supplementary information (RSI)	22 June 2023
Submission	03 July 2023
Start of procedure	03 July 2023
CHMP Rapporteur Assessment Report	5 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
Opinion	20 July 2023

2. Scientific discussion

2.1. Introduction

Currently Spikevax bivalent Original/Omicron BA.4-5 booster vaccination is authorised for individuals ≥6 years of age.

Within this submission, the MAH requests to modify the approved therapeutic indication to include the 2-dose series of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection, in young children (6m-5y) and to switch, regardless of vaccination history, to a

single dose of Spikevax bivalent Original/Omicron BA.4-5 (all presentations) for individuals 6 years of age and older.

The children 6 months through 5 years of age will receive 0.25 ml, which contains a total of 25 µg mRNA (12.5 µg Original/ 12.5 µg Omicron BA.4-5).

No clinical efficacy and safety data have been provided for Spikevax bivalent (Original/Omicron BA.4-5), used as primary series in young children (6 months to 5 years of age). To support the sought indication of 2-dose series of Spikevax bivalent Original/Omicron BA.4-5 (mRNA- 1273.222) in young children (6m-5y), the MAH has submitted safety and immunogenicity data for Spikevax Bivalent Original/Omicron BA.1 (mRNA-1273.214) in the same age group from the following study:

Study mRNA-1273-P306 built on the foundation established by Study P204 to evaluate the safety and immunogenicity of the Spikevax Bivalent Original/Omicron BA.1 (mRNA-1273.214) vaccine in children 6 months to <6 years of age.

Study P306 is an ongoing, Phase 3, open-label study; Part 1 evaluates Spikevax Bivalent Original/Omicron BA.1 (12.5 µg Original/12.5 µg Omicron BA.1 in 0.25 ml) as primary series administered to vaccine-naïve children compared with recipients of the Spikevax Original (mRNA-1273) vaccine in the same age group in Study P204. Part 2 examines mRNA-1273.214 (Original/BA.1) as a booster administered to children previously vaccinated with the 2-dose mRNA-1273 (Spikevax Original) primary series.

This submission summarises interim results from Study P306 Part 1 as of a data cut-off of 05 December 2022.

2.1.1. Problem statement

Disease or condition

Coronaviruses are a large family of viruses that cause illnesses 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 (PHEIC) on 30th January 2020 and a pandemic on 11th 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.

During the COVID-19 pandemic, the sequence of SARS-CoV-2 is constantly changing over time. 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).

State the claimed the therapeutic indication

Currently, Spikevax original is authorised as a 2-dose primary series in children and adults 6 months and older, and Spikevax bivalent Original/Omicron BA.4-5 booster vaccination is authorised for individuals ≥6 years of age.

Within this submission the MAH requests to modify the approved therapeutic indication to include the 2-dose series of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection in young children (6m-5y) and to switch, regardless of vaccination history, to a single dose of Spikevax bivalent Original/Omicron BA.4-5 (all presentations) for individuals 6 years of age and older.

The intended wording in section 4.1 of the SmPC is the follows:

"Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older (see sections 4.2 and 5.1).

The use of this vaccine should be in accordance with official recommendations."

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 stabilize 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, stabilization 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 stabilized SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the pre-fusion conformation (Wrapp *et al* 2020).

The mRNA-1273 vaccines are delivered via IM injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilizes 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 (Wuhan-Hu-1) 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 Wuhan 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.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Overview of the clinical study

Study mRNA-1273-P306 built on the foundation established by study P204 to evaluate the safety and immunogenicity of the Spikevax Bivalent Original/Omicron BA.1 (mRNA-1273.214) vaccine in children 6 months to <6 years of age.

Study P306 is an ongoing, Phase 3, open-label study. Part 1 evaluates Spikevax Bivalent.214 as primary series administered to vaccine-naïve children compared with recipients of the Spikevax Original (mRNA-1273) vaccine in the same age group in Study P204. Part 2 examines mRNA-1273.214 (Original/BA.1) as a booster administered to children previously vaccinated with the 2-dose mRNA-1273 (Spikevax Original) primary series.

2.4. Clinical efficacy

2.4.1. Main study

Study mRNA-1273-P306: An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years

Methods

Study participants

Inclusion Criteria

Participants, including those who are currently enrolled in Study P204, are eligible to be included in this study only if all the following criteria apply:

1. The participant is male or female, aged 6 months to < 6 years, at the time of consent (Screening Visit), who is in good general health in the opinion of the investigator, based on review of medical history and screening physical examination.

   Note: Participant must be at least 6 months and must not have completed 6 years of age at the time of administration of first dose.

2. If the participant has a chronic disease (e.g., asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimization (e.g., insulin dose changes, adjustments for age-related weight gain), change within class of medication, or reduction in dose are not considered signs of instability.

3. In the investigator's opinion, the parent(s)/legally authorised representative(s) (LAR[s]) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provide written informed consent. This includes inability to draw baseline blood samples (minimum amount needed).

4. The participant is 2 years or older and has a body mass index (BMI) at or above the 2nd percentile according to World Health Organization (WHO) Child Growth Standards at the Screening Visit.

   OR

   The participant is less than 2 years of age and the participant's height, and weight are both at or above the 2nd percentile according to WHO Child Growth Standards at the Screening Visit.

Special inclusion criteria for participants aged 6 months to < 12 months:

5. The participant was born at full-term (≥ 37 weeks gestation) with a minimum birth weight of 2.5 kg.

Inclusion criteria for Part 2:

6. The participant must have received 2 doses of mRNA-1273, approximately 28 to 35 days apart, as 25 µg primary series, and 2nd dose was given at least 4 months prior to enrolment.

Exclusion Criteria

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

1. Has a known history of SARS-CoV-2 infection (e.g., reported adverse event [AE] of coronavirus disease 2019 [COVID-19] or asymptomatic SARS-CoV-2 infection during Study P204) in the 90 days prior to dosing in this study.
2. Is acutely ill or febrile 24 hours prior to or at the Screening Visit. Fever is defined as a body temperature ≥38.0°C/≥100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
3. Has previously been administered an investigational or approved CoV (e.g., SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome coronavirus [MERS-CoV]) vaccine. For Part 2, this applies to vaccines other than the mRNA-1273 (prototype) vaccine.
4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (including receipt of SARS-CoV-2 monoclonal antibodies for prophylaxis or treatment) within 90 days prior to enrolment.
5. Has a known hypersensitivity to a component of the vaccine or its excipients. Hypersensitivity includes, but is not limited to, anaphylaxis or immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).
6. Has a medical or psychiatric condition that, according to the investigator's judgment, may pose additional risk as a result of participation, interfere with safety assessments, or interfere with interpretation of results.
7. Has a history of diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
    - Congenital or acquired immunodeficiency, other than well-controlled HIV infection as described in Inclusion Criterion 2
    - Chronic hepatitis or suspected active hepatitis
    - A bleeding disorder that is considered a contraindication to intramuscular (IM) injection or phlebotomy
    - Dermatologic conditions that could affect local solicited adverse reaction (AR) assessments
    - Any prior diagnosis of malignancy (excluding nonmelanoma skin cancer)
8. Has received the following:
    - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to study vaccination or plans to receive such a vaccine through 14 days following study vaccination.
        - Note: This excludes influenza vaccine that may be given anytime, but ideally at least 7 days before study dose. If a participant receives an influenza vaccine, this

should be captured within the concomitant medication electronic case report form (eCRF).

- Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrolment (for corticosteroids, ≥1 mg/kg/day or ≥10 mg/day prednisone equivalent, if participant weighs > 10 kg). Participants may have visits rescheduled for enrolment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids, and palivizumab are allowed.
- Intravenous (IV) or subcutaneous (SC) blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrolment.

9. Has participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this study (Note: The exception would be participants who rollover from the Study P204 into this study).
10. Is an immediate family member, or household contact, of an employee of the study site or Moderna or someone otherwise directly involved with the conduct of the study. As applicable, family members/household contacts of employees of the larger institution or affiliated private practice not part of the study site may be enrolled, as long as the investigator has no authority over the family member's employment or performance evaluation.
11. Is currently experiencing a serious adverse event (SAE) in Study P204 at the time of screening for this study.

Treatments

Spikevax mRNA-1273.214 bivalent vaccine (1:1, original and Omicron BA.1) to be given as a single IM injection on D1 and D29 (Part 1).

Objectives/endpoints

Study P306 Primary Immunogenicity Objectives and Endpoints

The primary immunogenicity objectives and endpoints are the following:

- To infer the effectiveness of mRNA-1273.214 primary series in participants 6 months to <6 years by comparing induced serum nAb levels with those obtained from children in the same age group after the original mRNA-1273 primary series in Study P204. nAb was measured 28 days after the second dose (Day 57) and the following coprimary endpoints were evaluated:
    - Co-primary Endpoint 1: Superiority of the GMR of nAb against Omicron BA.1 (i.e., lower bound of the 95% CI of the GMR >1.0)
    - Co-primary Endpoint 2: Noninferiority of the GMR of nAb against ancestral SARS-CoV-2 with a 1.5 margin (i.e., lower bound of the 95% CI of the GMR >0.667 [1/1.5])

Study P306 Secondary Immunogenicity Objectives and Endpoints

The secondary immunogenicity objectives and endpoints are the following:

- To evaluate the immune response induced after the second dose of mRNA-1273.214 primary series in participants 6 months to <6 years of age compared with that after the second dose of mRNA-1273 primary series in Study P204 of same age group based on:
    - SRR against SARS-CoV-2 VOC (Omicron BA.1)
    - SRR against ancestral SARS-CoV-2
    - Serum Ab GM value and SRR against SARS-CoV-2 VOC (Omicron BA.1) after mRNA-1273.214 primary series, compared with GM value and SRR against ancestral SARS-CoV-2 after mRNA-1273 primary series

Study P306 Exploratory Objectives and Endpoints

The study exploratory objectives and endpoints are as follows:

- To evaluate the incidence of SARS-CoV-2 infection and COVID-19 after vaccination with mRNA-1273.214 primary series as defined by the following endpoints:
    - The incidence of the first occurrence of COVID-19 postbaseline, where COVID-19 is defined as symptomatic disease based on the CDC case definition. The CDC case definition of COVID-19 includes at least 1 of the following systemic symptoms: fever (temperature >38ºC/ ≥100.4ºF) or chills (of any duration, including ≤48 hours); cough (of any duration, including ≤48 hours); shortness of breath or difficulty breathing (of any duration, including ≤48 hours); fatigue; headache; myalgia; nasal congestion or rhinorrhoea; new loss of taste or smell; sore throat; abdominal pain; diarrhoea; nausea or vomiting; poor appetite or poor feeding; AND a positive test for SARS-CoV-2 by RT-PCR.
    - The incidence of SARS-CoV-2 infection including symptomatic and/or asymptomatic infection (by serology and/or RT-PCR) at post-baseline
    - The incidence of asymptomatic SARS-CoV-2 infection (by serology and/or RT- PCR) at postbaseline

Sample size

For the Part 1 primary superiority hypothesis testing of Ab GM value against BA.1 after mRNA-1273.214 primary series in participants aged 6 months to < 6 years in Study P306 compared with Ab GM value against BA.1 after mRNA-1273 primary series in Study P204 of the same age group, assuming the true serum antibody GMR of 1.5 at D57 (mRNA-1273.214 primary series in Study P306 compared with mRNA-1273 primary series in Study P204), with a superiority margin of 1.0 and the standard deviation of the natural log-transformed levels of 1.8, 416 participants in the PPIS were considered to be needed to provide 90% power to demonstrate superiority of the serum Ab GM value at 1-sided alpha of 0.025.

With the consideration for some of the participants excluded from the PPIS, the target enrolment of Part 1 in Study P306 was approximately 480 participants.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

The primary objective of Part 1 of this study was to use the immunogenicity response to infer the effectiveness of mRNA-1273.214 vaccine administered as a primary series in participants aged 6 months to < 6 years who have not been previously vaccinated, regardless of their baseline SARS-CoV-2 infection status. Analyses of immunogenicity was to be performed based on the participants in the PPIS.

Key analysis sets

The Per-Protocol Immunogenicity Set (PPIS) includes participants in the Immunogenicity Set (defined as all participants in the FAS who provided immunogenicity samples) who received the planned doses of IP per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that impact key or critical data, regardless of baseline SARS-CoV-2 status. Participants with HIV who are receiving HAART were to be excluded.

Immunogenicity analyses

The immune response as measured by the serum Ab GM value against ancestral SARS-CoV-2 and Omicron BA.1 at D57 was to be compared to that after mRNA-1273 primary series in Study P204. An ANCOVA model was to be carried out with the serum Ab value at D57 as the dependent variable and a group variable (mRNA-1273.214 vs. mRNA-1273) as the fixed variable, adjusted by age group (2 age groups: 6 months to < 2 years and 2 to < 6 years), and by the baseline SARS-CoV-2 infection status. The serum Ab GM value at D57 was to be estimated by the GLSM from the model. The GMR (Study P306 vs. Study P204) was to be estimated by the ratio of GLSM. Its 2-sided 95% CI was also to be provided to assess the difference in immune response between the Study P306 and Study P204 at D57. If the lower bound of the 95% CI of the GMR against BA.1 is > 1, superiority of the serum Ab GM value of mRNA-1273.214 primary series compared with that of mRNA-1273 primary series was considered to be demonstrated. The noninferiority of the GM value against ancestral SARS-CoV-2 of mRNA-1273.214 primary series compared with mRNA-1273 primary series was to be demonstrated if the lower bound of the 95% CI of the GMR > 0.667 (1/1.5).

The geometric mean-fold rise (GMFR) of serum Ab values with its 95% CI at D57 over baseline (pre-Dose 1 of primary series) was to be provided. Its 95% CIs was to be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

The number and percentage of participants with seroresponse due to vaccination was be provided with 2-sided 95% CI using the Clopper-Pearson method at D57, where seroresponse at subject level has 2 definitions:

a) Seroresponse at subject level is defined as Ab value change from baseline (pre-Dose 1 of primary series) below the LLOQ to ≥ 4 x LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

b) Seroresponse at subject level is defined as an Ab value 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 and < 4 × LLOQ, or at least a 2-fold rise if baseline is ≥ 4 × LLOQ.

The SRR difference with its 95% CI (using Miettinen-Nurminen score method) between paediatric participants receiving mRNA-1273.214 primary series in Study P306 at D57 and paediatric participants

receiving mRNA-1273 primary series in Study P204 at D57 was to be provided. The stratified Miettinen-Nurminen method was to be used to adjust for the age group for sensitivity analysis.

Subgroup Analyses

Subgroup analyses were to be performed in select subgroups, including but not limited to, the following subgroups: sex (male, female), age (6 Months to < 2 Years and 2 Years to < 6 Years), SARS-CoV-2 status at baseline, race, ethnicity, race/ethnicity, obesity (defined as BMI >= 95th percentile based on WHO growth reference data).

Results

Participant flow

As of the data cut-off for this interim analysis (05 Dec 2022), the FAS and Safety Set included n = 179 participants who received at least 1 dose and n = 142 (79.3%) who received 2 doses. Three participants were lost to follow-up after the first dose and did not receive the second dose. Prior to study discontinuation, each of these participants completed the 7-day reactogenicity eDiaries and Day 8 safety call. No unsolicited AEs were reported in these participants.

Table 1: Participant disposition in Study P306 Part 1 (Full Analysis Set)

	≥6 Months and <6 Years (N=179) n (%)
Received first injection	179 (100)
Received second injection	142 (79.3)
Completed study vaccine schedule	142 (79.3)
Discontinued study vaccine[a]	3 (1.7)
Reasons for discontinuation of study vaccine	
Lost to follow-up	3 (1.7)
Completed study[b]	0
Withdrew from study	3 (1.7)
Reasons for withdrawal from study	
Lost to follow-up	3 (1.7)

[a] Study vaccine discontinuation is defined as a participant who received the first injection but did not receive the second injection.

[b] Study completion is defined as a participant who completed 12 months of follow-up after the last injection received. The study is ongoing; no participants have completed 12 months of follow-up.

Source: Table 14.1.1.1.1

Recruitment

The study is on-going in the USA. The enrolment started 21 Jun 2022.

Conduct of the study

According to the MAH, the study was conducted according to GCP guidelines and the Declaration of Helsinki.

The protocol was amended to Protocol Amendment 1 on 8th December 2022. Previous protocol version has been provided. As part of this amendment, the second co-primary endpoint (nAbs against ancestral strain) was included (based on an FDA suggestion) and the NI-margin (which was specified as 0.67 for other hypothesis in the initial protocol) was modified at that time to 0.667.

Numbers analysed

The number of participants in each analysis set in Study P306 Part1 is presented below.

Table 2: Study P306 Part 1 number of participants in each analysis set

	≥6 Months and <6 Years n (%)
Full Analysis Set	179
Per-Protocol Set[a], also used for the Per-Protocol Set for Efficacy	37 (20.7%)
Immunogenicity Set[a]	83 (46.4%)
Per-Protocol Immunogenicity Set[a]	71 (39.7%)
Per Protocol Immunogenicity Set—Negative[a]	26 (14.5%)
Safety Set	179
Solicited Safety Set[b]	179 (100%)
First Injection Solicited Safety Set[b]	179 (100%)
Second Injection Solicited Safety Set[b]	141 (78.8%)

[a] Percentages are based on the number of participants in the Full Analysis Set.
[b] Percentages are based on the number of participants in the Safety Set.
Source: Table 14.1.2.1.1

Baseline data

The demographics and baseline characteristics of participants are shown in Table 3 for the Study P306 and P204 PPIS.

Enrolment in Study P306 was distributed across the eligible age group. For the PPIS participants, baseline SARS-CoV-2 positivity was 63.4% in Study P306 and 6.6% in Study P204 comparator group.

Table 3: Participant Demographics and Baseline Characteristics in Study P306 Part 1 and Study P204 (Per-Protocol Immunogenicity Set)

	Study P306 ≥6 Months and <6 Years (N=71)	Historical Comparator Study P204 ≥6 Months and <6 Years (N=632)
Age, years		
Mean (SD)	2.53 (1.347)	2.17 (1.348)
Median	3.00	2.00
Min, max	0.5, 5.0	0.5, 5.0
Age (years), n (%)		
<1	10 (14.1)	53 (8.4)
1	7 (9.9)	251 (39.7)
2	18 (25.4)	74 (11.7)
3	20 (28.2)	122 (19.3)
4	9 (12.7)	96 (15.2)
5	7 (9.9)	36 (5.7)
Sex, n (%)		
Male	43 (60.6)	325 (51.4)
Female	28 (39.4)	307 (48.6)
Race, n (%)		
White	49 (69.0)	462 (73.1)
Black	12 (16.9)	43 (6.8)
Asian	4 (5.6)	34 (5.4)
American Indian or Alaska Native	1 (1.4)	2 (0.3)
Multiracial	4 (5.6)	72 (11.4)
Other	1 (1.4)	14 (2.2)
Unknown	0	1 (0.2)
Not Reported	0	4 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	6 (8.5)	115 (18.2)
Not Hispanic or Latino	65 (91.5)	513 (81.2)
Not reported	0	4 (0.6)
Race and ethnicity group[a], n (%)		
White non-Hispanic	46 (64.8)	377 (59.7)
Communities of Color	25 (35.2)	255 (40.3)
Weight, kg		
Mean (SD)	14.54 (4.062)	13.95 (3.855)
Median	15.18	13.30
Min, max	7.0, 28.9	7.0, 34.8
Baseline SARS-CoV-2 status[b], n (%)		
Negative	26 (36.6)	590 (93.4)
Positive	45 (63.4)	42 (6.6)
Missing	0	0

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

Percentages are based on the number of participants in the PPIS.

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

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

Source: Table 14.1.3.3.1

Outcomes and estimation

Study P306 Primary Objective: Co-primary Immunogenicity Endpoints

To infer the effectiveness of mRNA-1273.214 bivalent vaccine (1:1, original and Omicron BA.1) primary series in participants 6 months to <6 years, serum nAb levels were compared with those obtained from children in the same age group after original mRNA 1273 primary series in Study P204. In both groups, nAb was measured 28 days post-dose 2 (Day 57). Success criteria required superiority

of Study P306 to Study P204 nAb responses against BA.1 and noninferiority against ancestral strain. The primary analysis was conducted using the PPIS populations (including participants with or without prior SARS-CoV-2 infection) for both studies.

Omicron BA.1 Superiority Analysis: Day 57 nAb GMC against BA.1 from Study P306 and Study P204 PPIS groups were compared to assess superiority. The Study P306 GMC was 1890 (95% CI: 1520, 2349) compared with Study P204 GMC, which was 74 (95% CI: 69, 81). The resulting GMR adjusted by age and prior infection status was 25.4 (95% CI: 20.1, 32.1), meeting the prespecified success criterion for superiority compared to the original vaccine (lower bound of the 95% CI > 1.0).

Ancestral (D614G) Noninferiority Analysis: Day 57 nAb GMC against D614G strain from P306 and P204 PPIS groups were compared to assess noninferiority. The Study P306 GMC was 1433 (95% CI: 1173, 1750) compared with Study P204 GMC, which was 1733 (95% CI: 1621, 1852). The resulting GMR adjusted by age and prior infection status was 0.83 (95% CI: 0.67, 1.02), meeting the prespecified success criterion for noninferiority (lower bound of the 95% CI > 0.667).

These results are summarised in the below table.

Table 4: Pseudovirus Neutralising Antibody Values Against B.1.1.529 (VAC122) and Against Ancestral Strain (VAC 62) (Per-Protocol Immunogenicity Set)

	≥6 Months and <6 Years	
	P306 mRNA-1273.214 Primary Series 25 µg (N=71)	**Historical Comparator P204 mRNA-1273 Primary Series 25 µg (N=632)**
Against B.1.1.529 (VAC122)		
GMC (model based) (95% CI)[a] at Day 57	1890 (1520, 2349)	74 (69, 81)
GMR (P306 vs P204; model based) (95% CI)[a]	25.4 (20.1, 32.1)	
Against Ancestral Strain (VAC 62)		
GMC (model based) (95% CI)[a] at Day 57	1433 (1173, 1750)	1733 (1621, 1852)
GMR (P306 vs P204; model based) (95% CI)[a]	0.83 (0.67, 1.02)	

Abbreviations: ANCOVA = analysis of covariance; GMC = geometric mean concentration (noted as model based, which is estimated by geometric least squares mean); GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least squares; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.

[a] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P306 and in P204) as fixed variable, adjusted by age group (2 age groups: ≥6 months and <2 years, ≥2 and <6 years), and by the baseline SARS-CoV-2 infection status (negative and positive). Coefficients for LS means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.1.4.2.1 and Table 14.2.1.5.2.1

During the evaluation it was noted that the number of evaluable participants was smaller than 71. Neutralising antibody values against the BA.1 strain at Day 57 were only available for 58 participants in the overall population, for only 24 (instead of the reported 26) baseline seronegative participants, and for only 34 (instead of the reported 45) baseline seropositive participants. Neutralising antibody values against the ancestral strain at Day 57 were available for 66 participants in the overall population, for 25 (instead of the reported 26) baseline seronegative participants, and for 41 (instead of the reported 45) baseline seropositive participants.

Immunogenicity Analyses by SARS-CoV-2 Status at Baseline

The primary objective was to infer effectiveness-specified evaluation of nAb responses against BA.1 and D614G in the PPIS. Immunogenicity results were also assessed in participants without (PPIS-Neg) and with (PPIS-Pos) prior SARS-CoV-2 infection at baseline. Day 57 nAb results for Study P306 and Study P204 are presented first using the Omicron BA.1 and then the ancestral D614G PsVNA. Prior infection with SARS-CoV-2 at baseline was defined by either positive serology (measured against SARS-COV-2 nucleocapsid; Elecsys) or positive RT PCR nasal swab from samples collected prior to Dose 1.

Omicron BA.1 Analysis

In participants without prior SARS-CoV-2 infection, mRNA-1273.214 (P306) induced a Day 57 nAb GMC of 1038 (95% CI: 787, 1370), markedly higher than the GMC induced by mRNA-1273 in Study P204, 66 (95% CI: 61, 71). Assessment of GMR in the PPIS-Neg populations (Study P306/Study P204;15.8 [95% CI: 11.4, 21.9]), though not a prespecified hypothesis, would have met superiority criteria (lower bound of the 95% CI >1.0).

In participants with prior SARS-CoV-2 infection, nAb levels measured against BA.1 on Day 1 were higher in the Study P306 PPIS-Pos group (GMC 137 [95% CI: 85, 221]) than in the Study P204 PPIS-Pos group (GMC 22 [95% CI: 15, 30]). This likely reflects the enrolment of participants to Study P204 before the emergence of Omicron. Among participants with prior SARS-CoV-2 infection in Study P306, mRNA-1273.214 induced a GMFR by Day 57 of 21.3 (95% CI: 10.7, 42.4), with a Day 57 GMC of 2885 (95% CI: 2029, 4101). Assessment of GMR in the PPIS-pos populations (Study P306/Study P204;4.6 [95% CI: 2.6, 8.1]).

These results are summarised in the below table.

Table 5: Pseudovirus Neutralising Antibody Values Against B.1.1.529 (VAC122) by SARS-CoV-2 Status at Baseline (Per-Protocol Immunogenicity Set)

	≥6 Months and <6 Years	
	P306 mRNA-1273.214 Primary Series 25 µg	**Historical Comparator P204 mRNA-1273 Primary Series 25 µg**
Baseline SARS-CoV-2 Status: Overall		
N	71	632
Baseline GMC (95% CI)[a]	49 (30, 80)	5.9 (5.5, 6.2)
GMC observed at Day 57 (95% CI)[a]	1890 (1430, 2497)	74 (68, 82)
GMFR (95% CI)[a] at Day 57	48.2 (28.6, 81.2)	13.0 (11.6, 14.5)
GMC (model based) (95% CI)[b] at Day 57	1890 (1520, 2349)	74 (69, 81)
GMR (P306 vs P204; model based) (95% CI)[b]	25.4 (20.1, 32.1)	
Baseline SARS-CoV-2 Status: Negative		
N	26	590
Baseline GMC (95% CI)[a]	8 (5, 14)	5 (5, 6)
GMC observed at Day 57 (95% CI)[a]	1038 (787, 1370)	66 (61, 71)
GMFR (95% CI)[a] at Day 57	155.2 (89.6, 268.9)	12.2 (11.0, 13.7)
GMC (model based) (95% CI)[b] at Day 57	1038 (754, 1428)	66 (61, 71)
GMR (P306 vs P204; model based) (95% CI)[b]	15.8 (11.4, 21.9)	
Baseline SARS-CoV-2 Status: Positive		
N	45	42
Baseline GMC (95% CI)[a]	137 (85, 221)	22 (15, 30)
GMC observed at Day 57 (95% CI)[a]	2885 (1970, 4224)	625 (421, 928)
GMFR (95% CI)[a] at Day 57	21.3 (10.7, 42.4)	38.8 (29.7, 50.6)
GMC (model based) (95% CI)[b] at Day 57	2885 (2029, 4101)	625 (404, 969)
GMR (P306 vs P204; model based) (95% CI)[b]	4.6 (2.6, 8.1)	

Abbreviations: ANCOVA = analysis of covariance; GMC = geometric mean concentration (noted as observed or model based, which is estimated by geometric least squares mean); GMFR = geometric mean fold rise; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.

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

[b] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (Children in P306 and in P204) as fixed variable, adjusted by age group (2 age groups: ≥6 months and <2 years, ≥2 and <6 years) regardless of infection status, and by the baseline SARS-CoV-2 infection status (for the overall population only). Coefficients for LS means use margins by level. In each specific baseline SARS-CoV-2 infection status table, baseline SARS-CoV-2 infection status is not a covariate. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.3.5.2.1 and Table 14.2.1.5.2.1

It is noted that the number of evaluable participants was smaller than 71. Neutralising antibody values against the BA.1 strain at Day 57 were only available for 58 participants in the overall population, for only 24 (instead of the reported 26) baseline seronegative participants, and for only 34 (instead of the reported 45) baseline seropositive participants.

Ancestral (D614G) Analysis

In participants without prior SARS-CoV-2 infection, mRNA-1273.214 (Study P306) induced a Day 57 nAb GMC of 613 (95% CI: 449, 836), lower than the GMC induced by the original mRNA-1273 vaccine (Study P204; 1559 [95% CI: 1460, 1666]). This resulted in a lower GMR against ancestral D614G in Study P306 participants than in Study P204 participants (GMR 0.39 [95% CI: 0.29, 0.54]). While the primary immunogenicity analysis was met (conducted in the PPIS population), an analysis conducted in participants in the PPIS-Neg would not have met noninferiority criteria (lower bound of the 95% CI > 0.667).

In participants with prior SARS-CoV-2 infection, nAb levels measured against ancestral D614G on Day 1 were higher in the Study P204 PPIS-Pos (GMC 186 [95% CI: 136, 255]) than in the Study P306 PPIS-Pos (GMC 65 [95% CI: 40, 108]). This may reflect that participants in Study P306 who were enrolled after the Omicron peak may have had less chance of exposure to the ancestral SARS-CoV-2 strain. Participants in the PPIS-Pos in either Study P306 or the earlier enrolled Study P204 achieved similar GMFR (Study P306 GMFR 37.9 [95% CI: 24.6, 58.3]; Study P204 GMFR 42.9 [95% CI: 33.1, 55.6]) based on Day 57 nAb responses. GMR 0.29 [95% CI: 0.18, 0.46]).

These results are summarised in the below table.

Table 6: Pseudovirus Neutralising Antibody Values Against Ancestral Strain (VAC62) (PPIS)

	≥6 Months and <6 Years	
	P306 mRNA-1273.214 Primary Series 25 µg	**Historical Comparator P204 mRNA-1273 Primary Series 25 µg**
Baseline SARS-CoV-2 Status: Overall		
N	71	632
Baseline GMC (95% CI)[a]	36 (24, 53)	10 (9, 10)
GMC observed at Day 57 (95% CI)[a]	1433 (1055, 1947)	1733 (1612, 1863
GMFR (95% CI)[a] at Day 57	41.8 (30.1, 58.0)	183.8 (170.1, 198.7)
GMC (model based) (95% CI)[b] at Day 57	1433 (1173, 1750)	1733 (1621, 1852)
GMR (P306 vs P204; model based) (95% CI)[b]	0.83 (0.67, 1.02)	
Baseline SARS-CoV-2 Status: Negative		
N	26	590
Baseline GMC (95% CI)[a]	13 (8, 19)	8 (7, 8)
GMC observed at Day 57 (95% CI)[a]	613 (448, 837)	1559 (1459, 1667)
GMFR (95% CI)[a] at Day 57	49.0 (28.7, 83.6)	202.8 (188.3, 218.4)
GMC (model based) (95% CI)[b] at Day 57	613 (449, 836)	1559 (1460, 1666)
GMR (P306 vs P204; model based) (95% CI)[b]	0.39 (0.29, 0.54)	
Baseline SARS-CoV-2 Status: Positive		
N	45	42
Baseline GMC (95% CI)[a]	65 (40, 108)	186 (136, 255)
GMC observed at Day 57 (95% CI)[a]	2406 (1643, 3522)	8445 (6398, 11148)
GMFR (95% CI)[a] at Day 57	37.9 (24.6, 58.3)	42.9 (33.1, 55.6)
GMC (model based) (95% CI)[b] at Day 57	2406 (1734, 3338)	8445 (5983, 11921)
GMR (P306 vs P204; model based) (95% CI)[b]	0.29 (0.18, 0.46)	

Abbreviations: ANCOVA = analysis of covariance; GMC = geometric mean concentration (noted as observed or model based, which is estimated by geometric least squares mean); GMFR = geometric mean fold rise; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least squares; PPIS = Per Protocol Immunogenicity Set; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.

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

[b] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (Children in P306 and in P204) as fixed variable, adjusted by age group (2 age groups: ≥6 months and <2 years, ≥2 and <6 years), regardless of infection status, and by the baseline SARS-CoV-2 infection status (for the overall population only). Coefficients for LS means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.3.4.2.1 and Table 14.2.1.4.2.1

It is noted that the number of evaluable participants was smaller than 71. Neutralising antibody values against the ancestral strain at Day 57 were available for 66 participants in the overall population, for 25 (instead of the reported 26) baseline seronegative participants, and for 41 (instead of the reported 45) baseline seropositive participants.

Secondary Immunogenicity Endpoints

Results of nAb SRR in Study P306 and Study P204 PPIS are summarized here, first for responses against Omicron BA.1 and then for those against ancestral D614G.

Data shown here use the conventional definition for individual participant seroresponse: nAb change on Day 57 from a baseline (pre-Dose 1) level below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if the baseline level is ≥LLOQ (denoted as SR1). SRR results are presented for all participants in the PPIS regardless of prior SARS-CoV-2 status, in PPIS participants with no prior infection (PPISNeg), and in PPIS participants with prior infection (PPIS Pos).

Omicron BA.1 Analysis

In the PPIS, the SRR against BA.1 was 83.9% (95% CI: 71.7, 92.4) in Study P306 and 86.8% (95% CI: 82.0, 90.7) in Study P204. In the PPIS-Neg group, the SRR against BA.1 was greater than 95% after administration of the BA.1-containing mRNA-1273.214 (Study P306 SRR 95.7% [95% CI: 78.1, 99.9]; Study P204 SRR 86.1% [95% CI: 81.1, 90.2]).

Table 7: Pseudovirus Neutralising Antibody Values Against B.1.1.529 (VAC122)—Seroresponse Rate (PPIS)

	≥6 Months and <6 Years	
	P306 mRNA-1273.214 Primary Series 25 µg (N=71)	Historical Comparator P204 mRNA-1273 Primary Series 25 µg (N=632)
Baseline SARS-CoV-2 Status: Overall		
Participants achieving SR1[a], n/N1 (%)	47/56 (83.9)	223/257 (86.8)
95% CI[b]	(71.7, 92.4)	(82.0, 90.7)
Difference in seroresponse 1[a] rate (P306 vs P204), % (95% CI)[c]	-2.8 (-15.2, 6.0)	
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	-6.7 (-17.4, 4.0)	
Baseline SARS-CoV-2 Status: Negative		
Participants achieving SR1[a], n/N1 (%)	22/23 (95.7)	210/244 (86.1)
95% CI[b]	(78.1, 99.9)	(81.1, 90.2)
Difference in SR1[a] rate (P306 vs P204), % (95% CI)[c]	9.6 (-7.4, 16.2)	
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	0.1 (-12.7, 13.0)	
Baseline SARS-CoV-2 Status: Positive		
Participants achieving SR1[a], n/N1 (%)	25/33 (75.8)	13/13 (100)
95% CI[b]	(57.7, 88.9)	(75.3, 100.0)
Difference in SR1[a] rate (P306 vs P204), % (95% CI)[c]	-24.2 (-41.2, 0.6)	
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	-16.8 (-39.5, 5.9)	

Abbreviations: Ab = antibody; CI = confidence interval; LLOQ = lower limit of quantification; N = number of participants in the PPIS; N1=number of participants with non-missing data at baseline and the corresponding timepoint; PPIS = Per Protocol Immunogenicity Set; SR = seroresponse.

[a] SR1 at participant level is defined as an Ab value 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. Percentages are based on N1.

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

[c] 95% CI is calculated using the Miettinen-Nurminen score method.

[d] For this sensitivity analysis, common risk difference and 95% CI is calculated using the stratified Miettinen-Nurminen method adjusted by age group (2 age groups: ≥6 months and <2 years, ≥2 and <6 years).

Source: Table 14.2.2.5.2.1

It is noted that the number of evaluable participants was smaller than 71. 56 (N1) participants provided neutralising antibody values against BA.1 strain at Baseline and Day 57. In seronegative participants, only 23 participants provided nAb values against BA.1 at Baseline and Day 57. In seropositive participants, only 33 participants provided nAb values against BA.1 at Baseline and Day 57.

Ancestral (D614G) Analysis

In the PPIS, the SRR against ancestral D614G was 92.4% (95% CI: 83.2, 97.5) in Study P306 and 99.5% (95% CI: 98.5, 99.9) in Study P204. Even with administration of the lower dose of mRNA

encoding the ancestral strain spike protein sequence in Study P306 than in Study P204, SRRs of greater than 90% were achieved in both groups.

Table 8: Pseudovirus Neutralising Antibody Values Against Ancestral Strain (VAC62)—Seroresponse Rate (PPIS)

	≥6 Months and <6 Years	
	P306 mRNA-1273.214 Primary Series 25 µg (N=71)	Historical Comparator P204 mRNA-1273 Primary Series 25 µg (N=632)
Baseline SARS-CoV-2 Status: Overall		
Participants achieving SR1[a], n/N1 (%)	61/66 (92.4)	582/585 (99.5)
95% CI[b]	(83.2, 97.5)	(98.5, 99.9)
Difference in SR1[a] rate (P306 vs P204), % (95% CI)[c]	-7.1 (-16.0, -2.7)	
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	-8.0 (-14.0, -2.0)	
Baseline SARS-CoV-2 Status: Negative		
Participants achieving SR1[a], n/N1 (%)	23/25 (92.0)	545/548 (99.5)
95% CI[b]	(74.0, 99.0)	(98.4, 99.9)
Difference in SR1[a] rate (P306 vs P204), % (95% CI)[c]	-7.5 (-24.4, -1.6)	
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	-10.0 (-19.3, -0.7)	
Baseline SARS-CoV-2 Status: Positive		
Participants achieving SR1[a], n/N1 (%)	38/41 (92.7)	37/37 (100)
95% CI[b]	(80.1, 98.5)	(90.5, 100.0)
Sensitivity analysis for difference in SR1[a] rate (P306 vs P204), % (95% CI)[c]	-7.3 (-19.5, 2.5)	
Difference in SR1[a] rate (P306 vs P204), % (95% CI)[d]	-7.9 (-21.0, 5.2)	

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantification; N = number of participants in the PPIS; N1=number of participants with non-missing data at baseline and the corresponding timepoint; NA = not applicable; PPIS = Per Protocol Immunogenicity set; SR = seroresponse.

[a] SR1 at participant level is defined as an Ab value 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. Percentages are based on N1.

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

[c] 95% CI is calculated using the Miettinen-Nurminen score method.

[d] Common risk difference and 95% CI is calculated using the stratified Miettinen-Nurminen method adjusted by age group (2 age groups: ≥6 months and <2 years, ≥2 and <6 years).

Source: Table 14.2.2.4.2.1

It is noted that the number of evaluable participants was smaller than 71. 66 (N1) participants provided neutralising antibody values the ancestral strain at Baseline and Day 57. In seronegative participants, only 25 participants provided nAb values against BA.1 at Baseline and Day 57. In seropositive participants, only 41 participants provided nAb values against BA.1 at Baseline and Day 57.

Exploratory Endpoints

Participants were monitored for COVID-19 via symptom surveillance. The median length of follow up was 68 days (range: 1 to 138 days) after the second dose in participants who received the second dose. In the PP Set for Efficacy starting 14 days after the second injection, there were 3 cases of SARS-CoV-2 infection (incidence rate 298.3 [95% CI: 61.5, 871.8] per 1,000 person-years), which were all asymptomatic. There were no cases of COVID-19 according to the CDC definition that occurred starting 14 days after the second injection.

Given the increasing use of non-RT-PCR tests, sensitivity analyses were performed by inclusion of other tests for SARS-CoV-2 (e.g., home antigen test) that were self-reported by participants' caregivers (or legally authorised representatives). In the PP Set for Efficacy, starting 14 days after the second injection including all test results (RT-PCR and non-RT-PCR test results), there were 4 cases of SARS-CoV-2 infection (incidence rate 401.7 [95% CI: 109.5, 1028.5] per 1,000 person-years), of

which 3 were asymptomatic (incidence rate 301.3 [62.1, 880.5] per 1,000 person-years) and one met the CDC definition of COVID-19 (incidence rate 96.2 [95% CI: 2.4, 535.8] per 1,000 person years).

Sensitivity analyses were also conducted including participants regardless of baseline SARS-CoV-2 status (i.e., FAS). In the FAS starting 14 days after the second injection including all test results (RT-PCR and non-RT-PCR test results), there were 3 cases of COVID-19 according to the CDC definition (incidence rate 76.7 [95% CI: 15.8, 224.1] per 1,000 person-years), 6 cases of SARS-CoV-2 infection (incidence rate 155.5 [95% CI: 57.1, 338.4] per 1,000 person-years), of which 3 were cases of asymptomatic SARS-CoV-2 infection (incidence rate 77.7 [95% CI: 16.0, 227.1] per 1,000 person-years).

2.4.2. Simplification of vaccine regimen

This application aims to harmonise the primary series composition to align with the currently authorised and approved bivalent booster dose (Original + BA.4/BA.5) in line with recent recommendations from the FDA and VRBPAC (FDA 2023). In addition, this application aims to simplify the vaccine dosing and administration regimen, in line with recent recommendations from the FDA and VRBPAC (FDA 2023), and the EMA Emergency Task Force (EMA 2022). The combination of seroprevalence data and post-dose 1 nAb titres, with the evidence that at least 2 exposures to spike protein (through vaccination and/or infection) provide a degree of protective immunity, support a simplified immunisation schedule in which individuals 6 years of age and older receive a single dose of the bivalent COVID-19 vaccine.

Global Seroprevalence

Emerging evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection against COVID-19 (Pilz *et al* 2022). Global seroprevalence of SARS-CoV-2 among children and adolescents less than 19 years of age increased significantly since the start of the pandemic from 7.3% reported in studies conducted in late 2019 to 2020 to 56.5% observed in studies conducted in late 2021 to 2022 (Naeimi *et al* 2023). This significant increase in seroprevalence among children is driven by the emergence of the Delta (B.1.617.2) variant in Summer 2021, quickly followed by the Omicron variant (B.1.1.529; BA.1) and subvariants (BA.2, BA.2.75.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, XBB.1, and others). Recent serologic data on SARS-CoV-2 infection collected among children during the middle/end of 2022 in specific countries in Europe and in the US demonstrate continued increases as well as differences in seropositivity by age among children. A population-based serosurvey conducted in Portugal between April and June 2022 among 3,825 individuals, reported seropositivity due to vaccination and/or infection to be 76.2% and 78.7% among children <4 years and 5-10 years of age (respectively) as compared to 96.2% among children 10-19 years of age (Kislaya *et al* 2023). In Germany, anti-spike SARS-CoV-2 antibody positivity assessed among 59,786 children and adolescents 1-17 years of age between Jan-May 2022 reported a seroprevalence of 44.6% and 63.0% among children 1-4 years of age vs. 5-10 years of age, respectively (Ott *et al* 2022). In the United States, seroprevalence data collected by the US CDC between March and December 2022 demonstrated a similar pattern of increasing seropositivity by age with seroprevalence estimates of 75%, 85%, 92%, 97%, and 99% among children 6-11 months, 12-23 months, 2-4 years, 5-11 years, and 12-17 years, respectively (Advisory Committee on Immunization Practices 2023).

These seroprevalence estimates demonstrate a high level of immunity among children conferred by either vaccination or infection in both European and US settings with lower seropositivity rates observed among younger children less than 6 years of age relative to older children and adolescents. The lower seroprevalence rates in children less than 6 years of age suggests a primary vaccination

series may continue to benefit this age group. The higher seroprevalence in older children taken together with the evidence that at least 2 exposures to spike protein (through vaccination and/or infection) provide a degree of protective immunity, support a simplified immunisation schedule for this group (Andeweg *et a*l 2022, Babouee Flury *et al* 2022, Bates *et al* 2022, Chin *et al* 2022, Hansen *et al* 2023, Powell *et al* 2022).

Immunogenicity of a Single Dose of Moderna COVID-19 Vaccine in Participants 6 to 11 Years of Age and 18 Years and Older with Evidence of Prior SARS-CoV-2 Infection

As seroprevalence surveys estimate that majority of the global population 6 years of age and older now have antibodies (from vaccination and/or infection) against SARS-CoV-2, it is reasonable to expect that a single dose of mRNA 1273.222 will elicit a suitable protective response. As supporting data, nAb responses post-dose 1 in participants in P204 and P301 studies with evidence of prior infection were compared to nAb responses post-dose 2 in participants with no evidence of prior infection (groups in which effectiveness of the 2-dose primary series was established) (table below). In both age groups, neutralising antibody titres at 28 days post-Dose 1 in participants with evidence of prior infection were not statistically different from those of participants without evidence of prior infection at 28 days post-Dose 2.

Table 9: Geometric Mean Antibody Titres Against a Pseudovirus Expressing the SARS-CoV-2 Spike Protein (USA_WA1/2020 isolate carrying the D614G mutation) after Moderna COVID-19 Vaccine at 28 Days Post-Dose 1 in Participants With Evidence of Prior SARS-CoV-2 Infection and at 28 Days Post-Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection

	P204 6-11 years (50 µg mRNA)		P301 ≥18 years (100 µg mRNA)	
Baseline SARS-CoV-2 status	Positive N=15	Negative N=321	Positive N=130	Negative N=1053
Baseline GMT[a]	59.4	9.3	68.1	9.6
Timepoint	28 days post-Dose 1	28 days post-Dose 2	28 days post-Dose 1	28 days post-Dose 2
Post-Vaccination GMT (95% CI)	2110.0 (845.1, 5268.4)	1616.5 (1463.1, 1786.1)	1478.9 (1069.6, 2044.9)	1081.1 (1019.8, 1146.1)

Source: P204 Table 14.2.3.1.2.2 (6y12y, data cut 07 Sep 2022); P301 CSR Table 14.2.4.2.1.3.1 (≥18y, data cut 26 Mar 2021)

[a] The baseline GMT based on participants with available nAb values at both baseline and post-vaccination specific timepoint.

Summary of main study

The following table summarises the immunogenicity results from the main studies 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 10: Summary of immunogenicity for trial mRNA-1273-P306

Title: An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years		
Study identifier	IND: 019745	
Design	Immunobridging (6 months – 5 years of age) Open label non-randomised	
	Duration:	Study on-going (cut-off date 05 Dec 2022)
Hypothesis	Superiority; Non-inferiority	

Treatments groups	PPIS P306		mRNA-1237.214 (original Omicron BA.1). 28 days after 2nd dose, 71 individuals
	PPIS P204		mRNA-1237 (original). 28 days after 2nd dose, 632 individuals
Endpoints and definitions	Co-Primary endpoints	Superiority Non-Inferiority	Superiority of nAB GMTs against Omicron BA.1 Non-inferiority of nAB GMTs against ancestral SARS-CoV-2
Database lock	Cut-off date 05 Dec 2022		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	Other: Per-Protocol Immunogenicity Set (PPIS), 28 days after 2nd dose		

Descriptive statistics and estimate variability	Treatment group	PPIS P306	PPIS P204	Effect Estimate: Geometric Mean Ratio (GMR)
	Number of participants	71	632	71 vs. 632
	GMC against Omicron BA.1	1890	74	GMR 25.4
	CI	1520, 2349	69, 81	20.1, 32.1
	GMC against ancestral SARS-CoV-2	1433	1733	GMR 0.83
	CI	1173, 1750	1621, 1852	0.67, 1.02

Notes

- Combined analysis of subjects with and without prior SARS-CoV-2 infection for primary series vaccination; large differences in proportion of previously infected participants (63.4% in P306 vs. 6.6% in P204);
- Very low number of participants in P306 (n = 71 PPIS overall; PPIS-negative n = 26); lower number of evaluable participants (for nAb against Omicron BA.1 overall n = 58, and n = 24 in seronegatives; for nAbs against ancestral strain overall n = 66, and n = 25 in seronegatives);
- P204 is a historical comparator trial and not enrolled contemporaneously;
- Change to the boundaries of the CI for non-inferiority after cut-off date;
- Non-inferiority criteria for ancestral SARS-CoV-2 GMC values in sub-group analyses (positive / negative) not met (even point estimates strongly below NI margin).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study P306 was planned as an open-label single arm immunogenicity and safety study in children aged 6 months to 6 years of age. The study was designed with two parts: Part 1 assessed immunogenicity and safety after a primary two-dose series with mRNA-1273.214 the bivalent vaccine candidate against BA.1. Part 2 was designed to assess immunogenicity and safety after a single booster dose with the same vaccine and was not assessed as part of this procedure.

The co-primary endpoints for Part 1, were nAb titres at Day 57 against BA.1 and against the ancestral strain in comparison to P204 (historical comparator trial and not enrolled contemporaneously). For the

former endpoint, a superiority hypothesis was specified, whereas for the later a non-inferiority hypothesis with NI-margin of 0.667 was defined. Overall the statistical methods defined for Study 306 were adequate and in line with previous studies with similar objectives.

The protocol and SAP were updated once at 08 Dec 2022 (Protocol) and 15 Dec 2022 (SAP). The second co-primary endpoint (nAbs against ancestral strain) was only included at this stage based on an FDA suggestion and the NI-margin (which was specified as 0.67 for other hypothesis in the initial protocol) was modified to 0.667. It was noted that the result for GMR against the ancestral strain just met the modified NI-margin at the time of data cut-off (and would not have met the suggested margin) by the protocol, which defined the margin was finalised after the cut-off. The MAH argued that the database lock was only after the protocol amendment and no data was known previously. This could not be fully verified. For this procedure however is of no further relevance. The NI-hypothesis against the ancestral strain was considered of minor relevance.

The study planned to enrol 480 participants in the FAS and it was estimated that 416 participants were eligible for the primary immunogenicity population (per protocol immunogenicity set; PPIS). No interim analysis was planned "*with the exception of clinical or regulatory needs and requests*". The data presented was based on an interim data cut-off on 05 Dec 2022, with only 179 participants in the FAS and at maximum 71 participants in the PPIS. The MAH explained that the analysis was triggered by an FDA request to provide data at an VRBPAC regarding bivalent primary series. P306 part 1 was the only ongoing study by the MAH to study a primary series for a bivalent vaccine.

Finally, it was noted that the trial was conducted using a BA.1 containing bivalent vaccine candidate (mRNA-1273.214) and the analyses were based on superiority of this vaccine against BA.1. For the sought indication, results need to be extrapolated to the bivalent vaccine mRNA-1273.222 against BA.4-5.

Efficacy data and additional analyses

The sample size was smaller than pre-planned. Only ~39% (71 / 179) of participants in the FAS were included in the PPIS. This very high attrition rate was mainly caused by the very early data cut-off. The number of evaluable participants was even smaller than suggested by the sample size in the PPIS. Neutralising antibody values against the BA.1 strain at Day 57 were only available for 58 participants in the overall population, for only 24 (instead of the reported 26) baseline seronegative participants, and for only 34 (instead of the reported 45) baseline seropositive participants. Neutralising antibody values against the ancestral strain at Day 57 were available for 66 participants in the overall population, for 25 (instead of the reported 26) baseline seronegative participants, and for 41 (instead of the reported 45) baseline seropositive participants. This is not in line with the prior planning and impacts the immunogenicity assessment. The final CSR for P306 is expected as soon as it is available **(MEA)**.

For the PPIS participants, baseline SARS-CoV-2 positivity was 63.4% in Study P306 and 6.6% in Study P204 comparator group. This difference most likely reflects the non-contemporaneous enrolment in the 2 studies: P306 enrolment started on 21 Jun 2022; P204 PPIS enrolled between 18 Oct 2021 and 03 Nov 2021. The higher proportion of children in Study P306 with baseline prior SARS-CoV-2 infection is most likely related to enrolment of children after the Omicron surge in the US in Jan 2022.

Overall, the study met its co-primary objectives in the overall population, noting that the interim analysis was not pre-planned (hence no type 1 error control was in place) and that the pre-specification of the NI-margin was not fully evident. However, the results are heavily depending on baseline serostatus. Both, nAb values against BA.1 and the ancestral strain show a very distinct pattern based on baseline SARS-CoV-2 status. In the subgroups the effect is always lower than in the

combined group, which is a result of the strongly increased frequency of SARS-CoV-2 positive participants between the two studies. This is an example *par excellence* of confounding. Apparently, including SARS-CoV-2 status as (main) effect in the ANCOVA model was not sufficient to adjust for this confounding effect. Overall effects should hence be interpreted with great caution, and primarily subgroup results per SARS-CoV-2 status should be used to infer the effect of the vaccination:

- As compared to overall results, a diminished benefit in nAb values is observed against BA.1 with a GMR of 15.8 (95% CI: 11.4, 21.9) in SARS-CoV-2 negative and only 4.6 (95% CI: 2.6, 8.1) in SARS-CoV-2 positive participants, compared to overall population 25.4 (95% CI: 20.1, 32.1) ;
- Even lower were the effects on nAb values against the ancestral strain. It was on average below the NI-margin in both subgroups (and significantly below the margin as the upper CI margin is below 0.667). The GMR was 0.39 (95% CI: 0.29, 0.54) in SARS-CoV-2 negative participants and 0.29 (95% CI: 0.18, 0.46) in SARS-CoV-2 positive participants, compared to overall population 0.83 (95% CI: 0.67, 1.02).

The inclusion of the variant in the bivalent mRNA-1273.214 formulation (1:1 BA.1: original) results in administration of a lower dose of mRNA-1273 (i.e., the mRNA encoding the ancestral strain spike protein sequence), than in the monovalent mRNA-1273 vaccine evaluated in Study P204. Given this lower dose, the lower GMR in the ancestral strain is not surprising. These results confirm data that demonstrated administration of a bivalent formulation as primary series induces responses against both ancestral strain and variant.

In participants without prior SARS-CoV-2 infection, mRNA-1273.214 (P306) induced a Day 57 nAb GMC of 1038 (95% CI: 787, 1370), markedly higher than the GMC induced by mRNA-1273 in Study P204, 66 (95% CI: 61, 71). This analysis in immunologically naïve populations makes clear that inclusion of mRNA encoding variants of the spike protein are key to inducing nAb responses against those target variants.

Seroresponse was overall lower in the combined cohorts after mRNA-1273.214 both against BA.1 and the ancestral strain. Furthermore, against BA.1 strain it remained lower in the SARS-CoV-2 positive participants (which might indeed be partially attributed to prior infections with BA.1). Only SARS-CoV-2 negative participants seemed to benefit sufficiently from the primary vaccination series. Against the ancestral strain, the SRR is lower in both subgroups, showing no benefit over mRNA-1273 (SRRs of greater than 90% were achieved in both groups). As noted earlier, the higher seropositivity rate in P306 were linked to prior infections likely occurred during the Omicron surge. Together, higher rates of infection and higher exposure to Omicron resulted in the higher baseline GMC against BA.1 in the Study P306 PPIS than in the Study P204 PPIS. Achieving a 4-fold rise in nAb levels at Day 57 in participants with such an elevated GMC at baseline should not be interpreted as similar to a 4-fold rise in naïve participants.

The data presented was collected to support the efficacy of mRNA-1273.214 against BA.1. The MAH uses the data to bridge efficacy to mRNA-1273.222 against BA.4-5 and to support a simplification of the vaccination schedule for the primary series in participants older than 6 years to a single dose of mRNA-1273.222 (bivalent Original/Omicron BA.4-5). Extrapolation to a single dose of mRNA-1273.222 in participants above 6 years was based on (i) immunogenicity comparison of nAb GMTs in a PsVNA against the ancestral SARS-CoV-2 between a single vaccination after SARS-CoV-2 infection as compared to a 2-dose primary series with mRNA-1273 and (ii) results from seroprevalence analyses (e.g., Portugal 78.7% seropositivity in children 5-10 yoa; Germany 63.0% seropositivity in children 5-10 yoa). The results provided for neutralising antibody titres at 28 days post-Dose 1 in participants

with evidence of prior infection were comparable to those of participants without evidence of prior infection at 28 days post-Dose 2.

This approach was discussed in the Emergency Task Force and CHMP and was considered reasonable. During the procedure, the MAH amended the age cut-off in the product information for the 1 dose regimen to individuals 5 years of age and older, irrespective of their vaccination history, in line with the ETF recommendation on the COVID-19 vaccines (ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants, published on 7th June 2023). This age cut-off, i.e. 5 years of age, is conservatively based on epidemiological data indicating that children older than 5 years have largely been exposed to SARS-CoV-2, either by infection, vaccination, or both and therefore have already mounted an immune response specific to SARS-CoV-2.

2.4.4. Conclusions on the clinical efficacy

Superiority criteria for Omicron BA.1 nAb GMC values after vaccination with mRNA-1273.214 (Spikevax Bivalent Original/Omicron BA.1) compared to the historical control from P204 (mRNA-1273 original) were met overall including in the small sub-group of baseline seronegative participants.

The non-inferiority criteria for the ancestral strain, was marginally met, noting that the NI-criterion which was specified after the data cut-off. They were not met when accounting for the baseline serostatus. Nevertheless, the clinical meaning of ancestral SARS-CoV-2 nAb GMCs is limited as the ancestral strain does not further circulate but has been succeeded by other SARS-CoV-2 variants.

Therefore, the CHMP has agreed that it can be assumed that a bivalent original /omicron BA.4-5 will induce superior antibody responses to omicron BA.4-5 compared to the original vaccine.

2.5. Clinical safety

Introduction

To support the sought of indication, the use of primary series for Spikevax bivalent Original/Omicron BA.4-5 in young children (6m-5y) and to switch the posology, regardless of vaccination history, to a single dose of Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older, the MAH has submitted safety data from Study mRNA-1273-P306.

Study mRNA-1273-P306 built on the foundation established by Study P204 to evaluate the safety and immunogenicity of the Spikevax bivalent Original/Omicron BA.1 (mRNA-1273.214) in children 6 months to <6 years of age. Study P306 is an ongoing, Phase 3, open-label study; Part 1 evaluates mRNA- 1273.214 as a primary series (2 doses of 12.5 µg Original/ 12.5 µg Omicron BA.1 in 0.25mL) administered to vaccine-naïve children compared with recipients of the Spikevax Original (mRNA-1273) vaccine in the same age group in Study P204. Part 2 examines mRNA-1273.214 as a booster administered to children previously vaccinated with the 2-dose mRNA-1273 primary series. This submission summarizes interim results from Study P306 Part 1 as of a data cut-off of 05 Dec 2022.

The primary safety objectives included in the protocol refers to:

- To evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as a 2-dose primary series 28 days apart in participants aged 6 months to < 6 years;

- To evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series.

To support the indication for a single dose of Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older, the MAH has submitted the Summary Safety Report 21 (SSR 21) including post-marketing data from Spikevax original (mRNA-1273), Spikevax Bivalent .214 (Original/BA.1) booster, and Spikevax Bivalent .222 (Original/BA.4-5) booster.

Patient exposure

Enrolment in Study P306 started 21 June 2022 and is ongoing. As of the data cut-off for this interim analysis (05 Dec 2022), the Safety Set included 179 participants who received at least 1 dose of mRNA- 1273.214 and 142 (79.3%) participants who received 2 doses of Spikevax Bivalent.214 (Original/BA.1).

The number of participants in the safety set was described in Table 2.

Three participants were lost to follow-up after the first dose and did not receive the second dose. The median follow-up time in the Study P306 Safety Set was 85 days (range: 1 to 168 days) after the first dose in participants who received at least 1 dose of mRNA-1273.214 primary series, and 68 days (range: 1 to 138 days) after the second dose in participants who received 2 primary series doses. As of the data cut-off, 108 participants had been followed at least 28 days after the second dose (i.e., the planned time point for Day 57 immunogenicity analyses), and 84 participants had been followed at least 56 days after the second dose.

Table 11: Summary of Study Duration in Study P306 Part 1 (safety set)

	≥6 Months and <6 Years (N=179)
Number of Participants, n (%)	
≥7 days since first injection, n (%)	170 (95.0)
≥35 days since first injection, n (%)	146 (81.6)
≥56 days since first injection, n (%)	116 (64.8)
≥7 days since second injection, n (%)	133 (74.3)
≥21 days since second injection, n (%)	116 (64.8)
≥28 days since second injection, n (%)	108 (60.3)
≥56 days since second injection, n (%)	84 (46.9)
Study duration (days) from Dose 1, median (min, max)	85.0 (1, 168)
Study duration (days) from Dose 2[a], median (min, max)	68.0 (1, 138)

Abbreviations: max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set.
[a] Study duration from Dose 2 in participants who received Dose 2.
Source: Table 14.1.5.1

Table 12: Participant Demographics and Baseline Characteristics in Study P306 Part 1 (Safety Set)

	≥6 Months and <6 Years (N=179)
Age, years	
Mean (SD)	2.55 (1.387)
Median	3.00
Min, max	0.5, 5.0
Age (years), n (%)	
<1	21 (11.7)
1	27 (15.1)
2	41 (22.9)
3	46 (25.7)
4	23 (12.8)
5	21 (11.7)
Sex, n (%)	
Male	98 (54.7)
Female	81 (45.3)
Race, n (%)	
White	117 (65.4)
Black	46 (25.7)
Asian	5 (2.8)
American Indian or Alaska Native	1 (0.6)
Multiracial	8 (4.5)
Other	2 (1.1)
Ethnicity, n (%)	
Hispanic or Latino	21 (11.7)
Not Hispanic or Latino	158 (88.3)
Race and ethnicity group[a], n (%)	
White non-Hispanic	103 (57.5)
Communities of Color	76 (42.5)
Weight, kg	
Mean (SD)	14.87 (4.153)
Median	15.09
Min, max	6.0, 28.9
Male	98 (54.7)
Female	81 (45.3)
Race, n (%)	
White	117 (65.4)
Black	46 (25.7)
Asian	5 (2.8)
American Indian or Alaska Native	1 (0.6)
Multiracial	8 (4.5)
Other	2 (1.1)
Ethnicity, n (%)	
Hispanic or Latino	21 (11.7)
Not Hispanic or Latino	158 (88.3)
Race and ethnicity group[a], n (%)	
White non-Hispanic	103 (57.5)
Communities of Color	76 (42.5)
Weight, kg	
Mean (SD)	14.87 (4.153)
Median	15.09
Min, max	6.0, 28.9
Baseline SARS-CoV-2 status[b], n (%)	
Negative	42 (23.5)
Positive	113 (63.1)
Missing	24 (13.4)

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

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

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

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

Source: Table 14.1.3.2.1

Adverse events

Safety assessment in Study P306 included monitoring of:

- Solicited local and systemic ARs that occurred during the 7 days following each injection, recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following each injection.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
- SAEs, MAAEs and AESIs from the first dose on Day 1 through the entire study period.

Solicited Adverse Reactions

At least 1 solicited ARs were reported within 7 days after the first dose from 102 (57.0%) participants and after dose 2 from 89 (63.1%) participants.

The most reported local solicited ARs were pain (Dose 1 = 34.1%, Dose 2 = 44%), axillary (or groin) swelling or tenderness (Dose 1 =6.1%, Dose 2 = 3.5%), and erythema (Dose 1 = 1.7%, Dose 2 = 3.5%). The most reported systemic solicited ARs were irritability/crying (Dose 1 =44.3%, Dose 2 = 41.4%), sleepiness (Dose 1 = 30.4%, and Dose 2 = 31.4%), and fatigue (Dose 1= 25.6%; Dose 2 = 33.8%). Grade 3 events were: 3 participants (1.7%) after Dose 1 and 4 participants (2.8%) after Dose 2. No Grade 4 solicited ARs were reported.

Any fever >38 ºC was reported by 16 (8.9%) participants after Dose 1 and by 19 (13.5%) participants after Dose 2. Fever in the 39 to 40ºC range occurred in 3 participants (1.7%) after Dose 1 and 2 (1.4%) after Dose 2. Medications for treatment of pain/fever were received after Dose 1 and Dose 2 in 27 (15.1%) and 30 (21.3%) participants. There were no reports of fever >40ºC.

The median time to onset (TTO) for local solicited ARs was within 1 day after Dose 1 and Dose 2 and the median duration was 1 day after Dose 1 and 2 days after Dose 2. The median TTO of systemic solicited ARs was within 1 day after Dose 1 and 2 days after Dose 2 and the median duration was 2 days after Dose 1 and 1 day after Dose 2. There were no solicited ARs with TTO after Day 7, also no solicited ARs that persisted beyond 7 days after either Dose 1 or Dose 2.

According to SARS-CoV-2 status, participants without evidence of prior SARS-CoV-2 infection demonstrated overall less reactogenicity than those with evidence of prior infection (Dose 1 [66.7%] vs [51.3%] and Dose 2 = [69.4%] vs [61.4%]). The table below summarises the solicited ARs in the solicited safety set.

Table 13: Summary of Participants with Solicited Adverse Reactions Within 7 Days After Dose 1 and Dose 2 (Solicited Safety Set)

Solicited Adverse Reactions Category Grade	≥6 Months and <6 Years (N=179)	
	Dose 1 n (%)	Dose 2 n (%)
Solicited adverse reactions - N1	179	141
Any solicited adverse reactions	102 (57.0)	89 (63.1)
95% CI	49.4, 64.3	54.6, 71.1
Grade 1	70 (39.1)	57 (40.4)
Grade 2	29 (16.2)	28 (19.9)
Grade 3	3 (1.7)	4 (2.8)
Solicited local adverse reactions - N1	179	141
Any solicited local adverse reactions	67 (37.4)	64 (45.4)
95% CI	30.3, 45.0	37.0, 54.0
Grade 1	60 (33.5)	56 (39.7)
Grade 2	6 (3.4)	8 (5.7)
Grade 3	1 (0.6)	0
Pain - N1	179	141
Any	61 (34.1)	62 (44.0)
Grade 1	56 (31.3)	55 (39.0)
Grade 2	5 (2.8)	7 (5.0)
Grade 3	0	0
Erythema (Redness) – N1	179	141
Any	3 (1.7)	5 (3.5)
Grade 1	2 (1.1)	4 (2.8)
Grade 2	0	1 (0.7)
Grade 3	1 (0.6)	0
Swelling (Hardness) – N1	179	141
Any	2 (1.1)	3 (2.1)
Grade 1	1 (0.6)	3 (2.1)
Grade 2	0	0
Grade 3	1 (0.6)	0
Axillary (or Groin) swelling or tenderness – N1	179	141
Any	11 (6.1)	5 (3.5)
Grade 1	9 (5.0)	5 (3.5)
Grade 2	2 (1.1)	0
Grade 3	0	0
Solicited systemic adverse reactions – N1	179	141
Any solicited systemic adverse reactions	80 (44.7)	69 (48.9)
95% CI	37.3, 52.3	40.4, 57.5
Grade 1	50 (27.9)	39 (27.7)
Grade 2	28 (15.6)	26 (18.4)
Grade 3	2 (1.1)	4 (2.8)
Fever – N1	179	141
Any	16 (8.9)	19 (13.5)
Grade 1	10 (5.6)	10 (7.1)
Grade 2	4 (2.2)	7 (5.0)
Grade 3	2 (1.1)	2 (1.4)
Headache – N1	90	71
Any	10 (11.1)	8 (11.3)
Grade 1	7 (7.8)	7 (9.9)
Grade 2	3 (3.3)	1 (1.4)
Grade 3	0	0

Fatigue – N1	90	71
Any	23 (25.6)	24 (33.8)
Grade 1	9 (10.0)	10 (14.1)
Grade 2	13 (14.4)	14 (19.7)
Grade 3	1 (1.1)	0
Myalgia – N1	90	71
Any	11 (12.2)	11 (15.5)
Grade 1	7 (7.8)	7 (9.9)
Grade 2	4 (4.4)	4 (5.6)
Grade 3	0	0
Arthralgia – N1	90	71
Any	7 (7.8)	9 (12.7)
Grade 1	4 (4.4)	7 (9.9)
Grade 2	3 (3.3)	2 (2.8)
Grade 3	0	0
Nausea/Vomiting – N1	90	71
Any	5 (5.6)	5 (7.0)
Grade 1	3 (3.3)	3 (4.2)
Grade 2	2 (2.2)	2 (2.8)
Grade 3	0	0
Chills – N1	90	71
Any	4 (4.4)	6 (8.5)
Grade 1	3 (3.3)	5 (7.0)
Grade 2	1 (1.1)	1 (1.4)
Grade 3	0	0
Irritability/crying – N1	79	70
All	35 (44.3)	29 (41.4)
Grade 1	26 (32.9)	22 (31.4)
Grade 2	9 (11.4)	6 (8.6)
Grade 3	0	1 (1.4)
Sleepiness – N1	79	70
Any	24 (30.4)	22 (31.4)
Grade 1	23 (29.1)	20 (28.6)
Grade 2	1 (1.3)	2 (2.9)
Grade 3	0	0
Loss of appetite – N1	79	70
Any	20 (25.3)	19 (27.1)
Grade 1	18 (22.8)	16 (22.9)
Grade 2	2 (2.5)	2 (2.9)
Grade 3	0	1 (1.4)

Unsolicited Adverse Events

Unsolicited AEs within 28 days, regardless to the relationship to study vaccine and after either dose, were reported from 55 (30.7%) participants. Of those Grade 3/severe events were reported by 1 (0.6%) participant. Unsolicited AEs considered vaccine related were reported by 2 (1.1%) participants. Detailed information is presented in the table below.

Table 14: Summary of Participants with Unsolicited TEAE up to 28 Days After Any Injection in Part 1 (Safety Set)

Category	≥6 Months and <6 Years (N=179)
Unsolicited TEAEs Regardless of Relationship to Study Vaccination	**n (%)**
All	55 (30.7)
Serious	1 (0.6)
Fatal	0
Medically attended	45 (25.1)
Leading to discontinuation from study vaccine	0
Leading to discontinuation from participation in the study	0
Grade 3/severe	1 (0.6)
Grade 3 or higher	1 (0.6)
Nonserious[a]	54 (30.2)
Grade 3/severe	0
Grade 3 or higher	0
At least 1 nonserious[b]	55 (30.7)
Grade 3/severe	1 (0.6)
Grade 3 or higher	1 (0.6)
Special Interest (AESI)	0
MIS-C	0
Other	0
Unsolicited TEAEs related to study vaccination	
All	2 (1.1)
Serious	0
Fatal	0
Medically attended	0
Leading to discontinuation from study vaccine	0
Leading to discontinuation from participation in the study	0
Grade 3/Severe	0
Grade 3 or higher	0
Nonserious[a]	2 (1.1)
Grade 3/severe	0
Grade 3 or higher	0
At least 1 nonserious[b]	2 (1.1)
Grade 3/severe	0
Grade 3 or higher	0
Special Interest (AESI)	0
MIS-C	0
Other	0

Abbreviations: AESI = adverse event of special interest; MIS-C = multisystem inflammatory syndrome in children; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: A treatment-emergent adverse event (TEAE) was 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.

[a] Participants who reported at least one non-serious TEAE and did not report any serious AE are included in the summary.

[b] Participants who reported at least one non-serious TEAE regardless of reporting any SAE or not are included in the summary.

Source: Table 14.3.1.7.1.1.1

Most of unsolicited AEs up to 28 days after any injection were SOC Infections and infestations (22.9%), within the most reported upper respiratory tract infection (8.9%), rhinorrhea (2.8%), and ear infection (2.2%). There were 2 reported TEAEs (1.1%) up to 28 days, considered related to vaccine due to the temporal association with vaccination:

- One event of mild diarrhoea (verbatim: diarrhea of unknown etiology) in a 2 yo female, 2 days after Dose 1 and resolved in 1 day. The event did not occur after Dose 2.
- One event of mild croup (verbatim: croup infectious) 9 days after Dose 1 and resolved after 4 days. No recurrence of croup symptoms after Dose 2.

There was 1 severe event of asthma (SAE) which is described below in the SAEs section. A summary of the unsolicited TEAEs by SOC and PT is presented in the table below.

Table 15: Participant Incidence (≥ 1%) of Any Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Any Injection in Part 1 (Safety Set)

System Organ Class Preferred Term	≥6 Months and <6 Years (N=179) n (%)
Number of participants reporting unsolicited adverse events	55 (30.7)
Number of unsolicited adverse events	81
Infections and infestations	41 (22.9)
Upper respiratory tract infection	16 (8.9)
Ear infection	4 (2.2)
Gastroenteritis viral	3 (1.7)
Influenza	3 (1.7)
Nasopharyngitis	3 (1.7)
Otitis media	3 (1.7)
Respiratory syncytial virus infection	3 (1.7)
Otitis media acute	2 (1.1)
Pharyngitis streptococcal	2 (1.1)
Rhinovirus infection	2 (1.1)
Viral infection	2 (1.1)
Respiratory, thoracic and mediastinal disorders	12 (6.7)
Rhinorrhoea	5 (2.8)
Nasal congestion	3 (1.7)
Cough	2 (1.1)

Abbreviations: COVID-19 = coronavirus disease 2019; TEAE = treatment-emergent adverse event.
Note: 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.
MedDRA version 23.0.
Source: Table 14.3.1.8.1.1.1

Medically Attended AEs

MAAEs up to 28 days were reported by 45/179 (25.1%) participants, of which 21.2% were reported in the Infections and infestations SOC, with the same most reported events (upper respiratory tract infection, 7.8%; ear infection, 2.2%; rhinorrhea, 2.2%). There were no MAAES considered vaccine related.

MAAEs through the entire study period were reported in 71/179 (39.7%) participants, of which 34.6% in the Infections and infestations SOC within the most common upper respiratory tract infection (12.8%); ear infection, pharyngitis streptococcal, and rhinorrhea (4.5% each); and influenza, otitis media, and otitis media acute (3.4% each).

Adverse Events of Special Interest

There were no AESIs, including myocarditis, pericarditis or multisystem inflammatory syndrome in children (MIS-C), reported during the study period. There were no TEAEs of anaphylaxis and no other events suggestive of a hypersensitivity reaction occurring up to 28 days after any injection.

Serious adverse event/deaths/other significant events

Deaths

There were no fatal events reported within 28 days after either dose.

Other Serious adverse events

There was 1 SAE of asthma exacerbation reported by one participant (0.6%). The event occurred in a patient with medical history of asthma who was diagnosed with rhinovirus and asthma exacerbation 14 days after Dose 1 of mRNA-1273.214. The patient was hospitalised in the intensive care unit and treatment included bronchodilators and corticosteroids, discharged from the hospital after 3 days. Symptoms of asthma persisted for several weeks, requiring a repeated course of oral corticosteroids. The asthma exacerbation was considered resolved 36 days after Dose 1 (duration of 22 days). The event was considered not related to vaccine by the investigator. Dose 2 was delayed but was tolerated without incident, and the participant remains in the study at the time of the data cut-off 05 December 2022.

During the procedure, the MAH provided the reported SAEs and AESIs with a later cut-off (23 May 2023) as following: 4 SAEs in 3 participants:

- 1 SAE of pneumonia and 1 SAE bronchiolitis occurred in a patient 7 days after Dose 2 of Bivalent.214 vaccine and the event was reported resolved 6 days later;
- 1 SAE of asthma exacerbation in a patient 59 days after Dose 2 and considered resolved 42 days later;
- 1 SAE with worsening of symptomatic vascular ring, occurred in a patient, 80 days later after Dose 2, the event was considered resolved the same day with the surgical repair procedure.

The SAEs were all considered as not related to the vaccine.

There were 2 AESIs:

- 1 event of febrile seizure (full body seizure) 98 days after Dose 2 of Bivalent.214 vaccine, and the duration of the seizure was 3 minutes. The individual was observed for 3 hours and treatment for cold and fever were prescribed. The event was considered not related to the vaccine.
- 1 AESI of Henoch-Schonlein purpura in a patient who developed a rash primarily in lower extremities 2 days after Dose 2 of Bivalent.214 vaccine. Participant had a medical history of eczema and seasonal allergy and the event was assessed as related to the vaccine by the investigator. There is no other clinical information regarding the event and the temporal relation with the vaccination might lead to the causality assessment with the study vaccine.

However as it is stated by the MAH, these data are subject to change as the data collection is ongoing.

Comparative tables of primary series from study P204 and both primary series from Study P306 are provided in the following tables.

Table 16: Solicited Local and Systemic Adverse Reactions overall figures Starting Within 7 Days After Each Dose in Participants 6 months Through 5 Years (Solicited Safety Set, Dose 1 and Dose 2, Primary Series) in Studies mRNA-1273-P204 and mRNA-1273-P306

	mRNA-1273-P204 mRNA-1273				mRNA-1273-P306 (2-dose series) mRNA-1273.214			
	6 months to < 2 years		2 years to 5 years		6 months to < 2 years		2 years to 5 years	
Solicited adverse reactions Category Grade	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
Solicited ARs – N1	1746	1596	2957	2938	48	36	131	105
Any SAR	1469 (84.1)	1329 (83.3)	2332 (78.9)	2478 (84.3)	35 (72.9)	20 (55.6)	67 (51.1)	69 (65.7)
Grade 4	1 (<0.1)	3 (0.2)	4 (0.1)	7 (0.2)	0	0	0	0
Grade 3 or Above	54 (3.1)	69 (4.3)	91 (3.1)	167 (5.7)	1 (2.1)	0	2 (1.5)	4 (3.8)
Solicited local ARs – N1	1745	1596	2956	2938	48	36	131	105
Any SAR	775 (44.4)	868 (54.4)	1874 (63.4)	2157 (73.4)	18 (37.5)	13 (36.1)	49 (37.4)	51 (48.6)
Grade 4	0	0	0	0	0	0	0	0
Grade 3 or Above	9 (0.5)	22 (1.4)	23 (0.8)	34 (1.2)	1 (2.1)	0	0	0
Solicited systemic ARs – N1	1745	1596	2955	2938	48	36	131	105
Any SAR	1334 (76.4)	1174 (73.6)	1595 (54.0)	1814 (61.7)	33 (68.8)	19 (52.8)	47 (35.9)	50 (47.6)
Grade 4	1 (<0.1)	3 (0.2)	4 (0.1)	7 (0.2)	0	0	0	0
Grade 3 or Above	46 (2.6)	47 (2.9)	69 (2.3)	135 (4.6)	0	0	2 (1.5)	4 (3.8)

Study P204 data cut-off date: 21 Feb 2022, Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1, Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1. Study P306 data cut-off date: 05 Dec 2022, Table 14.3.1.1.1.2.1.1 and Table 14.3.1.1.1.2.2 for Part 1 primary series

Table 17: Unsolicited AEs up to 28 days with occurrence of ≥ 1% after any injection in participants 6 months Through 5 Years who received primary series (Safety Set) in Studies mRNA-1273-P204 and mRNA-1273-P306

	Study: mRNA-1273-P204 IP: mRNA-1273		Study: mRNA-1273-P306 (2-dose series) IP: mRNA-1273.214	
System Organ Class Preferred Term	**6 months to < 2 years**	**2 years to 5 years**	**6 months to < 2 years**	**2 years to 5 years**
Number of participants reporting unsolicited AEs	869 (49.3)	1212 (40.0)	19 (39.6)	36 (27.5)

Study mRNA-1273-P306 Part 2

A summary of safety data from study P306 Part 2 was also provided. Study P306 part 2 data include 539 boosted participants with a median follow up time of 117 days, and a median time between dose 2 of primary series and booster dose of 7.85 months.

At least one solicited AR was reported by 70.9% participants within 7 days after booster; the most reported local solicited AR was pain (47.3%) and the most reported systemic solicited AR was irritability/crying (53.2%). Any fever ≥ 38 ºC was reported by 41 participants and Grade 3 fever was reported by 5 (0.9%) participants, all in the 2-to-5-year age group. No Grade 4 solicited adverse reactions were reported.

Any unsolicited AEs within 28 days were reported by 22.3% participants, mostly within SOC 'Infections and infestations' (15.6%) and the most commonly reported were upper respiratory tract infection (5.8%). One AESI of erythema multiple was deemed related to study vaccine.

The reactogenicity and safety profile of a booster dose of Bivalent.214 vaccine was comparable to that of the primary series (Spikevax original) and no new safety concerns were identified.

Post-marketing experience

In this submission the MAH also provided the monthly summary safety report 19 (MSSR 19) for the reporting period 18 December 2022 to 17 January 2023, which includes a summary of the post-marketing data with Spikevax Original and the Bivalent Booster Vaccines.

Cumulatively until 17 January 2023, approximately 700 million doses of the mRNA-1273 (Spikevax Original) have been administered to individuals in around 91 countries. Approximately more than 70 million booster doses of Spikevax Bivalent.214 (Original/BA.1) and more than 82 million booster doses of Spikevax Bivalent.222 (Original/BA.4/5) have been administered to individuals in the USA, Canada, Europe and Asia.

Cumulatively, as of 17 January 2023, there have been 663,641 cases (of which 135,766 were serious) involving 2,540,188 events (of which 421,010 events were serious). The mean age was 48.9 years (SD: 17.8; median: 48.0 years). The 3 most common events reported cumulatively for Spikevax, by Preferred Term (PT) were headache (5.8%), pyrexia (5.5%), and fatigue (5.1%).

Age group 0-5 months old

Spikevax (Original) mRNA-1273

There were 229 cases (Including 67 SAEs and 7 fatal cases) reported for children 5 months of age or younger. During this reporting period, no new or follow-up cases were received. 1 SAE reported and summarised in MSSR #12, was captured again because the events/PT's were updated.

Age group 6 months to 5 years old

Spikevax (Original) mRNA-1273

Cumulatively, there have been 874 cases in total, 670 cases were medically confirmed, 74 cases were SAEs, and 2 cases had a fatal outcome (none during the reporting period of this MSSR). No important differences were noted in reports involving females (45.7%) when compared to those in males

(42.8%), with a small proportion of cases (11.6 %) having no gender reported. The median patient age was 2.0 years.

Table 18: post-authorisation cases for Children (6 Months to 5 Years Old) by Seriousness During the Review Period and Cumulatively– Spikevax (Original)

Case Seriousness	Prior to Review Period		Review Period		Cumulative	
	# Cases	% of Total Cases	# Cases	% of Total Cases	# of Total Cases	% of Total Cases
Nonserious	742	84.9	58	6.6	800	91.5
Serious	71	8.1	3	0.3	74	8.5
Total	813	93.0	61	7.0	874	100.0

The below table presents the most frequently reported events (by PT) in children 6 Months to 5 Years Old. It should be noted that PT "No adverse event" (56 events, 36.4% in reporting period and 419 events, 18.1% cumulatively) is not included.

Table 19: Most Frequently Reported MedDRA Preferred Terms (PTs) by Event Count for Children 6 Months to 5 Years Old (Reporting Period and Cumulative Counts) – Spikevax (Original)

Reporting Period			Cumulative		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Expired product administered	35	22.7	Expired product administered	269	11.6
Product storage error	17	11.0	Product storage error	240	10.3
Product temperature excursion issue	10	6.5	Pyrexia	121	5.2
Poor quality product administered	9	5.8	Exposure via breast milk	107	4.6
Inappropriate schedule of product administration	6	3.9	Product temperature excursion issue	91	3.9
Wrong product administered	5	3.2	Poor quality product administered	88	3.8
Pyrexia	2	1.3	Inappropriate schedule of product administration	65	2.8

Cumulatively and during reporting period, when dose number and time to onset could be determined, events were most often reported within the first two days of vaccination.

There were 3 SAEs reported during the reporting period:

- SAE with events of pyrexia, pruritus and rash in a patient, same day of Dose 2 mRNA-1273. The symptoms of rash persisted for more than a month and ultimately the child diagnosed with urticaria.
- SAE of fever and febrile convulsion in a patient one day after Dose 2, the child was diagnosed with mycoplasma pneumonia which might be a likely cause of the events.
- SAE of pericarditis in a patient, with a TTO 2 days after the 1st dose of Spikevax Original, reported from a Health Authority; the outcome was recovered/ resolved.

Spikevax Bivalent.214 (Original/BA.1)

During reporting period, no adverse events reported. One report in a ~~2 years old~~ participant with product administered to patient of 'inappropriate age'. No other information provided.

Spikevax Bivalent.222 (Original/BA.4/5)

During this reporting period, 9 cases (1 serious) were reported for children less than 5 years. The SAE with a fatal outcome concerning a patient who died approx. 3 weeks after receiving an unspecified dose of mRNA-1273 Bivalent.222. Multiple follow-up efforts were performed to obtain further information including the patient's medical history, concomitant medications, details of vaccination, clinical course, date/cause of death, and results of autopsy, if performed. The case was reported by a consumer and despite repeated attempts to obtain further information about the case, the only further detail provided was that the child died from 'sudden death syndrome.' As such, there unfortunately remains insufficient information to assess causality.

The 8 nonserious reports involved product use issues with no adverse events reported.

Children 6-11 Years Old

Spikevax (Original)

Table below summarises the post-authorisation cases received by seriousness during the reporting interval and cumulatively for this age group.

Table 20: Post-authorisation cases received by seriousness during the reporting interval and cumulatively for this age group

Case Seriousness	Prior to Review period		Review Period		Cumulative	
	# Cases	% of Total Cases	# Cases	% of Total Cases	# of Total Cases	% of Total Cases
Nonserious	378	77.6	6	1.2	383	78.6
Serious	104	21.4	0	0.0	104	21.4
Total	482	99.0	6	1.2	487	100.0

* The addition of the cases from prior to review period and cases from the review period do not always add up to the number of total cases because a case that was reported prior to review period can also be included in this review period if a new event was reported during the review period.

The below table presents the most frequently reported events (by PT) in children 6 to 11 years of age vaccinated with Spikevax (Original). It should be noted that 5 of the 6 nonserious cases included the PT "No adverse event" (5 events (33.3%) in reporting period and 76 events (7.3%) cumulatively) which is not included.

Table 21: Most Frequently Reported MedDRA Preferred Terms (PTs) by Event Count for Children 6-11 Years Old (Reporting Period and Cumulative)

Reporting Period			Cumulative		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Wrong product administered	4	26.7	Pyrexia	90	8.7
Pyrexia	1	6.7	Product administered to patient of inappropriate age	83	8.0
Headache	1	6.7	Medication error	62	6.0
Vaccination site pain	1	6.7	Chest pain	37	3.6
Product storage error	1	6.7	Wrong product administered	28	2.7
Product administration interrupted	1	6.7	Rash	26	2.5
Product availability issue	1	6.7	Vomiting	23	2.2

Table 22: Distribution of Events for Children (6-11 Years Old) by Dose Number and Seriousness During this Reporting Period

Dose Number	Nonserious		Serious		# of Total Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Dose 1	2	13.3	0	0.0	2	13.3
Dose 2	1	6.7	0	0.0	1	6.7
Dose 3	0	0.0	0	0.0	0	0.0
Dose 4	1	6.7	0	0.0	1	6.7
Unknown	11	73.3	0	0.0	11	73.3
Grand total	15	100.0	0	0.0	15	100.0

Cumulatively, there were 2 fatal cases reported in children 6 to 11 years of age overall. There were no SAE or fatal cases reported during the reporting period.

Spikevax Bivalent.214 (Original/BA.1)

There were no cases reported in children 6 to 11 years of age during this reporting period.

Spikevax Bivalent.222 (Original/BA.4/5)

During this reporting period there were received 17 cases (7 serious cases) in children 6 to 11 years of age who received Spikevax Bivalent.222 (Original/BA.4/5). No case had a fatal outcome. There were more reporting in females (55.8%) compared to males (35.3%) and one case did not have gender reported. The median patient age was 8.0.

The 7 serious cases were received from Taiwan Health Authorities and they were:

- 1 case of rash
- 1 cases of rash with additionally a Liptschutz ulcer case
- 1 case of seizure in a patient same day of vaccine administration
- 1 case of abdominal pain, pyrexia and diarrhea in a patient 2 days after vaccination
- 1 case of chest pain and unremarkable cardiac workup, in a patient with unknown TTO'
- 1 case of anaphylactic shock and hypersensitivity 5 minutes after Dose 3 mRNA-1273 Bivalent.222 vaccination
- 1 case with electrocardiogram ST segment elevation, after Dose 3 mRNA-1273 Bivalent .222 vaccination in a patient with thalassemia. On post vaccination day one the patient experienced chest pain/tightness, decreased activity, decreased appetite and occasional nausea and vomiting. The cardiac enzymes resulted elevated (high Troponin I; high CK-MB, diffuse ST elevation on EKG. The CXR showed no cardiomegaly. Diagnose was peri-, myocarditis related to vaccination; the enzymes started to decrease four days after vaccination and went normal 8 days after vaccination.

  According to the MAH, based on the clinical presentation and laboratory evaluation demonstrating elevated troponin, elevated CPK, elevated NT-proBNP, and EKG changes, this case is Brighton Classification Level 2 for myocarditis and WHO-UMC is considered "possible" with thalassemia as a confounder.

Adolescents 12-17 Years Old

Spikevax (Original) mRNA-1273

Cumulatively, the MAH received 8,581 cases (which includes 983 serious, 26 fatal, and 7,040 medically confirmed cases) for adolescents (12-17 years of age) who received Spikevax (Original). There were 52.7% females compared to males (42.9%), with a small proportion of cases (4.4%) having no gender reported. The patient median age was 16.0 years (min: 12.0/max: 17.0).

The most reported events by PT were Product administered to patient of inappropriate age (25.1%), pyrexia (6.7%), headache (4.9%) and fatigue (2.2%). The events were most frequently reported after Dose 1, and most often reported to occur on the day of vaccination.

During the reporting period, there were received 7 serious cases with 23 events (of which 22 were serious events) in adolescents (12-17 years old). No cases reported a fatal outcome. One literature report was a SAE of pancytopenia and anorexia nervosa, although this case was subject to pending further information. The other 6 cases were healthy authorities reports: 2 of them were unassessable; 3 reports had alternate etiologies (possible rhinovirus infection, were unlikely related due to extended TTO, or had events known to occur following vaccination with Spikevax original such as mechanical urticaria and vaccination site swelling). There was one case of myocarditis, a backlog report from 2021, received in July 2022, occurred in a patient with unknown medical history, one day after the 2nd dose of Spikevax Original presented cardiac symptoms (chest pain); lab results included showed an elevated troponin and abnormal ECG. Treatment included ibuprofen, colchicine, pantoprazole and metoprolol and the patient was recovering at the time of this reporting.

Spikevax Bivalent .214 (Original/BA.1)

There were reported 6 non SAEs with product use issues and no SAE reported.

Spikevax Bivalent .222 (Original/BA.4/5)

During the reporting period, there were received 22 cases (17 serious cases) for adolescents (12-17-years-old) who received Spikevax Bivalent .222 (Original/BA.4-5). 11 of the 17 serious cases were consistent with reactogenicity, nonspecific events such as chest pain or other expected events such as pyrexia and myalgia. Remaining were:

- A health authority reported case in a patient with muscular weakness on the day of vaccination. Insufficient information received; the patient was treated in the "psychosomatic department."
- 1 case of cardiac arrest 6 days after Spikevax Bivalent.222 in a patient with medical history or concomitant medications the evolution of the events is unclear; however, it was reported that the patient collapsed, was hospitalized, and intubated, and had asystole again requiring CPR. Amiodarone and epinephrine were administered on an unknown date. Workup on an unknown date revealed leukocytosis, hyperglycemia, hypokalemia, respiratory acidosis combined with metabolic acidosis and EKG showing right bundle branch block. It was reported that on day 9, the patient's family indicated the "patient was substantially better that day." The information provided is insufficient to properly perform an assessment of causality.
- 1 case of anaphylactic reaction;
- 3 cases of myocarditis.

Elderly and non-elderly subpopulations /Spikevax Families

In the reporting period, reported preferred terms (PT) were compared by vaccine type, in elderly and non-elderly subpopulations who received either Spikevax (Original), Spikevax Bivalent.214 (Original/BA.1) booster, or Spikevax Bivalent.222 (Original/BA.4-5) booster and presented below.

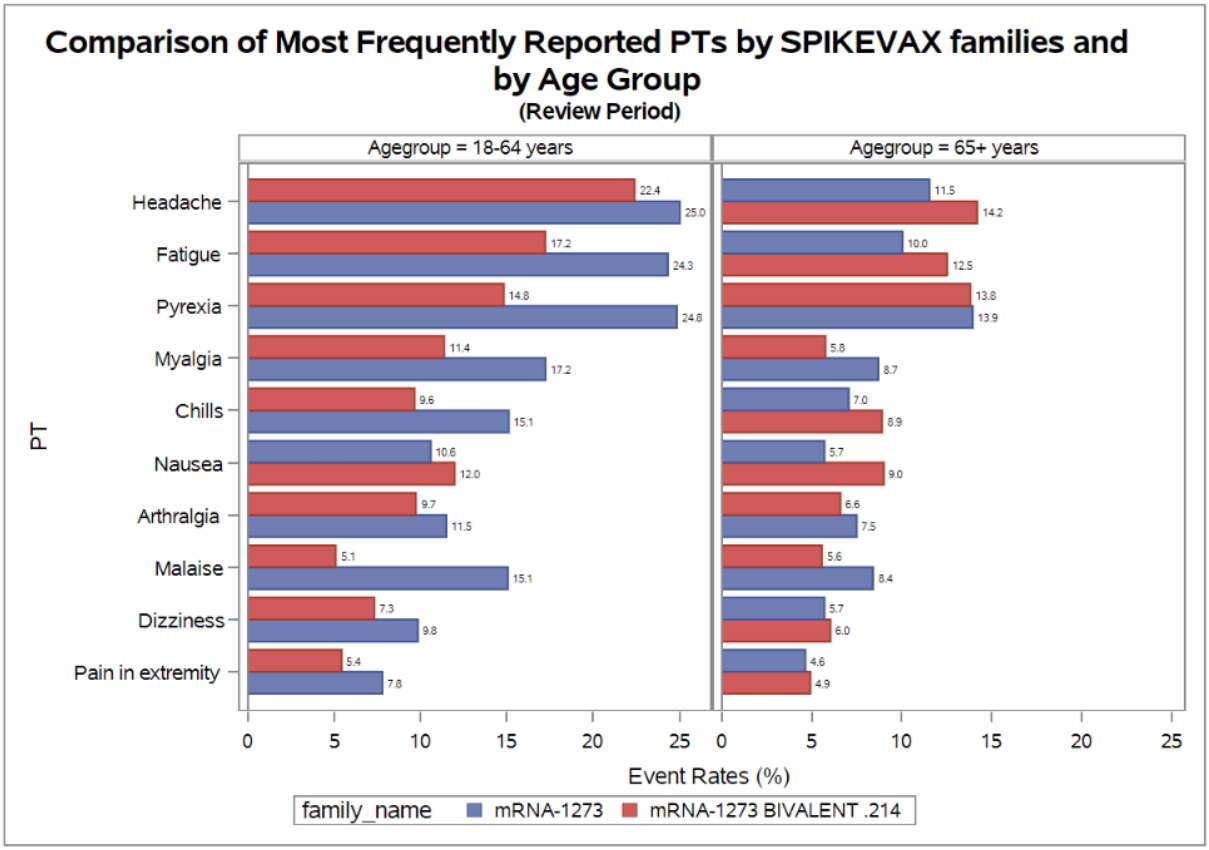
There were similar events, mainly reactogenicity, reported for all vaccine types, within Spikevax family. The highest proportion of reported events was in Spikevax Original booster, while the lowest proportion of events was reported in Spikevax Bivalent.222.

For Spikevax Bivalent.222 (Original/BA.4-5) booster, the smaller percents noted reflect that the most common PTs were for non-clinical adverse events (No Adverse Event, Expired Product Administered, Product Storage Error and Underdose). In addition, the low number of events reported for the bivalent vaccines may be due to their recent authorisation, with lower denominators of total recipients. The event rates percent were calculated by dividing the number of reported events by total reported events for each age group.

Table 23: Comparison of Most Frequently Reported PTs in Unique Cases by Spikevax Families and by Age Group for Spikevax (Original), Bivalent .214, and Bivalent .222 (Review Period)

mRNA-1273 Original					mRNA-1273 Bivalent .214					mRNA-1273 Bivalent .222				
Total cases available in Review Period by Vaccine type														
Count=5192					Count=2716					Count=984				
Total Elderly and Non-Elderly cases available in Review Period by Vaccine type														
Count=4519 (87%)					Count=2239 (82%)					Count=549 (56%)				
PT	Elderly 65+	%	Non-Elderly 18to64	%	PT	Elderly 65+	%	Non-Elderly 18to64	%	PT	Elderly 65+	%	Non-Elderly 18to64	%
All	667		3852		All	1078		1161		All	125		424	
Headache	77	11.5	964	25.0	Headache	153	14.2	260	22.4	COVID-19	4	3.2	11	2.6
Pyrexia	93	13.9	957	24.8	Pyrexia	149	13.8	172	14.8	Pyrexia	5	4.0	9	2.1
Fatigue	67	10.0	937	24.3	Fatigue	135	12.5	200	17.2	Rash	5	4.0	7	1.7
Myalgia	58	8.7	664	17.2	Nausea	97	9.0	139	12.0	Headache	3	2.4	7	1.7
Chills	47	7.0	582	15.1	Chills	96	8.9	112	9.6	Chest pain	0	0.0	7	1.7
Malaise	56	8.4	580	15.1	Arthralgia	71	6.6	113	9.7	Myalgia	7	5.6	6	1.4
Arthralgia	50	7.5	443	11.5	Dizziness	65	6.0	85	7.3	Dizziness	5	4.0	6	1.4
Nausea	38	5.7	408	10.6	Myalgia	62	5.8	132	11.4	Pruritus	4	3.2	6	1.4
Dizziness	38	5.7	379	9.8	Malaise	60	5.6	59	5.1	Dyspnoea	5	4.0	5	1.2
Pain in extremity	31	4.6	300	7.8	Diarrhoea	57	5.3	53	4.6	Pain in extremity	4	3.2	4	0.9

Figure 1: Comparison of Most Frequently Reported PTs in Unique Cases by Spikevax Families and by Age Group for Spikevax (Original), Bivalent .214 (Review Period)



Spikevax (Original)

During this reporting period, a total of 667 cases (2,068 events) were reported in the elderly subpopulation of which 204 cases (30.6%) were serious, 337 (50.5 %) cases were medically confirmed, and 11 cases (1.6 %) reported fatal outcomes. Mostly of the reports were from health authorities; a higher proportion of cases were reported in females (58.9%) compared to males (35.8%) and 35 (5.2%) cases did not identify gender. The median age of reported cases was 71.0 years, with a range from 65.0 years to 96.0 years.

There were 60 SAEs reported after administration of a booster dose (dose 3 and above) of Spikevax original; 30 (50%) of these cases were medically confirmed, and three cases (5%) reported fatal outcomes. The three fatal cases were reported in males, with a median age of 82.0 years, with multiple comorbidities including cardiovascular disease, diabetes, COVID-19 infection, and malignancy.

Spikevax Bivalent .214

There were reported 1,078 cases, of these 632 cases (58.6%) were serious, 278 cases (25.8%) 79 were medically confirmed, and fourteen cases (1.3%) had fatal outcomes.

Spikevax Bivalent .222

During the reporting interval there were 125 cases, of these 110 (88.0%) were medically confirmed, 11 (8.8%) were serious cases, and two cases (1.6%) reported a fatal outcome. Cases were reported more in females (43.2%) than in males (43; 34.4%) and 28 cases (22.4%) did not report gender. The median age was 73.0 years.

Overview of myocarditis and pericarditis

The MAH's global safety database for valid case reports of myocarditis and pericarditis received from multiple sources (HCP, HA, consumers, and literature, worldwide) for Spikevax original and the Spikevax bivalent booster vaccines. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Jan 2023.

The methods of evaluation for the valid and identified cases of myocarditis and pericarditis are shortly described as following:

The use of MedDRA narrow SMQ non-infectious myocarditis/pericarditis

Identified cases were classified into one of five categories, following the Brighton Collaboration Myocarditis/ Pericarditis case definition (Brighton-Myocarditis 2021a, Brighton-Myocarditis 2021b). The Brighton definition and the CDC definition identifies the strength of evidence to support a diagnosis of myocarditis and/or pericarditis.

The CDC working case definition (Gargano 2021) for Acute Myocarditis and Acute Pericarditis.

The company causality assessment is provided utilising the WHO-UMC standardized case causality assessment (WHO 2013).

Further evaluation was conducted in males and females younger than 40 years of age, after the 2nd or the 3rd dose of Spikevax, regardless of the time to onset (TTO) of events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients < 18 years of age.

Cumulatively, through 17 Jan 2023, a total of 6,769 cases of myocarditis and pericarditis have been received for all the Spikevax vaccines, original monovalent and bivalents. A summary of all the cases is presented in the table below.

Table 24: Number and Percentage of Reported Cases of Myocarditis and Pericarditis for Spikevax (Original), Spikevax Bivalent .214 and Spikevax Bivalent .222 – Cumulative as of 17 January 2023

Product Name	Prior Review Period		Review Period		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
SPIKEVAX (Original)	6,665	99.6	52	66.7	6,717	99.2
SPIKEVAX Bivalent .214 (Original/Omicron BA.1)	21	0.3	17	21.8	38	0.6
SPIKEVAX Bivalent .222 (Original/Omicron BA.4/5)	5	0.1	9	11.5	14	0.2
Grand total	**6,691**	**100**	**78**	**100**	**6,769**	**100**

An important decrease in the number of reported cases have been observed for the past reporting period, which continued during this reporting period.

The majority of cases reporting myocarditis and/or pericarditis continues to involve more males (66.2%), especially males between 18 to 39 years of age (39.1%) than females (31.7%).

There were 29 (55.8%) cases that involved males and 21 (40.4%) that involved females; 2 cases (3.8%) did not include gender information, with most of the reports occurring in the 25 to 39 years of age population group. Two cases were reported in the paediatric population: 1 between 2 and 5 years of age and 1 between the ages of 16 and 17 years of age.

2.5.1. Discussion on clinical safety

Current Spikevax bivalent Original/Omicron BA.4-5 booster vaccination is authorised for individuals ≥ 6 years of age.

Within this submission the MAH requested to modify the approved therapeutic indication to include Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg Original/ 12.5 µg Omicron BA.4-5 in 0.25 ml) in young children (6m-5y) and to amend the posology, regardless of vaccination history, to a single dose of Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older.

No clinical safety data have been provided for Spikevax bivalent (Original/Omicron BA.4-5), used as primary series in young children (aged 6 months to 5 years of age) and the safety will be extrapolated from Spikevax Bivalent and Spikevax Original vaccines.

Study mRNA-1273-P306

To support the indication of 2-dose series of Spikevax bivalent Original/Omicron BA.4-5 in young children (6m-5y), the MAH has submitted safety data from Study mRNA-1273-P306. Study P306 is ongoing, up to the data cut-off (05 Dec 2022) in the safety set have been included 179 (100%) participants who received 1 dose of Spikevax Bivalent .214 Original/BA.1 with a median follow up of 85 days after dose 1; and 142 (79.3%) participants who received 2 doses of mRNA- 1273.214, with a median follow up of 68 days post Dose 2. The median age of the participants was 3.0 years and the median weight 15.09. There were enrolled more males compare to females' participants, respectively 54.7% vs 45.3%.

Overall there were more participants who reported at least any solicited ARs after Dose 2 (63.1%) compare to Dose 1 (57.0%). Mostly the solicited ARs were Grade 1 and 2; Grade 3 (1.7% after Dose 1 vs 2.8% after Dose 2). No grade 4 events were reported. The TTO was 1-2 days after each dose and the median duration 1-2 days for both doses, with no solicited ARs that persisted beyond 7 days.

Unsolicited AEs within 28 days, regardless to the relationship to study vaccine and after either dose, were reported from 55 (30.7%) participants. Of those Grade 3/severe events were reported by 1 (0.6%) participant. Unsolicited AEs considered vaccine related were reported by 2 (1.1%) participants: 1 case of mild diarrhoea and 1 case of mild croup.

It is acknowledged that Study P306 Part 1 evaluates mRNA- 1273.214 as a primary series (2 doses of 25 µg each) administered to vaccine-naïve children compared with recipients of the original mRNA-1273 vaccine in the same age group in Study P204. The MAH provided comparative results regarding solicited and unsolicited events between the two vaccine groups. The frequencies of the solicited adverse reactions where lower after administration of Spikevax bivalent Original/Omicron BA.1, as primary series vaccination compared to the Spikevax Original group in the age group 6 months to 5 years of age. The same applied on regarding the unsolicited adverse events across the two vaccines groups. Therefore, based on the extrapolation of the safety data, it is awaited the same regarding the Spikevax bivalent Original/Omicron BA.4-5 when administered as primary series doses in children aged 6 months to 5 years of age.

During the procedure the MAH reported SAEs and AESIs with a later cut-off (23 May 2023): 4 SAEs in 3 participants none related to the vaccine, and 2 AESIs: 1 event of febrile not related to the vaccine and 1 event of Henoch-Schonlein purpura 2 days after Dose 2 of .214 vaccine. The latter event was assessed as related to the vaccine by the investigator. There is no other clinical information regarding the event and the temporal relation with the vaccination might lead to the causality assessment with the study vaccine. These data are subject to change as the data collection is ongoing.

The safety set from Study P306 Part 2, includes 539 boosted participants with a median follow up time of 117 days, and a median time between dose 2 of primary series and booster dose of 7.85 months. At least one solicited AR was reported by 70.9% participants within 7 days after booster; the most reported local solicited AR was pain (47.3%) and the most reported systemic solicited AR was irritability/crying (53.2%). Any fever ≥ 38 ºC was reported by 41 participants and Grade 3 fever was reported by 5 (0.9%) participants, all in the 2-to-5-year age group. No Grade 4 solicited adverse reactions were reported. Any unsolicited AEs within 28 days were reported by 22.3% participants, mostly within SOC 'Infections and infestations' (15.6%) and the most commonly reported were upper respiratory tract infection (5.8%). One AESI of erythema multiple was deemed related to study vaccine. The reactogenicity and safety profile of a booster dose of Bivalent.214 vaccine was comparable to that of the primary series (Spikevax original) and no new safety concerns were identified. The CSR for Study P306 Part 2 with 6 months of follow-up on the full cohort will be available in Q3 2023.

There were no new safety signals identified during study P306 until the data cut-off. However, the safety follow-up is relatively short. There were no MAAES considered vaccine related. Of note, the sample size is not sufficiently large to detect rare or very rare adverse events in paediatric population, which can be detected through post-marketing experience.

In conclusion, the clinical safety profile in children from 6 months to 5 years of age after receiving one dose or 2 doses of Spikevax Bivalent .214 appears comparable to the safety profile of mRNA-1273 in the same age group.

Post marketing experience

In this submission the MAH provided a summary of the post-marketing data with Spikevax Original and the bivalent vaccines, including the monthly summary safety report 19 (MSSR 19) for the reporting period 18 December 2022 to 17 January 2023.

Approximately 700 million doses of the mRNA-1273 (Spikevax Original) have been administered to individuals in around 91 countries. Approximately more than 70 million booster doses of Spikevax Bivalent .214 (Original/BA.1) and more than 82 million booster doses of Spikevax Bivalent.222 (Original/BA.4-5) had been administered to individuals in the USA, Canada, Europe and Asia.

Cumulatively as of 17 January 2023, there have been 663,641 cases (of which 135,766 were serious) involving 2,540,188 events (of which 421,010 events were serious). The 3 most common events reported cumulatively for Spikevax, by Preferred Term (PT) were headache (5.8%), pyrexia (5.5%), and fatigue (5.1%).

There were 11 SAEs in patients less than 18 years of age vaccinated with Spikevax original. Among them these cases there were 2 cases each reported for myocarditis and pericarditis. One case was a backlog report from 2021, received in July 2022. Many of the other serious cases lacked clinical information to adequately assess a relationship to vaccine administration other than temporality. Overall, most cases were non-serious and when serious, these serious events were reported only once that did not demonstrate any unusual groupings by medical concept or by region. Furthermore, most cases classified as serious due to be included in the list of important medical events (IME) or for hospitalisation had minimal to no information provided such as vaccination and event dates, medical history, concomitant medications, diagnostic evaluation, and clinical course, thus precluding further assessment for causality.

There were 25 serious cases for children < 18 years of age who received Spikevax Bivalent.222 (Original/BA.4/5) during this period. Among these cases, there were three cases that reported events of myocarditis.

The review of the data received during the reporting review showed that the events of myocarditis and pericarditis continue to primarily occur in young adult males, shortly after the second dose of the vaccine with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a booster dose of Spikevax. There were 26 reports of myocarditis after any of the 2 Spikevax bivalent vaccines in the reporting period covered by the MSSR 19.

The observed reporting rates for AESI including age and gender stratified estimates, remained largely similar to rates described in the most recent summary safety report. There was no meaningful change in interpretation of observed to expected analyses compared to earlier reports that affected the known safety profile. No safety concerns were identified among AESIs analysed.

Based on the information provided by MAH from multiple sources (post-authorisation safety database, literature, routine pharmacovigilance, signal management) from the Spikevax original given as primary immunisation and booster and the bivalent variant vaccines (Original/BA.1 and Original BA.4/5) given as booster are considered to have an acceptable safety profile and similar to that observed during the clinical trials.

Information received on the Spikevax bivalent vaccines is limited given the much lower number of individuals who have received the bivalent vaccines when compared to the original Spikevax. No changes were observed in the reports received after vaccination with either of the Spikevax bivalent vaccines.

There were no new safety concerns raised during the assessment of the provided safety data.

2.5.2. Conclusions on clinical safety

Based on the results provided from Study P306, the frequencies of the solicited adverse reactions were lower after administration of Spikevax bivalent Original/Omicron BA.1, as primary series vaccination compared to the Spikevax Original group in the age group 6 months to 5 years of age. The same applied on regarding the unsolicited adverse events across the two vaccines groups. Therefore, based on the extrapolation of the safety data, it is awaited to have similar findings for the Spikevax bivalent Original/Omicron BA.4-5 when administered as primary series doses in children aged 6 months to 5 years of age.

Based on the information provided by MAH from multiple sources (post-authorisation safety database, literature, routine pharmacovigilance, signal management) from the Spikevax original given as primary immunisation and booster and the bivalent variant vaccines (Original/BA.1 and Original BA.4/5) given as booster are considered to have an acceptable safety profile and similar to that observed during the clinical trials.

From a safety perspective, the Spikevax bivalent (Original/Omicron BA.4-5) could be used as primary series for the age group ≥6 months to 5 years of age and as 1 dose series in individuals 5 years of age and older.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 7.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Myocarditis Pericarditis
Important potential risks	None
Missing information	Use in pregnancy and while breast-feeding Long-term safety

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	19 Dec 2023
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	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 Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
12 to < 18 years of age Study Status: Ongoing				
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 Final CSR	15 Mar 2021 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 Interim report: Final CSR	28 May 2021 30 Jun 2022 30 Apr 2024
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 Interim report Final CSR	05 Feb 2021 31 Mar 2023 31 May 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 -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)*	Protocol submission Interim updates Final study report	31 Jan 2021 30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022, 30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Jan 2023 30 Jun 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing		Long-term safety AESI and emerging validated safety signals		
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	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
	Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy			
Study mRNA-1273-P901 Real-world study of the effectiveness of the Moderna COVID-19 Vaccine Study Status: Ongoing	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection2. 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 SARS-CoV-2 infection by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection 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 SARS-CoV-2 infection 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 SARS-CoV-2 infection 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 SARS-CoV-2 infection in frail individuals 7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine administered during pregnancy in preventing SARS-CoV-2 infection in pregnant women 8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection among	Use in immunocompromised subjects* Interaction with other vaccines, as possible* Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders)* Use in subjects with autoimmune or inflammatory disorders*	Protocol submission	01 Mar 2021
			Interim updates	14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 30 Jun 2023; 20 Dec 2023
			Final study report	14 Apr 2025

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	individuals with a history of SARS-CoV-2 infection 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic SARS-CoV-2 infection 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic SARS-CoV-2 infection 12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection 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 SARS-CoV-2 infection 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease. 16. To assess the effectiveness of two doses of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design) 17. To assess the effectiveness of one dose of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design) 18. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in non-immunocompromised individuals 19. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in immunocompromised individuals			
mRNA-1273-P910 Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 Study status: Planned	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Myocarditis, Pericarditis	Protocol submission	26 Apr 2022
			Interim report	30 Aug 2022 31 Jan 2023 30 Jun 2023 31 Jan 2024 30 Jun 2024 31 Jan 2025
			Final study report	30 Jun 2025
mRNA-1273-P911	The overarching goal of this study is to characterize long-term outcomes of	Myocarditis	Protocol submission	30 Apr 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) Study status: Ongoing	myocarditis temporally associated with administration of elasomeran (SPIKEVAX) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).		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	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to Spikevax during pregnancy.	Use in pregnancy	Protocol submission	28 Oct 2022
			Study completion	30 Sep 2023
			Final study report	31 Mar 2024
mRNA-1273-P920 Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States Study status: Planned	The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice.	Anaphylaxis* Myocarditis Pericarditis Use in immunocompromised subjects* AESI and emerging validated safety signals	Protocol submission	01 Nov 2022
			Interim report	15 Sep 2023
			Final study report	15 Sep 2024
mRNA-1273-P306 An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years Study status: Ongoing	Evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as a 2-dose primary series 28 days apart in participants aged 6 months to < 6 years Evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose (BD) at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series	Anaphylaxis* Myocarditis Pericarditis Long-term safety	Protocol submission	27 May 2022
			Study completion:	31 May 2024
			Final study report:	31 Jan 2025

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 (see Section III.1). 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: 19 Dec 2023) Study mRNA-1273-P304 (final CSR: 31 May 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025) Study mRNA-1273-P910 (final CSR: 28 Feb 2025) Study mRNA-1273-P911 (final CSR: 31 Oct 2028) Study mRNA-1273-P920 (final CSR: 15 Sep 2024)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis	Routine risk minimisation measures: SmPC Sections 4.4 Special Warnings and Precautions for Use; 4.8 Undesirable effects; PL Section 2 and 4. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of pericarditis in individuals who have received Spikevax (see Section III.1). 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: 19 Dec 2023) Study mRNA-1273-P304 (final CSR: 31 May 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025) Study mRNA-1273-P920 (final CSR: 15 Sep 2024) Study mRNA-1273-P910 (final CSR: 28 Feb 2025)
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: 19 Dec 2023) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P205 (final CSR: 30 Apr 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 4.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Editorial changes were also made to the Product Information (Annexes I, II, IIIA and IIIB) which were reviewed and accepted by the CHMP.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Coronaviruses are a large family of viruses that cause illnesses 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 (PHEIC) on 30th January 2020 and a pandemic on 11th 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.

During the COVID-19 pandemic, the sequence of SARS-CoV-2 is constantly changing over time. 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).

3.1.2. Available therapies

While the efficacy of COVID-19 vaccine encoding the Wuhan 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 vaccines containing the original Wuhan strain together with the Omicron BA.1 or the Omicron BA.4-5 strain have been authorised for a booster use in individuals 6 years of age and older. Spikevax Original (mRNA-1273) is authorised as primary immunisation in young children (6m to 5y) of age.

In the adult clinical development program, two doses of 100µg 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. Vaccine efficacy of mRNA-1273 against SARS-CoV-2 Omicron related COVID-19 is reduced and is waning over time. Vaccination of children 2 years – 5 years of age with mRNA-1273 resulted in 36.8% (95% CI: 12.5, 54.0) efficacy, and in children 6 months - <2 years in 50.6% (95% CI: 21.4, 68.6) efficacy. There is currently no SARS-CoV-2 Omicron variant adapted vaccine authorised for primary series vaccination in children 6 months – 5 years of age.

3.1.3. Main clinical studies

Study mRNA-1273-P306 is an ongoing, Phase 3, open-label study to evaluate the safety and immunogenicity of the Spikevax Bivalent Original/Omicron BA.1 (mRNA-1273.214) vaccine in children 6 months to <6 years of age.

Part 1 evaluates Spikevax Bivalent Original/Omicron BA.1 (mRNA-1273.214) as primary series (2 doses of 25 µg each, respectively 12.5 µg Original/12.5 µg Omicron BA.1 in 0.25 ml) administered to vaccine-naïve children compared with recipients of the Spikevax Original (mRNA-1273) vaccine in the same age group in the historical comparator study P204.

Part 2 examines mRNA-1273.214 as a booster administered to children previously vaccinated with the 2-dose mRNA-1273 primary series.

3.2. Favourable effects

In the absence of a correlate of protection neutralising antibodies lay the basis for protection against COVID-19 disease.

Results from study mRNA-1273-P306 has demonstrated superiority of the neutralising Ab response against Omicron BA.1 variant after primary vaccination with mRNA-1273.214 (bivalent Original/Omicron BA.1) as compared to an historical control of young children of the same age group from study P204 after primary vaccination with mRNA-1273 (original). Based on these immunobridging results efficacy can be inferred for infants and children (6 months < 6 years).

It is reasonably likely that the variant adapted bivalent Original/Omicron BA.4-5 mRNA-1273.222 will elicit a superior neutralising antibody response against SARS-CoV-2 Omicron BA.4-5 in young children (6m-4y) as a 2-dose series, and a single dose of Spikevax bivalent Original/Omicron BA.4-5 for individuals 5 years of age and older as compared to vaccination with mRNA-1273.

3.3. Uncertainties and limitations about favourable effects

No clinical results have been provided for the sought indication of a 2-dose series with Spikevax bivalent Original/Omicron BA.4-5 (mRNA-1273.222) in young children.

The results are based on a very small sample size and on an early unplanned data cut-off.

Immunogenicity results against BA.1 are less pronounced in baseline serostatus subgroups than in the overall population. Immunogenicity induced against the ancestral strain did not meet the pre-specified criteria if baseline serostatus is taken into account.

3.4. Unfavourable effects

Data from study P306, showed that in young children 6 months to <6 years of age, after receipt of 25 µg mRNA- 1273.214 (bivalent Original/Omicron BA.1) vaccine, solicited ARs were reported from 57.0% participants after the first dose and from 63.1% participants after dose 2. The most reported local solicited ARs were pain, axillary (or groin) swelling or tenderness, and erythema. The most reported systemic solicited ARs were irritability/crying, sleepiness, and fatigue. The TTO was 1-2 days after each dose and the median duration 1-2 days for both doses, with no solicited ARs that persisted beyond 7 days.

The frequencies of the solicited adverse reactions where lower after administration of Spikevax bivalent Original/Omicron BA.1, as primary series vaccination compared to the Spikevax Original group in the age group 6 months to 5 years of age. The same applied on regarding the unsolicited adverse events across the two vaccines groups. Therefore, based on the extrapolation of the safety data, it is awaited the same regarding the Spikevax bivalent Original/Omicron BA.4-5 when administered as primary series doses in children aged 6 months to 5 years of age.

There is a very large safety database for Spikevax Original based on post-marketing data base, showing an acceptable safety profile.

No changes were observed in the reports received after vaccination with either of the Spikevax bivalent vaccines compared to Spikevax original.

3.5. Uncertainties and limitations about unfavourable effects

The assumption of acceptable reactogenicity and safety data are based on extrapolation from Spikevax Original, as well as bivalent variant vaccines. While there may be minor differences in reactogenicity, there are presently limited data with the Original/BA.4-5 vaccine, only used as a booster.

Information received on the Spikevax bivalent vaccines is limited given the much lower number of individuals who have received the bivalent vaccines when compared to the original Spikevax.

3.6. Effects Table

Table 25: Effects Table for Spikevax vaccine (data cut-off: 5 Dec 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
		P306 Overall	**P306 PPIS-Neg**	**P306 PPIS-Pos**	
GMC against Omicron **BA.1** Day 57	nAb GMC	1890 (95% CI: 1520, 2349)	**1038** (95% CI: 754, 1428)	2885 (95% CI: 2029, 4101)	Very few evaluable participants (baseline seronegative participants n=24)
GMC against **ancestral** SARS-CoV-2 Day 57	nAb GMC	1433 (95% CI: 1173, 1750)	**613** (95% CI: 449, 836)	2406 (95% CI: 1734, 3338)	Very few evaluable participants (baseline seronegative participants n=25)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
GMR (GMC values against **BA.1**; P306 vs. P204)	Geometric mean ratio	25.4 (95% CI: 20.1, 32.1)	**15.8** (95% CI: 11.4, 21.9)	4.6 (95% CI: 2.6, 8.1)	Superiority in all PPIS Sets
GMR (GMC values against **ancestral** SARS-CoV-2; P306 vs. P204)	Geometric mean ratio	0.83 (95% CI: 0.67, 1.02)	**0.39** (95% CI: 0.29, 0.54)	0.29 (95% CI: 0.18, 0.46)	Borderline (overall) or no (seronegative and seropositive separately) non-inferiority against ancestral SARS-CoV-2
Unfavourable Effects					
		mRNA- **1273.214**-(Bivalent Original/BA.1) 25 µg Primary Series (Study **P306** Part 1)	mRNA-1273-**P306** (2-dose series) mRNA-**1273.214**(Bivalent Original/BA.1)		mRNA-1273-**P204 mRNA-1273**(Spikevax Original)
Age groups		**6months - < 6 years of age**	**6m to < 2yo**	**2 to 5 yo**	**6m to <2 yo** / **2 to 5 yo**
Any solicited ARs		**Dose 1**: 102/179 (57.0%) / **Dose 2**: 89/141 (63.1)	**D1**: 72.9 % / **D2**: 55.6 %	**D1**: 51.1% / **D2**: 65.7%	**D1**: 84.1% / **D2**: 83.3 % / **D1**: 78.9% / **D2**: 84.3%
Grade 3 or above		3/179 (1.7%) / 4/141 (2.8%)	2.1% / 0	1.5% / 3.8%	3.1% / 4.3% / 3.1% / 5.7%
Any solicited local ARs		67/179 (37.4%) / 64/141 (45.4%)	37.5 % / 36. 1%	37.4 % / 48.6 %	44.4 % / 54. 4% / 63.4% / 73.4%
Grade 3 or above		1/179 (0.6%) / 0	2.1% / 0	0 / 0	0.5% / 1.4 % / 0.8% / 1.2%
Any solicited systemic ARs		80/179 (44.7%) / 69/141 (48.9%)	68.8 % / 52.8 %	35.9% / 47.6%	76.4 % / 73. 6% / 54.0 % / 61.7%
Grade 3 or above		2/179 (1.1%) / 4/141 (2.8%)	0 / 0	1.5% / 3.8%	2.6% / 2.9% / 2.3% / 4.6%
Any unsolicited ARs		55/179 (30.7 %)	39.6%	27.5%	49.3% / 40.0%
SAEs		1/179 (0.6%)			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

While protection against severe COVID-19 disease remains high, the efficacy against any clinical disease of Spikevax Original is obviously lower against Omicron strains, compared to what was seen against the original strain (wuhan).

It has been demonstrated that boosting with a bivalent original/BA.1 vaccine with the same total amount of mRNA, yields higher immunogenicity versus BA.1. The CHMP is of the opinion that the same would be the case for the Original/BA.4-5 vaccine versus BA.4-5.

Based on established principles of immunology, the CHMP considers that a vaccine more closely matching what is presently circulating would optimise immunogenicity against that variant. It is also considered by the Committee that the responses obtained against the ancestral virus are of limited clinical meaning as the ancestral strain does not further circulate but has been succeeded by other SARS-CoV-2 variants.

Regarding safety, there is a very large safety database for Spikevax Original, showing an acceptable safety profile.

The approval of this vaccine is deemed helpful to cater to the public health needs related to ongoing vaccination campaigns, given the present epidemiological situation. Although the current BA.5 wave is declining in Europe, it cannot be predicted what variant will constitute the next wave. It is therefore considered by the CHMP beneficial to have different variant vaccines available that can be used in the vaccination campaigns with a posology aligned with epidemiological data.

This is considered acceptable by the CHMP based on the established principles of immunology and the large amount of safety data available for Spikevax vaccine variants.

3.7.2. Balance of benefits and risks

Given the evolution of SARS-CoV-2, the CHMP is of the view that the benefits of an approval of this grouped extension of indication application outweighs the uncertainties related to extrapolations on immunogenicity and reactogenicity.

3.8. Conclusions

The overall B/R of Spikevax Bivalent (Original/Omicron BA.4/5) as a primary 2-dose series in children 6 months to 4 years of age is considered positive.

The overall B/R of Spikevax Bivalent (Original/Omicron BA.4/5) as a single dose regardless of prior vaccination history, in individuals 5 years of age and older is considered positive.

4. 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.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Grouped variation:

C.I.6.a: Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection in children 6 months through 4 years of age, based on data from study mRNA-1273-P306 (NCT05436834) part 1; this is an Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 (Original/Omicron BA.1) vaccine for SARS-CoV-2 in participants aged 6 months to < 6 years; as a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has been approved.

C.I.6.a: Extension of indication to include the use of Spikevax bivalent Original/Omicron BA.4-5 (all presentations) as a single-dose in individuals 5 years of age and older, irrespective of their vaccination history, based on epidemiology and clinical data from study mRNA-1273-P306; as a consequence, section 4.2 of the SmPC is updated. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes throughout the SmPC, Annex II, labelling and package leaflet.

Amendments to the marketing authorisation

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

5. 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-0104-G