EMA/87565/2025
Committee for Medicinal Products for Human Use (CHMP)

# Type II variation assessment report

Invented name: Spikevax

Procedure No. EMEA/H/C/005791/II/0149

Common name: COVID-19 mRNA vaccine

## Note

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

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| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 09 Dec 2024 | 09 Dec 2024 |
| ☐ | CHMP Rapporteur Assessment Report | 13 Jan 2025 | 03 Feb 2025 |
| ☐ | CHMP members comments | 27 Jan 2025 | N/A |
| ☐ | Updated CHMP Rapporteur Assessment Report | 30 Jan 2025 | N/A |
| ☐ | Start of written procedure | 04 Feb 2025 | 04 Feb 2025 |
| ☒ | Opinion | 06 Feb 2025 | 06 Feb 2025 |

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain S.L. submitted to the European Medicines Agency on 22 November 2024 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.13 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | Type II | None |

Submission of the final report from study mRNA-1273-P204 listed as a category 3 study in the RMP. This is interventional Phase 2/3, 3-part, dose-escalation, open-label, age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in children 6 months through 11 years of age.

The requested variation proposed no amendments to the Product Information.

# 2. Overall conclusion and impact on the benefit/risk balance

Within this type II variation, the MAH submitted the final study clinical study report for study mRNA-1273-P204. Immunogenicity results from this study laid the basis for the approval of Spikevax (mRNA-1273) as a primary series and as a booster dose in children and adolescents 6 months to 11 years of age

The co-primary endpoint for P204 was planned to determine the proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection; if an accepted serum antibody threshold of vaccine protection against COVID-19 was available, this analysis would have formed the basis to infer efficacy. As a threshold of protection was not available, efficacy was inferred by establishing non-inferiority for each age group (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years in Study P204) compared with 18- to 25-year old participants (Study P301) by both geometric mean (GM) value of serum antibody levels and seroresponse rates (SRR).

Effectiveness of mRNA-1273 as a primary series in children aged 6 to 11 years was successfully inferred by bridging neutralising antibodies (nAb) responses based on GMR and SRR results observed in study P204 Part 2 to those observed in young adults in the pivotal P301 clinical efficacy study.

The non-inferiority endpoints of a primary series to infer effectiveness were met for both GMR and SRR for the 2 to 5 years age group as compared to the 18 to 25 years age group from P301.

Effectiveness of a primary series of mRNA-1273 against COVID-19 in children at ages 6 to 23 months was successfully inferred by bridging nAb responses (GMR and SRR) observed in study P204 to those observed in young adults in the pivotal P301 clinical efficacy study.

Long-term immunogenicity analysis was performed to assess the persistence of immune response after Dose 2 of mRNA-1273 through Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) in each age group. Overall, the long-term analyses of nAbs show persistence of immune response against SARS-CoV-2 D614G (ancestral strain) through 12 months after vaccination. Measurable nAb responses persisted through 12 months (Day 394) after Dose 2 of mRNA-1273 and remained elevated compared with pre-dose Day 1 values in all age groups. Persistence of nAb levels against ancestral SARS-CoV-2 was accompanied with the emergence of

SARS-CoV-2 variants leading to breakthrough infections. Expectedly, participants who had an intercurrent SARS-CoV-2 infection had higher nAb levels than participants without intercurrent infection.

In the analysis of mRNA-1273 booster dose (BD), results from pre-booster SARS-CoV-2 negative participants in the age groups 6 to 11 years and 6 months to 5 years, respectively, met the non-inferiority criteria compared to results from the P301 young adult Primary Series.

Subsequently, given the increasing seroprevalence in the general population, dosing for Spikevax variant vaccines were simplified and a single 25 µg dose is currently recommended for children 5 years through 11 years of age regardless of prior vaccination status. Given the lower seroprevalence in younger children, a 25 µg 2-dose primary series is recommended for previously unvaccinated children 6 months through 4 years of age while those who are previously vaccinated or have a known history of SARS-CoV-2 infection, are recommended to receive a single 25 µg dose of the current variant-adapted formulation.

The spectrum of safety data generated during this study is as known. No new safety issues were observed and no cases of myocarditis/pericarditis is recorded.

The requested variation proposed no amendments to the Product Information.

The benefit-risk balance of Spikevax, remains positive.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.13 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | Type II | None |

Submission of the final report from study mRNA-1273-P204 listed as a category 3 study in the RMP; this is interventional Phase 2/3, 3-part, dose-escalation, open-label, age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of Spikevax (mRNA-1273) in children 6 months through 11 years of age.

☒is recommended for approval.

### *Amendments to the marketing authorisation*

The variation leads to no amendments to the terms of the Community Marketing Authorisation.

# 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

### *Scope*

Please refer to the Recommendations section above

## *Summary*

Please refer to Scientific Discussion ‘Spikevax-H-C-005791-II-0149’.

# Annex: Rapporteur’s assessment comments on the type II variation

# 1. Introduction

**Background and overview of clinical efficacy**

This Summary of Clinical Efficacy describes the immunogenicity and efficacy data from Study mRNA 1273-P204, hereafter referred to as Study P204, to fulfil commitments related to this clinical study.

**Overview of the Design of Study P204**

Study P204 was a Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, immunogenicity (to infer effectiveness), and efficacy of mRNA-1273 in healthy participants 6 months through 11 years of age.

The study included participants who had no known history of SARS-CoV-2 infection within 2 weeks prior to administration of the study vaccine or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of the study vaccine.

The study consisted of 3 parts (1, 2, and 3). The study population, study design, dose schedule, number of participants exposed, and key objectives for each part are provided in Table 1.

The study began by dosing participants 6 years through 11 years of age in the open-label, dose-selection part (Part 1) before advancing to Part 2. The mRNA-1273 doses were selected based on the following dose levels tested in Part 1: 50 µg and 100 µg in the 6 years through 11 years age group; 25 µg and 50 µg in the 2 years through 5 years age group; and 25 µg in the 6 months through 23 months age group. It should be noted that data from participants in Part 1 were not used to infer efficacy. The dose levels evaluated in Part 2 were based on a review of safety, reactogenicity, and immunogenicity data from Part 1 suggesting that nAb responses with these doses could meet prespecified noninferiority criteria for immuno-bridging to Study mRNA-1273-P301 (hereafter, referred to as "Study P301"). The selected doses demonstrated an acceptable reactogenicity and safety profile, guided by recommendations from an internal safety review team.

The aim of Part 2 of the study was to support an indication for use of the selected age-appropriate doses of mRNA-1273 (50 µg, 6 years through 11 years age group or 25 µg, 2 years through 5 years and 6 months through 23 months age groups) given as 2 IM injections, 28 days apart. The basis for inferring vaccine effectiveness was serum antibody responses in the study participants. Effectiveness of a 2-dose primary series was inferred by establishing noninferiority of the immune response (as assessed by nAbs) 28 days after Dose 2 for each of the 3 age groups in Study P204 compared with that of young adult participants (18 years through 25 years of age) in Study P301, where efficacy was demonstrated.

Blinded follow-up for each age group continued until all participants in their respective age groups became eligible for unblinding and crossover vaccination based on the availability of any COVID-19 vaccine under EUA in the US. Participants in all 3 age groups were offered an optional BD once they entered the Open-label Phase of follow-up, initially with mRNA-1273 and later with a variant-containing formulation (mRNA-1273.214).

Part 3 (open label) was added to the study protocol with Amendment 6 in January 2022 to evaluate an alternate primary series dosing regimen in children 6 years through 11 years of age (2 doses of mRNA 1273 25 µg on Days 1 and 29 followed by a third dose of mRNA-1273 25 µg at least 3 months and up to 5 months after Dose 2). However, the planned enrolment in Part 3 was not completed due to authorization of the 50 µg dose in this age group.

*Table 1: Description of Study P204*

| Study Number<br>Phase<br>Country<br>Study Status | Study Population | Study Part<br>Active Treatment (Sponsor Vaccine) | Study Population and Study Design | Dose, Schedule, and Number of Participants Exposed[a] | Key[b] Efficacy and/or Immunogenicity Objectives and Endpoints | CSR EOS Database Lock Dates |
|---|---|---|---|---|---|---|
| mRNA-1273-P204<br>2/3<br>US and Canada<br>Completed | Healthy children (6 months through 11 years of age) | Parts 1 and 2<br>Primary Series mRNA-1273[c] | OL dose-finding (dose-escalation, age de-escalation) phase (Part 1) and randomized, placebo-controlled, observer-blind phase (Part 2). Part 1 began with dosing of the oldest age group and age de-escalation.<br>Part 2 enrollment began after the dose was selected for each age group, with a 3:1 ratio of mRNA-1273 to placebo. The selected primary series doses were:<br>• 6 years through 11 years: 50 µg<br>• 2 years through 5 years: 25 µg<br>• 6 months through 23 months: 25 µg | **Part 1 Primary Series (2 doses, 28 days apart)**<br>**6 years through 11 years**<br>mRNA-1273 50 or 100 µg<br>50 µg (N=380); 100 µg (N=371)<br>**2 years through 5 years**<br>mRNA-1273 25 or 50 µg<br>25 µg (N=69); 50 µg (N=155)<br>**6 months through 23 months**<br>mRNA-1273 25 µg (only dose level administered; N=150)<br>**Part 2 Primary Series (2 doses, 28 days apart)**<br>**6 years through 11 years**<br>mRNA-1273 50 µg (selected dose level from Part 1) or placebo<br>50 µg (N=3007); placebo (N=995)<br>*After study unblinding:*<br>placebo-mRNA-1273 crossover (N=701)<br>**2 years through 5 years**<br>mRNA-1273 25 µg (selected dose level from Part 1) or placebo<br>25 µg (N=3031); placebo (N=1007)<br>*After study unblinding:*<br>placebo-mRNA-1273 crossover (N=640)<br>**6 months through 23 months**<br>mRNA-1273 25 µg (selected dose level from Part 1) or placebo<br>25 µg (N=1994); placebo (N=666)<br>*After study unblinding:*<br>placebo-mRNA-1273 crossover (N=444) | Primary:<br>To infer the efficacy (effectiveness)[d] of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups.<br>• The GM value of serum antibody level and SRR[e] from Study P204 participants at Day 57 compared with those from young adult participants (18 years through 25 years of age) (Day 57) in Study P301.<br>Secondary:<br>To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg).<br>• The GM values of SARS-CoV-2 S-protein-specific bAb and SARS-CoV-2-specific nAb on Days 1, 57 (1 month after Dose 2), 209 (6 months after Dose 2), and 394 (1 year after Dose 2).<br>To evaluate the incidence of SARS-CoV-2 infection[f] after vaccination with mRNA-1273 or placebo.<br>• The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR) postbaseline.<br>To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo.<br>• The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) post baseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms.<br>To evaluate the incidence of COVID-19[g] after vaccination with mRNA-1273 or placebo.<br>• The incidence of the first occurrence of COVID-19 | **Part 2**<br>Final CSR for primary series in the 6 years through 11 years age group (17 May 2024 EOS database lock)<br>Final CSR for primary series in the 2 years through 5 years age group (17 May 2024 EOS database lock)<br>Final CSR for primary series in the 6 months through 23 months age group (17 May 2024 EOS database lock)<br>**Part 1** data were used for assessment of long-term immunogenicity. |

| Study Number<br>Phase<br>Country<br>Study Status | Study Population | Study Part<br>Active Treatment (Sponsor Vaccine) | Study Population and Study Design | Dose, Schedule, and Number of Participants Exposed[a] | Key[b] Efficacy and/or Immunogenicity Objectives and Endpoints | CSR EOS Database Lock Dates |
|---|---|---|---|---|---|---|
| | | | | | postbaseline, where COVID-19 was defined as symptomatic disease based on CDC case definition[h]. | |
| | | Booster Phase<br>mRNA-1273[c]/ mRNA-1273.214[i] | OL optional BDs offered to all participants who had completed primary series in Part 1 or Part 2.<br>mRNA-1273 BD offered to Part 1 and Part 2 participants of 6 years through 11 years age group and Part 1 participants 6 months through 5 years of age.<br>mRNA-1273.214 BD offered to all unboosted participants including Part 2 participants 6 months through 5 years of age. | **6 years through 11 years**<br>mRNA-1273 25 µg BD (N=2519)[j]<br>mRNA-1273.214 25 µg BD (N=184)[k]<br>**6 months through 5 years**<br>mRNA-1273-BD (N=301)[l]<br>mRNA-1273.214 10 µg BD (N=2766)[m] | Primary:<br>To infer effectiveness of the mRNA-1273 booster by establishing noninferiority of antibody response after the BD in participants in Study P204 compared with post-primary series in young adult recipients (18 years through 25 years of age) in Study P301.<br>• GM value and SRR[e] of post-booster antibody from baseline in Study P204 participants compared with post-primary series (post-Dose 2) in Study P301 young adult participants (18 years through 25 years of age).<br>Secondary:<br>To evaluate the persistence of the immune response to the BD with mRNA-1273 vaccine.<br>• The GM values of SARS-CoV-2 | Final CSR for the BD in the 6 years through 11 years age group (17 May 2024 EOS database lock).<br>Final CSR for the BD in the 6 months through 5 years age group (17 May 2024 EOS database lock) (includes immunogenicity for a small number of participants [N=76] who received the mRNA-1273 BD). |

| Study Number<br>Phase<br>Country<br>Study Status | Study Population | Study Part<br>Active Treatment (Sponsor Vaccine) | Study Population and Study Design | Dose, Schedule, and Number of Participants Exposed[a] | Key[b] Efficacy and/or Immunogenicity Objectives and Endpoints | CSR EOS Database Lock Dates |
|---|---|---|---|---|---|---|
| | | | | | S-protein-specific bAb and nAb on BD-Day 1 (at least 6 months after Dose 2 in the primary series), BD-Day 29 (1 month after the BD), BD-Day 181 (6 months after the BD), and BD-Day 366 (1 year after the BD).<br>Immune persistence was not assessed in participants 6 months through 5 years of age who received the mRNA-1273.214 BD. | |
| | | Part 3<br>mRNA-1273[c] | OL alternate dosing assessment for the 6 years through 11 years age group.<br>2 doses of mRNA-1273 25 µg on Days 1 and 29 followed by Dose 3 of mRNA-1273 25 µg at least 3 months and up to 5 months after Dose 2. | Dose 1 of mRNA-1273 25 µg (N=90)<br>Dose 2 of mRNA-1273 25 µg (N=84)<br>Dose 3 of mRNA-1273 25 µg (N=70) | Primary:<br>To infer effectiveness of mRNA-1273 (25 µg, administered as 2 doses, 28 days apart) based on immunogenicity.<br>• The GM value of serum antibody level and SRR[e] from Study P204 vaccine recipients at Day 57 compared with those from adult (18 years through 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy study (Study P301).<br>To infer effectiveness of mRNA-1273 Dose 3 by establishing | Final CSR for mRNA-1273-P204 Part 3 analysis in the 6 years through 11 years age group (17 May 2024 EOS database lock). |

| Study Number<br>Phase<br>Country<br>Study Status | Study Population | Study Part<br>Active Treatment (Sponsor Vaccine) | Study Population and Study Design | Dose, Schedule, and Number of Participants Exposed[a] | Key[b] Efficacy and/or Immunogenicity Objectives and Endpoints | CSR EOS Database Lock Dates |
|---|---|---|---|---|---|---|
| | | | | | noninferiority of antibody response after Dose 3 in Study P204 participants compared with post-primary series of mRNA-1273 in young adult participants (18 years through 25 years of age) in Study P301.<br>• The GM value and SRR[e] of post-third dose antibody in Study P204 compared with post-primary series (post-Dose 2) from adults (18 years through 25 years of age) in Study P301.<br>Secondary:<br>To evaluate the persistence of the immune response to mRNA-1273 vaccine.<br>• The GM values of SARS-CoV-2 S protein-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), Day 394 (1 year after Dose 2), BD-Day 1 (at least 3 months or 6 months after Dose 2), BD-Day 29 (1 month after third dose), BD-Day 181 (6 months after third dose), and BD-Day 366 (1 year after third dose).<br>• The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), Day 394 (1 year after Dose 2), BD-Day 1 (at least 3 months or 6 months after Dose 2), BD-Day 29 (1 month after third dose), BD-Day 181 (6 months after third dose), and BD-Day 366 (1 year after third dose). | |

Abbreviations: bAb = binding antibody; BD =booster dose; CDC = US Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; CSR = clinical study report; EOS = end of the study; GM = geometric mean; LLOQ = lower limit of quantification; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; OL = open label; RT-PCR = reverse transcription polymerase chain reaction; S-2P = spike protein modified with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; US = United States.

a. Participants who received at least 1 dose of the study vaccine (placebo group participants in the mRNA-1273-P204 Primary Series who received mRNA-1273 after study unblinding are not included, as data from these participants were not used for immunogenicity assessments).

b. Key immunogenicity/efficacy objectives refer to the primary and secondary immunogenicity/efficacy objectives presented in the table.

c. mRNA-1273 contains a single mRNA (CX-024414) that encodes S-2P of the Wuhan Hu 1 isolate of SARS-CoV-2.

d. Vaccine effectiveness was inferred by establishing noninferiority for each age group (6 years through 11 years, 2 years through 5 years, and 6 months through 23 months in Study P204) compared with those from young adult participants (18 years through 25 years of age) in Study P301 by both GM value of serum antibody levels and SRR.

e. Seroresponse was defined as an antibody change from baseline (pre-Dose 1) below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if baseline was ≥LLOQ.

f. SARS-CoV-2 infection was defined in participants with negative SARS-CoV-2 at baseline based on bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1, that became positive (as measured by Roche Elecsys) postbaseline or positive RT-PCR postbaseline.

g. COVID-19 was defined as clinical symptoms consistent with COVID-19 and positive RT-PCR for SARS-CoV-2.

h. 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 rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea or vomiting, poor appetite or poor feeding, and a positive test for SARS-CoV-2 by RT-PCR.

i. mRNA-1273.214 contains 2 mRNAs: CX-024414 that encodes S-2P of the Wuhan Hu 1 isolate of SARS-CoV-2 and CX-031302 that encodes S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529 subvariant BA.1).

j. Includes Part 1 and Part 2 participants 6 years through 11 years of age (N=2519) who received the mRNA-1273 50 µg primary series followed by the mRNA-1273 25 µg BD. In addition, there were 247 participants from Part 1 of the study who had received the mRNA-1273 100 µg primary series followed by the mRNA-1273 25 µg BD; data for these participants are presented in tabulated summaries and listings appended in the CSR (Study P204 Final CSR Booster Dose [6 years to 11 years], Appendix 16.5).

k. Includes Part 1 and Part 2 participants 6 years through 11 years of age (N=184) who received the mRNA-1273 primary series followed by the mRNA-1273.214 BD. Of these, 184 participants, 181 participants received the 25 µg BD of mRNA-1273.214, and 3 participants received the 10 µg BD of mRNA-1273.214 instead of the 25 µg BD in error. Together, these 184 participants were assessed as part of the mRNA-1273.214 25 µg BD analysis in Study P204 participants 6 years through 11 years of age

l. Includes Part 1 (N=259) and Part 2 (N=42) participants 6 months through 5 years of age who received the mRNA-1273 BD. Of the 259 Part 1 participants, 212 received the 10 µg BD of mRNA-1273 and 47 received the 25 µg BD of mRNA-1273, while all 42 Part 2 participants received the 25 µg BD of mRNA-1273. Data for these 301 participants are presented in tabulated summaries and listings appended in the CSR (Study P204 Final CSR Booster Dose [6 months to 5 years], Table 14.1.1.2.1.1, Table 14.1.1.2.1.2, and Appendix 16.5).

m. Includes Part 2 participants 6 months through 5 years of age (N=2766) who received the mRNA-1273 25 µg primary series followed by the mRNA-1273.214 BD. Of these, 2766 participants, 2760 participants received the 10 µg BD of mRNA-1273.214, and 6 participants received a 5 µg BD of mRNA-1273.214 instead of the 10 µg BD in error. Together, these 2766 participants were assessed as part of the mRNA-1273.214 10 µg BD analysis in Study P204 Part 2 participants 6 months through 5 years of age. In addition to these 2766 BD participants, there were 5 Part 1 participants who received the mRNA-1273.214 10 µg BD and 28 Part 2 participants who received a 25 µg BD of mRNA-1273.214 instead of the 10 µg BD; data for these 33 participants are presented in tabulated summaries and listings appended in the CSR (Study P204 Final CSR Booster Dose [6 months to 5 years], Appendix 16.5).

# 2. Clinical Efficacy aspects

## *2.1. Methods – analysis of data submitted*

### Efficacy Endpoints

Key (primary and secondary) immunogenicity and/or efficacy objectives in the study are listed in Table 1. In this document, immunogenicity and/or efficacy results for the following study parts are presented.

- Immunogenicity (including vaccine effectiveness) and efficacy data for Part 2 participants 6 months through 11 years of age who received the mRNA-1273 2-dose primary series.
- Immunogenicity (including vaccine effectiveness) data for Part 1 and Part 2 participants 6 months through 11 years of age who received the mRNA-1273 25 µg BD.
- Immunogenicity data for Part 3 participants 6 years through 11 years of age who received the mRNA 1273 25 µg 2-dose primary series followed by Dose 3 of mRNA-1273 25 µg. Data were summarised using descriptive statistics only.

Data for the primary series stage from participants in Part 1 were not used to infer efficacy. The safety, reactogenicity, and immunogenicity data from Part 1 were reviewed for dose selection in Part 2. Results for Part 1 are presented in the individual CSRs.

Vaccine effectiveness was inferred based on immunogenicity (serum nAb responses at prespecified timepoint after dosing with the primary series or booster), and the coprimary endpoints were based on GM value of serum nAb levels and SRR. The immune response as measured by GM value and SRR in each age group based on Day 57 antibody levels was compared with that in young adult participants (18 years through 25 years of age) using data from Study P301. Seroresponse at a participant level was defined as a change from baseline (pre-Dose 1) below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold rise if baseline was equal to or above the LLOQ. Note that, for the Booster Phase, immunogenicity was assessed only for participants who received the mRNA-1273 BD in the 6 years through 11 years age group and in a subgroup of Part 1 participants 6 months through 5 years of age who received the mRNA-1273 BD (N=76).

Immunogenicity analysis was not planned for the participants 6 months through 5 years and 6 years through 11 years of age who received the mRNA-1273.214 BD.

Vaccine efficacy, based on incidence rates of COVID-19 and SARS-CoV-2 infection, was assessed as a secondary endpoint in Part 2 (Primary Series), results of which are summarised in this document. For the Booster Phase, incidence rates of COVID-19 and SARS-CoV-2 infection were assessed, albeit as exploratory endpoints; results are presented in Study P204 Final CSR Booster Dose (6 years to 11 years).

**PRIMARY ENDPOINTS**

**mRNA-1273 Primary Series (Part 2, 6 Months Through 11 Years)**

The coprimary endpoints to infer effectiveness of mRNA-1273 based on immunogenicity were the GM value of serum nAb levels and the SRR. For each age group, the following coprimary endpoints were evaluated.

- For GMR, noninferiority of nAb response against D614G using a margin of 1.5 (ie, a lower bound of the 95% CI >0.667), and a point estimate of GMR ≥0.8.
- For SRR difference, noninferiority of nAb seroresponse against D614G using a margin of 10% (ie, a lower bound of the 95% CI >-10%), and a point estimate of SRR difference ≥-5%.

Analyses of immunogenicity were performed for each age group separately at the selected dose level.

The primary analysis population for immunogenicity was the PPIS, which included all participants in the Immunogenicity Subset who also received the planned doses of the study vaccine per schedule, complied with the immunogenicity testing schedule, had no major protocol deviations that impacted key or critical data, were not receiving HAART if diagnosed with HIV, had baseline and Day 57 antibody assessments for the analysis endpoint, and had a negative SARS-CoV-2 status at baseline (pre-Dose 1).

**mRNA-1273 Booster (Parts 1 and 2, 6 Months Through 11 Years)**

Efficacy was inferred based on establishing noninferiority of both GMR and SRR of serum nAb against D614G in Study P204 participants 6 years through 11 years of age at BD-Day 29 (28 days after the BD) compared with post-primary series (Day 57; 28 days after Dose 2) in Study P301 young adult participants (18 years through 25 years of age). Vaccine effectiveness was also evaluated in a subgroup of Part 1 participants aged 6 months through 5 years who had received the mRNA-1273 BD (N=76). The following coprimary endpoints were evaluated:

- For GMR, noninferiority of nAb response against D614G using a margin of 1.5 (ie, a lower bound of the 95% CI >0.667).
- For SRR, noninferiority of nAb seroresponse against D614G from pre-Dose 1 baseline using a margin of 10% (ie, a lower bound of the 95% CI >-10%).

The primary analysis population for immunogenicity was the PPIS-Pre-booster SARS-CoV-2 Negative (BD Analysis), which included all participants in the PPIS (BD Analysis) who were pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (prebooster). The PPIS (BD Analysis) included all participants in the Immunogenicity Subset (BD Analysis) who received 2 planned doses of the study vaccine in Study P204 Part 1 Open-label Phase or Part 2 Blinded Phase per schedule and received a BD, had a negative SARS-CoV-2 status at baseline (pre Dose 1), had BD-Day 29 antibody assessments for the analysis endpoint, had no major protocol deviations that impacted key or critical data, had not received off-study COVID-19 vaccination prior to the BD-Day 29 Visit, and were not receiving HAART if diagnosed with HIV.

**mRNA-1273 Alternate Primary Series Regimen (Part 3, 6 Years Through 11 Years)**

In Part 3, inference of vaccine effectiveness following the alternate primary series regimen (mRNA-1273 25 µg 2-dose primary series followed by a third dose of mRNA-1273 25 µg) was planned to be assessed in the same way as done for the mRNA-1273 2-dose primary series in Part 2 (ie, based on GM value of serum nAb levels and SRR). The immune response as measured by GM value and SRR in each age group based on Day 57 antibody levels was to be compared with that in young adults (18 years through 25 years of age) using data from Study P301. However, given that the number of participants who received at least 1 dose (N=90) in Part 3 was substantially smaller than the planned sample size of approximately 300 required for the immunogenicity hypothesis testing after Dose 2 and Dose 3 of the alternate primary series regimen, the hypothesis testing was not performed. Instead, all the analyses of immunogenicity endpoints are descriptive. Even though no formal hypothesis testing was performed, the immunogenicity results from the Study P301 were included as a reference.

**SECONDARY ENDPOINTS**

In both Part 2 (Primary Series [all age groups] and Booster Phase [mRNA-1273 BD, 6 years through 11 years age group]) and Part 3, long-term immunogenicity analysis was performed to assess the persistence of immune response at approximately 6 months and 1 year after dosing.

For Part 2 (Primary Series), secondary objectives were to assess incidence rates of COVID-19, SARS-CoV-2 infection regardless of symptoms, and asymptomatic SARS-Cov-2 infection, compared between mRNA-1273 and placebo groups. Incidence rates were calculated as the number of cases divided by the total person-time. The vaccine efficacy in the Blinded Phase was defined as 1 – ratio of incidence rate (mRNA 1273 versus placebo). The number and percentage of participants who had an event were summarised in the PP Set for Efficacy and the mITT1 Set for the long-term analysis. COVID-19 cases were assessed using the CDC case definition. A second case definition was also used based on the Study P301 case definition.

## *2.2. Results*

**SUMMARY OF RESULTS OF INDIVIDUAL STUDIES**

This section presents key (primary and secondary) immunogenicity and efficacy data from Study P204 Part 2 (including Booster Phase) and Part 3. Results for exploratory immunogenicity and/or efficacy analyses are presented in the individual CSRs.

Data from Part 2 Primary Series and Part 1 and Part 2 Booster Phase summarised here support inference of effectiveness of mRNA-1273 against COVID-19 administered as a 2-dose primary series and/or a BD in participants 6 months through 11 years of age through immuno-bridging to the prespecified comparator groups. Direct vaccine efficacy was also observed for each age group, assessed as a secondary endpoint, further supporting the inferred vaccine effectiveness. The immunogenicity of a BD of mRNA-1273 in participants 6 years through 11 years of age and in a subgroup of Part 1 participants aged 6 months through 5 years (administered at least 6 months after the primary series) suggests enhanced protection against COVID-19 compared with the mRNA-1273 2-dose primary series alone.

**mRNA-1273 Primary Series (Study P204 Part 2, 6 Months Through 11 Years)**

The ensuing subsections present an overview of the immunogenicity and efficacy results for the mRNA-1273 2-dose primary series in Part 2 participants 6 months through 11 years of age. The results are presented in the following order of sections.

- Primary immunogenicity analysis demonstrating noninferiority of the immune response elicited by the mRNA-1273 2-dose primary series administered during the Blinded Phase in Study P204 Part 2 participants 6 months through 11 years of age compared with that observed in Study P301 young adult participants 18 years through 25 years of age.
- Vaccine efficacy analysis (secondary endpoint) showing lower COVID-19 incidence rates in participants who received the mRNA-1273 2-dose primary series than in participants who received placebo.
- Long-term immunogenicity analyses demonstrating immune persistence up to 12 months after Dose 2 of mRNA-1273.

The primary analysis population for immunogenicity was the PPIS.

Results are presented separately for each age group (6 years through 11 years, 2 years through 5 years, and 6 months through 23 months).

**CO-PRIMARY ENDPOINTS: IMMUNOGENICITY ANALYSIS TO INFER VACCINE EFFECTIVENESS**

The coprimary endpoints to infer effectiveness of the mRNA-1273 2-dose primary series based on immunogenicity were the GM value of serum nAb levels and the SRR.

***Assessor's comment:***

The co-primary endpoint for P204 was planned to determine the proportion of participants with a serum antibody level at Day 57 ≥antibody threshold of protection; if an accepted serum antibody threshold of vaccine protection against COVID-19 was available, this analysis would have formed the basis to infer efficacy. As a threshold of protection was not available, efficacy was inferred by establishing non-inferiority for each age group (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years in Study P204) compared with 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and SRR.

**6 Years Through 11 Years Age Group**

The GMR of Study P204 Part 2 participants 6 years through 11 years of age to Study P301 young adult participants 18 years through 25 years of age for Day 57 nAb levels against D614G was 1.224 (95% CI: 1.061, 1.413). Seroresponse after the primary series at Day 57 was achieved by nearly all participants (99.0% [95% CI: 97.2%, 99.8%]). The difference in SRR (relative to pre-Dose 1) was –0.3% (95% CI:  2.2%, 1.6%) (Study P204 Final CSR Primary Series [6 years to 11 years], Table 21). Thus, the noninferiority criteria for GMR (lower bound of the CI >0.667 and point estimator ≥0.8) and SRR difference (lower bound of the CI >-10% and point estimator ≥-5.0) were met.

***Assessor's comment:***

Compare Table 20 P204 CSR: Summary of Pseudovirus Neutralizing Antibody $ID_{50}$ and $ID_{80}$ Titres for the 6 to 11 Years Age Group (Per-Protocol Immunogenicity Subset)

| Timepoint<br>Data Category<br>Statistic | Part 2<br>P204 mRNA-1273 50 µg<br>(N=311) | <br>P301 mRNA-1273 100 µg<br>(N=296) |
|---|---|---|
| **Antibody: Pseudovirus Neutralizing Antibody $ID_{50}$ Titers (LLOQ: 18.5, ULOQ: 45118)** | | |
| Baseline (Day 1) | | |
| n[a] | 308 | 296 |
| GMT | 9.3 | 9.3 |
| 95% CI[b] | (NE, NE) | (9.2, 9.4) |
| Median | 9.250 | 9.250 |
| Min, Max | 9.25, 9.25 | 9.25, 28.50 |
| Number of participants <LLOQ, n (%)[c] | 308 (100) | 295 (99.7) |
| Number of participants ≥LLOQ, n (%)[c] | 0 | 1 (0.3) |
| Day 29 | | |
| n[a] | 93 | 294 |
| GMT | 108.9 | 97.4 |
| 95% CI[b] | (93.3, 126.9) | (87.4, 108.6) |
| Median | 113.512 | 99.306 |
| Min, Max | 9.25, 748.13 | 9.25, 2544.76 |
| N1 | 92 | 294 |
| GM Fold Rise | 11.7 | 10.5 |
| 95% CI[b] | (10.0, 13.7) | (9.4, 11.7) |
| Seroresponse[d] | | |
| n (%)[e] | 63 (68.5) | 196 (66.7) |
| 95% CI[f] | (58.0, 77.8) | (61.0, 72.0) |
| In participants <LLOQ at Baseline, n/N2 (%)[g] | 63/92 (68.5) | 195/293 (66.6) |
| In participants ≥LLOQ at Baseline, n/N3 (%)[h] | 0/0 | 1/1 (100) |
| ≥4-fold increase from Baseline[i] | | |
| n (%)[e] | 63 (68.5) | 196 (66.7) |
| 95% CI[f] | (58.0, 77.8) | (61.0, 72.0) |

| Timepoint<br>Data Category<br>Statistic | Part 2<br>P204 mRNA-1273 50 µg (N=311) | <br>P301 mRNA-1273 100 µg (N=296) |
|---|---|---|
| Day 57 | | |
| n[a] | 309 | 294 |
| GMT | 1618.3 | 1321.9 |
| 95% CI[b] | (1460.0, 1793.9) | (1196.5, 1460.5) |
| Median | 1644.083 | 1213.391 |
| Min, Max | 9.25, 26280.05 | 9.25, 31206.69 |
| N1 | 307 | 294 |
| GM Fold Rise | 174.6 | 142.4 |
| 95% CI[b] | (157.4, 193.7) | (128.9, 157.2) |
| Seroresponse[d] | | |
| n (%)[e] | 304 (99.0) | 292 (99.3) |
| 95% CI[f] | (97.2, 99.8) | (97.6, >99.9) |
| In participants <LLOQ at Baseline, n/N2 (%)[g] | 304/307 (99.0) | 291/293 (99.3) |
| In participants ≥LLOQ at Baseline, n/N3 (%)[h] | 0/0 | 1/1 (100) |
| ≥4-fold increase from Baseline[i] | | |
| n (%)[e] | 304 (99.0) | 292 (99.3) |
| 95% CI[f] | (97.2, 99.8) | (97.6, >99.9) |
| **Antibody: Pseudovirus Neutralizing Antibody ID80 Titers (LLOQ: 14.3, ULOQ: 10232)** | | |
| Baseline (Day 1) | | |
| n[a] | 308 | 296 |
| GMT | 7.2 | 7.2 |
| 95% CI[b] | (NE, NE) | (NE, NE) |
| Median | 7.150 | 7.150 |
| Min, Max | 7.15, 7.15 | 7.15, 7.15 |
| Number of participants <LLOQ, n (%)[c] | 308 (100) | 295 (100) |
| Number of participants ≥LLOQ, n (%)[c] | 0 | 0 |
| Day 29 | | |
| n[a] | 93 | 294 |
| GMT | 31.6 | 30.5 |
| 95% CI[b] | (27.3, 36.5) | (27.6, 33.6) |
| Median | 32.594 | 27.979 |
| Min, Max | 7.15, 98.60 | 7.15, 710.71 |
| N1 | 92 | 294 |
| GM Fold Rise | 4.4 | 4.3 |

| Timepoint<br>Data Category<br>Statistic | Part 2<br>P204 mRNA-1273 50 µg (N=311) | <br>P301 mRNA-1273 100 µg (N=296) |
|---|---|---|
| 95% CI[b] | (3.8, 5.1) | (3.9, 4.7) |
| Seroresponse[d] | | |
| n (%)[e] | 23 (25.0) | 73 (24.8) |
| 95% CI[f] | (16.6, 35.1) | (20.0, 30.2) |
| In participants <LLOQ at Baseline, n/N2 (%)[g] | 23/92 (25.0) | 73/294 (24.8) |
| In participants ≥LLOQ at Baseline, n/N3 (%)[h] | 0/0 | 0/0 |
| ≥4-fold increase from Baseline[i] | | |
| n (%)[e] | 23 (25.0) | 73 (24.8) |
| 95% CI[f] | (16.6, 35.1) | (20.0, 30.2) |
| Day 57 | | |
| n[a] | 309 | 294 |
| GMT | 494.9 | 430.3 |
| 95% CI[b] | (453.2, 540.6) | (393.9, 470.1) |
| Median | 477.788 | 406.037 |
| Min, Max | 7.15, 8313.93 | 7.15, 8023.31 |
| N1 | 307 | 294 |
| GM Fold Rise | 69.1 | 60.2 |
| 95% CI[b] | (63.2, 75.5) | (55.1, 65.8) |
| Seroresponse[d] | | |
| n (%)[e] | 302 (98.4) | 292 (99.3) |
| 95% CI[f] | (96.2, 99.5) | (97.6, >99.9) |
| In participants <LLOQ at Baseline, n/N2 (%)[g] | 302/307 (98.4) | 292/294 (99.3) |
| In participants ≥LLOQ at Baseline, n/N3 (%)[h] | 0/0 | 0/0 |
| ≥4-fold increase from Baseline[i] | | |
| n (%)[e] | 302 (98.4) | 292 (99.3) |
| 95% CI[f] | (96.2, 99.5) | (97.6, >99.9) |

Abbreviations: CI = confidence interval; GM = geometric mean; GMT = geometric mean titer; $ID_{50}$ = 50% inhibitory dose; $ID_{80}$ = 80% inhibitory dose; LLOQ = lower limit of quantification; Max = maximal; Min = minimal; N/n = number of participants; NE = not evaluated; ULOQ = upper limit of quantification.

N1 = number of participants with no missing data at Baseline and the corresponding timepoint. N2 = number of participants with no missing data (<LLOQ) at Baseline and no missing data at the corresponding post-Baseline timepoint. N3 = number of participants with no missing data (≥LLOQ) at Baseline and no missing data at the corresponding post-Baseline timepoint.

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

P301 mRNA-1273 group included young adults (18-25 years of age).

a. Number of participants with no missing data at the timepoint (Baseline or post-Baseline).

b. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GM fold rise, respectively, then back transformed to the original scale for presentation.

c. Percentages were based on n[a].

d. Seroresponse at a participant level was defined as a change from below the LLOQ to equal to or above 4 x LLOQ, or at least a 4-fold rise if Baseline was equal to or above the LLOQ.

e. Number of participants meeting the criterion at the timepoint. Percentages were based on N1.

f. 95% CI was calculated using the Clopper-Pearson method.

g. Number of participants with no missing data (<LLOQ) at Baseline and have seroresponse at the corresponding post-Baseline timepoint. Percentages were based on N2.

h. Number of participants with no missing data (≥LLOQ) at Baseline and have seroresponse at the corresponding post-Baseline timepoint. Percentages were based on N3.

i. ≥z-fold increase from Baseline at participant level was defined as a ≥z × LLOQ for participants with Baseline antibody titer below LLOQ, or a z-times, or higher titer ratio in participants with Baseline antibody titer equal to or above the LLOQ.

Source: Table 14.2.3.1.1.2.

And Table 21 P204 CSR: Immunobridging Analysis: Comparison of Day 57 nAb Levels and Seroresponse Rates (PsVNA ID50) between P204 and P301 (PP Immunogenicity Subsets): ANCOVA Model

| Timepoint<br>Statistic | P204 mRNA-1273<br>(N=311) | P301 mRNA-1273<br>(N=296) |
|---|---|---|
| **Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)** | | |
| Day 57 | | |
| n | 309 | 294 |
| GLSM (P204 vs P301) | 1618.3 | 1321.9 |
| 95% CI | (1464.3, 1788.6) | (1193.1, 1464.6) |
| GMR (P204 vs P301)[a] | 1.224 | |
| 95% CI[a] | (1.061, 1.413) | |
| N1 | 307 | 294 |
| Seroresponse, n (%)[b] | 304 (99.0) | 292 (99.3) |
| 95% CI[c] | (97.2, 99.8) | (97.6, >99.9) |
| Difference (P204 vs P301) (%) | -0.3 | |
| 95% CI[d] | (-2.2, 1.6) | |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; $ID_{50}$ = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares.
N1 = Number of subjects with non-missing data at Baseline and the corresponding post-Baseline timepoint.
a. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if Baseline is equal to or above the LLOQ. Percentages are based on N1.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: Table 14.2.1.1.3.1.2 and Table 14.2.1.2.3.1.2.

Effectiveness of mRNA-1273 in children aged 6 to 11 years was successfully inferred by bridging nAb responses based on GMR and SRR results observed in study P204 Part 2 to those observed in young adults in the pivotal P301 clinical efficacy study.

**2 Years Through 5 Years Age Group**

The GMR of Study P204 Part 2 participants 2 years through 5 years of age to Study P301 young adult participants 18 years through 25 years of age for Day 57 nAb levels against D614G was 0.995 (95% CI: 0.870, 1.139). Seroresponse after the primary series at Day 57 was achieved by nearly all participants (98.9% [95% CI: 96.9%, 99.8%]). The difference in SRR (relative to pre-Dose 1) was –0.4% (95% CI:  2.5%, 1.5%) (Study P204 Final CSR Primary Series [2 years to 5 years], Table 11). Thus, the noninferiority criteria for GMR (lower bound of the CI >0.667 and point estimator ≥0.8) and SRR difference (lower bound of the CI >-10% and point estimator ≥-5.0) were met.

***Assessor's comment:***

Compare Study P204 Final CSR, Table 11: Summary of Pseudovirus Neutralizing Antibody VAC62 Values for the 2 to 5 Years Age Group (Per-Protocol Immunogenicity Subset)

| Timepoint<br>Statistic | Part 2<br>P204 mRNA-1273<br>25 µg<br>(N=304) | <br>P301 mRNA-1273<br>100 µg<br>(N=296) |
|---|---|---|
| Baseline (Day 1) | | |
| n | 296 | 295 |
| GMC | 7.8 | 11.1 |
| 95% CI | (7.3, 8.2) | (10.5, 11.6) |
| Number of Participants <LLOQ, n (%)[a] | 151 (51.0) | 58 (19.7) |
| Number of Participants ≥LLOQ, n (%)[a] | 145 (49.0) | 237 (80.3) |
| Day 57 | | |
| n | 289 | 294 |
| GMC | 1394.1 | 1400.4 |
| 95% CI | (1267.7, 1533.1) | (1272.7, 1541.0) |
| GLSM (P204 Part 2 vs. P301) | 1394.1 | 1400.4 |
| 95% CI | (1267.0, 1533.9) | (1273.8, 1539.6) |
| GMR (P204 vs. P301) [b] | 0.995 | |
| 95% CI [b] | (0.870, 1.139) | |
| GM Fold Rise | 179.9 | 126.6 |
| 95% CI [c] | (162.0, 199.9) | (113.8, 140.9) |
| N1 | 284 | 294 |
| Seroresponse, n (%)[d] | 281 (98.9) | 292 (99.3) |
| 95% CI[e] | (96.9, 99.8) | (97.6, >99.9) |
| Difference (P204 vs. P301) (%) | -0.4 | |
| 95% CI[f] | (-2.5, 1.5) | |
| In Participants <LLOQ at Baseline, n/N2 (%)[g] | 142/145 (97.9) | 58/58 (100) |
| In Participants ≥LLOQ at Baseline, n/N3 (%)[h] | 139/139 (100) | 234/236 (99.2) |
| ≥4-fold Increase from Baseline[i] | | |
| n (%)[a] | 281 (98.9) | 292 (99.3) |
| 95% CI[e] | (96.9, 99.8) | (97.6, >99.9) |

Abbreviations: ANCOVA= analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GM = geometric mean; GMC = geometric mean concentration; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; LS = least squares; ULOQ = upper limit of quantitation.

Note: n = number of participants with no missing data at the corresponding timepoint.

Note: N1 = number of participants with no missing data at Baseline and the corresponding post-Baseline timepoint.

Note: P301 mRNA-1273 group included young adults (18-25 years of age).

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

a. Percentages were based on n.

b. The log-transformed antibody levels were analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI were back transformed to the original scale for presentation.

c. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GM fold rise, respectively, then back transformed to the original scale for presentation.

d. Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if Baseline was equal to or above the LLOQ. Percentages were based on N1.

e. 95% CI was calculated using the Clopper-Pearson method.

f. 95% CI was calculated using the Miettinen-Nurminen (score) confidence limits.

g. Number of participants with no missing data (<LLOQ) at Baseline and have seroresponse at the corresponding post-Baseline timepoint. Percentages were based on N2.

h. Number of participants with no missing data (≥LLOQ) at Baseline and have seroresponse at the corresponding post-Baseline timepoint. Percentages were based on N3.

i. ≥ z-fold increase from Baseline at participant level was defined as a ≥ z x LLOQ for participants with Baseline antibody value below LLOQ, or a z-times, or higher value ratio in participants with Baseline antibody value equal to or above the LLOQ.

Source: Table 14.2.3.1.1.3, Table 14.2.1.1.3.1.3 and Table 14.2.1.2.3.1.3

The non-inferiority endpoints to infer effectiveness were met for both GMR and SRR for the 2 to 5 years age group as compared to the 18 to 25 years age group from P301.

**6 Months Through 23 Months Age Group**

The GMR of Study P204 participants 6 months through 23 months of age to Study P301 young adult participants 18 years through 25 years of age for Day 57 nAb levels against D614G was 1.257 (95% CI: 1.101, 1.434). Seroresponse after the primary series at Day 57 was achieved by all participants (100% [95% CI: 98.6%, 100.0%]). The difference in SRR (relative to pre-Dose 1) was 0.7% (95% CI: –0.8%, 2.4%) (Study P204 Final CSR Primary Series [6 months to 23 months], Table 10). Thus, the noninferiority criteria for GMR (lower bound of the CI >0.667 and point estimator ≥0.8) and SRR difference (lower bound of the CI >-10% and point estimator ≥-5.0) were met.

***Assessor's comment:***

Compare Study P204 Final CSR, Table 10: Summary of Pseudovirus Neutralizing Antibody VAC62 Values (Including Participants from Study P301) for the 6 to 23 Months Age Group (Per Protocol Immunogenicity Subset)

| | Part 2 | |
|---|---|---|
| | P204 mRNA-1273 | P301 mRNA-1273 |
| Timepoint<br>Statistic | 25 µg<br>(N=286) | 100 µg<br>(N=296) |
| Baseline (Day 1) | | |
| n | 279 | 295 |
| GMC | 7.7 | 11.1 |
| 95% CI | (7.3, 8.2) | (10.5, 11.6) |
| Number of Participants <LLOQ, n (%)[a] | 150 (53.8) | 58 (19.7) |
| Number of Participants ≥LLOQ, n (%)[a] | 129 (46.2) | 237 (80.3) |

| Timepoint<br>Statistic | Part 2<br>P204 mRNA-1273<br>25 µg<br>(N=286) | P301 mRNA-1273<br>100 µg<br>(N=296) |
|---|---|---|
| Day 57 | | |
| n | 268 | 294 |
| GMC | 1759.8 | 1400.4 |
| 95% CI | (1606.7, 1927.4) | (1272.7, 1541.0) |
| GLSM (P204 Part 2 vs. P301) | 1759.8 | 1400.4 |
| 95% CI | (1599.2, 1936.5) | (1278.1, 1534.4) |
| GMR (P204 vs. P301) [b] | 1.257 | |
| 95% CI[b] | (1.101, 1.434) | |
| GM Fold-Rise | 230.7 | 126.6 |
| 95% CI[c] | (208.0, 255.8) | (113.8, 140.9) |
| N1 | 264 | 294 |
| Seroresponse, n (%)[d] | 264 (100) | 292 (99.3) |
| 95% CI[e] | (98.6, 100.0) | (97.6, >99.9) |
| Difference (P204 vs. P301) (%) | 0.7 | |
| 95% CI[f] | (-0.8, 2.4) | |
| In Participants <LLOQ at Baseline, n/N2 (%)[g] | 142/142 (100) | 58/58 (100) |
| In Participants ≥LLOQ at Baseline, n/N3 (%)[h] | 122/122 (100) | 234/236 (99.2) |
| ≥4-fold Increase from Baseline[i] | | |
| n (%)[j] | 264 (100) | 292 (99.3) |
| 95% CI[e] | (98.6, 100.0) | (97.6, >99.9) |

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GM = geometric mean; GMC = geometric mean concentration; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantification; LS = least square; ULOQ = upper limit of quantification.

Note: n = number of participants with no missing data at the corresponding timepoint.

Note: N1 = number of participants with no missing data at Baseline and the corresponding postbaseline timepoint.

Note: P301 mRNA-1273 group included young adults (18 to 25 years of age).

Note: For P301 18 to 25 years age group, pseudovirus neutralizing antibody was previously tested by VAC62 assay with ULOQ = 281600.

Note: Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.

a. Percentages were based on n.

b. The log-transformed antibody levels were analyzed using an analysis of covariance model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI were back transformed to the original scale for presentation.

c. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GM fold rise, respectively, then back transformed to the original scale for presentation.

d. Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if Baseline is equal to or above the LLOQ. Percentages were based on N1.

e. 95% CI was calculated using the Clopper-Pearson method.

f. 95% CI was calculated using the Miettinen-Nurminen (score) confidence limits.

g. Number of participants with no missing data (<LLOQ) at Baseline and have seroresponse at the corresponding postbaseline timepoint. Percentages were based on N2.

h. Number of participants with no missing data (≥LLOQ) at Baseline and have seroresponse at the corresponding postbaseline timepoint. Percentages were based on N3.

i. ≥ z-fold increase from Baseline at participant level was defined as a ≥ z x LLOQ for participants with Baseline antibody concentration below LLOQ, or a z-times, or higher concentration ratio in participants with Baseline antibody concentration equal to or above the LLOQ.

j. Percentages were based on N1.

Source: Table 14.2.3.1.1.3, Table 14.2.1.1.3.1.3 and Table 14.2.1.2.3.1.3

Effectiveness of mRNA-1273 against COVID-19 in children ages 6 to 23 months was successfully inferred by bridging nAb responses (GMR and SRR) observed in study P204 to those observed in young adults in the pivotal P301 clinical efficacy study.

**Subgroup Analysis**

**Primary Immunogenicity Analyses by Baseline SARS-CoV-2 Status**

As expected, the baseline nAb levels were higher among baseline SARS-CoV-2-positive participants than among those who were baseline SARS-CoV-2 negative. Although participants who were previously infected with SARS-CoV-2 had higher baseline nAb levels, mRNA-1273 induced an increase in Day 57 nAbs against D614G. These results were consistent with those of Study P301 subgroup analyses. It should be noted that a limited number of participants (<9% in each age group) were baseline SARS-CoV-2 positive.

**Other Subgroups**

No meaningful differences were observed in nAb responses (GMR and SRR) for the following examined subgroups within each age group: gender (male and female), race (Black or African American, White, and others), ethnicity (Hispanic or Latino, Not Hispanic or Latino, or missing), race and ethnicity (White non- Hispanic, communities of colour), and obesity status (body mass index <95th percentile/age and ≥95th percentile/age).

**SECONDARY ENDPOINT: VACCINE EFFICACY (COVID-19 INCIDENCE RATES)**

In the ensuing subsections, analyses of the COVID-19 incidence rates up to the end of the Blinded Phase and in the long-term analysis for each age group are presented. Additional details for incidence rates (including rates for asymptomatic SARS-CoV-2 infection and infection regardless of symptoms) are provided in the respective CSRs.

**6 Years Through 11 Years Age Group**

**Blinded Phase**

For Study P204 Part 2 participants in the 6 years through 11 years age group, the availability of a COVID-19 vaccine outside of the study under EUA in this age group as of 26 Oct 2021 rendered this age group eligible for unblinding. The effective end of the Blinded Phase for this age group was designated as 30 Nov 2021. This date marked the loss of a control group for vaccine efficacy calculations based on incidence rates. The period for observing cases for the PP Set for Efficacy (starting 14 days after Dose 2) was thus cut very short and included a low number of cases, leading to large CI for each assessment. Therefore, mITT1-based vaccine efficacy starting 14 days after Dose 1, which included a larger number of cases, was also evaluated and provided a more precise estimate of vaccine efficacy in this age group. Both vaccine efficacy calculations (based on PP Set for Efficacy and mITT1 Set) are presented below.

- CDC case definition: The observed vaccine efficacy against cases occurring 14 days or more after Dose 2 was 76.0% (95% CI: -41.6%, 96.5%) for the PP Set for Efficacy. The case split was 3/2606 cases (5.292/1000 person-years) in the mRNA-1273 group and 4/849 cases (22.088/1000 person-years) in the placebo group. For the mITT1 Set, vaccine efficacy against cases occurring 14 days or more after Dose 1 was 80.7% (95% CI: 58.1%, 91.5%). The case split was 12/2687 cases (23.665/1000 person-years) in the mRNA-1273 group and 19/881 cases (122.584/1000 person-years) in the placebo group.
- P301 case definition: The observed vaccine efficacy against confirmed cases occurring 14 days or more after Dose 2 was 68.0% (95% CI: -138.7%, 95.7%) for the PP Set for Efficacy. The

case split was 3/2606 cases (5.288/1000 person-years) in the mRNA-1273 group and 3/849 cases (16.542/1000 person-years) in the placebo group. For the mITT1 Set, vaccine efficacy against cases occurring 14 days or more after Dose 1 was 82.8% (95% CI: 58.7%, 93.3%). The case split was 9/2688 cases (17.728/1000 person years) in the mRNA-1273 group and 16/881 cases (103.052/1000 person-years) in the placebo group.

**Long-Term Analysis**

Long-term assessment of incidence rates by calendar month among all participants who received mRNA-1273 as randomised and who remained in the study up to 31 Oct 2022 (included both the Blinded and Open-label Phases) showed low monthly incidence rates of COVID-19 through November 2021. During the predominance of the Delta variant in the US (August to November 2021), incidence rates among vaccinated study participants generally remained low. Not unexpectedly, an increase in COVID-19 incidence rates was observed during the winter of 2021 to 2022, when the Omicron variant prevailed.

**2 Years Through 5 Years Age Group**

**Blinded Phase**

For Study P204 Part 2 participants in the 2 years through 5 years age group, 30 Jun 2022 was designated as the effective end of the Blinded Phase because of the availability of COVID-19 vaccines outside of study under EUA in this age group. Vaccine efficacy calculations (based on the PP Set for Efficacy) are presented.

- CDC case definition: The observed vaccine efficacy against cases occurring 14 days or more after Dose 2 was 46.6% (95% CI: 32.8%, 57.4%). The case split was 207/2592 cases (152.215/1000 person-years) in the mRNA-1273 group and 125/854 cases (285.018/1000 person-years) in the placebo group.
- P301 case definition: The observed vaccine efficacy against confirmed cases occurring 14 days or more after Dose 2 was 44.3% (95% CI: 26.1%, 57.8%). The case split was 142/2592 cases (102.874/1000 person-years) in the mRNA-1273 group and 83/854 cases (184.778/1000 person-years) in the placebo group.

Vaccine efficacy results based on the mITT1 Set were similar to those based on the PP Set for Efficacy.

**Long-Term Analysis**

Long-term assessment of incidence rates by calendar month among all participants who received mRNA-1273 as randomised and who remained in the study up to 31 Oct 2022 (included both the Blinded and Open-label Phases) showed an increase in COVID-19 incidence rates (based on both the CDC and P301 case definitions) in January and February 2022, during the time of the first Omicron wave. Later, not unexpectedly, an increase in COVID-19 incidence rates was observed in May, June, and July 2022, corresponding to subsequent Omicron subvariant waves in the US.

**6 Months Through 23 Months Age Group**

**Blinded Phase**

For Study P204 Part 2 participants in the 6 months through 23 months age group, 30 Jun 2022 was designated as the effective end of the Blinded Phase because of availability of COVID-19 vaccines outside of study under EUA in this age group. Vaccine efficacy calculations (based on the PP Set for Efficacy) are presented below.

- CDC case definition: The observed vaccine efficacy against cases occurring 14 days or more after Dose 2 was 43.2% (95% CI: 23.2%, 57.6%). The case split was 130/1686 cases (150.184/1000 person-years) in the mRNA-1273 group and 73/563 cases (264.181/1000 person-years) in the placebo group.
- P301 case definition: The observed vaccine efficacy against confirmed cases occurring 14 days or more after Dose 2 was 21.9% (95% CI: -18.0%, 47.4%). The case split was 88/1686 cases (100.617/1000 person-years) in the mRNA-1273 group and 37/563 cases (128.820/1000 person-years) in the placebo group.

Vaccine efficacy results based on the mITT1 Set were similar to those based on the PP Set for Efficacy.

**Long-Term Analysis**

The COVID-19 incidence rates increased substantially during the months of January and February 2022 with another rise noted in the months of May, June, and July 2022, primarily due to Omicron and Omicron subvariant waves in the US. This was similar to the long-term COVID-19 incidence rates observed for the 2 years through 5 years age group. The changes in COVID-19 incidence rates over time were consistent across the CDC and P301 case definitions.

**SECONDARY ENDPOINT: LONG-TERM IMMUNOGENICITY ANALYSES**

Long-term immunogenicity analysis was performed to assess the persistence of immune response after Dose 2 of mRNA-1273 through Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) in each age group.

For this analysis, the Day 394 nAb level data in the 6 years through 11 years age group were only available for Part 1 participants in the mRNA-1273 50 µg group as of the EOS database lock date (17 May 2024). In the younger age groups, the long-term analysis data from Part 2 participants for serum nAb were insufficient to draw conclusions about the durability of mRNA-1273 response. Therefore, the long term analysis data in the younger age groups are presented from Part 1 participants since the Part 1 participants had longer follow-up due to the earlier timing of their enrollment. Additionally, the younger age groups (6 months through 23 months and 2 years through 5 years) were combined for this analysis. This was justifiable given the similar nAb levels measured in these 2 age groups. Note that the participants in Part 1 and Part 2 in each age group were similar with respect to percentage of seropositive participants, intercurrent COVID-19 infections, and demographics.

Overall, the long-term analyses of nAbs show persistence of immune response against D614G through 12 months after vaccination. Measurable nAb responses persisted through 12 months (Day 394) after Dose 2 of mRNA-1273 and remained markedly elevated compared with pre-dose Day 1 values in all age groups.

***Assessor's comment:***

Long-term immunogenicity analysis was performed to assess the persistence of immune response after Dose 2 of mRNA-1273 through Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) in each age group.

Overall, the long-term analyses of nAbs show persistence of immune response against D614G through 12 months after vaccination. Measurable nAb responses persisted through 12 months (Day 394) after Dose 2 of mRNA-1273 and remained markedly elevated compared with pre-dose Day 1 values in all age groups.

Persistence of nAb levels against ancestral SARS-CoV-2 was accompanied with the emergence of SARS-CoV-2 variants leading to breakthrough infections.

Expectedly, participants who had an intercurrent SARS-CoV-2 infection had higher nAb levels than participants without intercurrent infection.

Long-term analyses of bAbs were also performed. In general, results of the long-term analyses of bAbs were consistent with those of the nAbs. Detailed results are presented in Study P204 Final CSRs Primary Series.

**6 Years Through 11 Years Age Group**

Measurable nAb responses persisted through 12 months after Dose 2 of the primary series (Day 394), regardless of the participants' baseline SARS-CoV-2 status. nAb levels remained steady through Day 394 (640.9 [95% CI: 482.1, 852.0]). All participants' nAb levels remained at least 4-fold higher than the pre-vaccination nAb levels at Day 394 (SRR of 100.0% [95% CI: 95.4%, 100.0%]).

Participants who had an intercurrent SARS-CoV-2 infection had higher nAb levels at both these timepoints (Day 209 and Day 394) than participants without intercurrent infection.

**2 Years Through 5 Years and 6 Months Through 23 Months Age Groups**

Measurable nAb responses persisted through 12 months after Dose 2 of the primary series (Day 394) for both age groups (6 months through 23 months and 2 years through 5 years) combined, regardless of the participants' baseline SARS-CoV-2 status. nAb levels remained steady through Day 394 (547.7 [95% CI: 432.9, 692.9]). The majority of participants' nAb levels remained at least 4-fold higher than the pre-vaccination nAb levels at Day 394 (SRR of 99.1% [95% CI: 95.2%, >99.9%]).

Participants who had an intercurrent SARS-CoV-2 infection had higher nAb levels at both Day 209 and Day 394 than participants without intercurrent infection, similarly as in the 6 years through 11 years age group.

**mRNA-1273 Booster (Study P204 Parts 1 and 2, 6 Months Through 11 Years)**

The ensuing subsections present an overview of the immunogenicity results for the mRNA-1273 25 µg BD in Part 1 and Part 2 participants 6 years through 11 years of age who had received mRNA-1273 50 µg 2 dose primary series at least 6 months prior to the BD. Additionally, the immunogenicity results of a smaller subgroup of Part 1 participants aged 6 months through 5 years age group who had received the BD with mRNA-1273 (N=76) are also presented. The results are presented in the following order of sections.

- Primary immunogenicity analysis demonstrating noninferiority of the immune response elicited by the mRNA-1273 BD in Study P204 participants 6 years through 11 years of age as well as in a subgroup of Part 1 participants aged 6 months through 5 years age compared with that observed in Study P301 young adult participants 18 years through 25 years of age.
- Long-term immunogenicity analyses demonstrating immune persistence up to 6 months after the mRNA-1273 BD.

The primary analysis population for immunogenicity was the PPIS-Pre-booster SARS-CoV-2 Negative (BD Analysis).

**CO-PRIMARY ENDPOINTS: IMMUNOGENICITY ANALYSIS TO INFER BD VACCINE EFFECTIVENESS IN 6 YEARS THROUGH 11 YEARS AGE GROUP**

The GMR of Study P204 participants 6 years through 11 years of age at BD-Day 29 to Study P301 young adult participants 18 years through 25 years of age for Day 57 D614G levels was 3.982 (95% CI: 3.404, 4.657). Seroresponse from pre-Dose 1 baseline after the BD at Day 29 (BD-Day 29) was achieved by all participants (100% [95% CI: 97.2%, 100.0%]) in the PPIS Pre-booster SARS-CoV-2

Negative (BD Analysis) of Study P204 6 years through 11 years age group. The difference in SRR was 0.7% (95% CI: -2.2%, 2.4%) (Study P204 Final CSR Booster Dose [6 years to 11 years], Table 12). Thus, the noninferiority criteria for GMR (lower bound of CI >0.667) and SRR difference (lower bound of CI >-10%) were met.

***Assessor's comment:***

Compare Study P204 Final CSR Booster Dose, Table 12: Immunobridging Analysis: Comparison of BD Day 29 nAb Levels and Seroresponse Rates (VAC62) Between P204 and P301 for the BD for the 6 to 11 Years Age Group for Participants who were Pre-booster SARS-CoV-2 Negative (PPIS)

| | Part 1 + Part 2 | |
|---|---|---|
| Timepoint<br>Statistic | P204 mRNA-1273 50 µg Booster 25 µg (N=137) | P301 mRNA-1273 100 µg (N=296) |
| BD-Day 29 (P204/ Day 57 P301) | | |
| n | 137 | 294 |
| GLSM (P204 vs P301) | 5575.9 | 1400.4 |
| 95% CI | (4899.2, 6346.0) | (1282.0, 1529.7) |
| GMR (P204 vs P301)[a] | 3.982 | |
| 95% CI[a] | (3.404, 4.657) | |
| N1 | 129 | 294 |
| Seroresponse, n (%)[b] | 129 (100) | 292 (99.3) |
| 95% CI[c] | (97.2, 100.0) | (97.6, >99.9) |
| Difference (P204 vs P301) (%) | 0.7 | |
| 95% CI[d] | (-2.2, 2.4) | |

Abbreviations: BD = booster dose; CI = confidence interval; GLSM = geometric least squares mean; LLOQ = lower limit of quantification; GMR = geometric mean ratio; PPIS = Per-Protocol Immunogenicity Subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

Note: n = number of participants with no missing data at the corresponding timepoint. N1 = number of participants with no missing data at Baseline and the corresponding post-Baseline timepoint.

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

P301 mRNA-1273 group included young adults (18-25 years of age).

[a] The log-transformed antibody levels were analyzed using an analysis of covariance model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI were back transformed to the original scale for presentation.

[b] Seroresponse from pre-Dose 1 Baseline at a participant level was defined as a change from below the LLOQ to equal or above 4×LLOQ, or at least a 4-fold rise if Baseline was equal to or above the LLOQ. Percentages were based on N1.

[c] 95% CI was calculated using the Clopper-Pearson method.

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

Source: Table 14.2.1.1.4.1.1.2 and Table 14.2.1.2.5.1.1.2.

*Immunobridging Analysis by Subgroups*

There were no notable differences in nAb responses or SRR among the subgroups examined (gender, race, ethnicity, or obesity status). nAb responses by subgroup are provided in Table 14.2.1.1.4.1.3.2, and SRRs by subgroup are provided in Table 14.2.1.2.5.1.3.2.

In summary, pre-booster negative participants ages 6-11 years met the non-inferiority criteria compared to the P301 young adult Primary Series.

**Primary Immunogenicity Subgroup Analyses**

The primary immunogenicity analysis was also performed for mRNA-1273 BD participants who were pre-booster SARS-CoV-2 positive and regardless of the pre-booster SARS-CoV-2 status. The overall nAb results (i.e., regardless of the pre-booster SARS-CoV-2 status) and those for the pre-booster SARS-CoV-2 positive participants were consistent with the results of the primary analysis based on the PPIS – Pre booster SARS-CoV-2 Negative (BD Analysis).

There were no notable differences in nAb responses or SRR among the other subgroups examined (gender, race, ethnicity, or obesity status).

**CO-PRIMARY ENDPOINTS: IMMUNOGENICITY ANALYSES TO INFER BD VACCINE EFFECTIVENESS IN THE 6 MONTHS THROUGH 5 YEARS AGE GROUP**

The primary endpoint to infer effectiveness of the mRNA-1273 BD was evaluated in a subgroup of Part 1 participants in the 6 months through 5 years age group who had received the BD with mRNA-1273. Immunogenicity noninferiority was met for these Part 1 participants. The GMR of the nAb levels of Study P204 participants (N=76; PPIS Pre-booster SARS-CoV-2 Negative [BD Analysis]) compared with Study P301 young adult participants 18 years through 25 years of age was 3.897 (95% CI: 3.158, 4.808), and the SRR difference between the participants in Study P204 and Study P301 was 0.7% (95% CI: -4.4%, 2.4%).

**SECONDARY ENDPOINT: LONG-TERM IMMUNOGENICITY ANALYSES**

mRNA-1273 BD maintained a persistent immunogenic effect for at least 6 months to 12 months after dosing. Participants who were pre-booster SARS-CoV-2 negative and those who were pre-booster SARS CoV-2 positive both showed similar nAb levels at BD-Day 181 (3030.7 [95% CI: 2402.3, 3823.5] and 2556.4 [95% CI: 2080.0, 3141.8], respectively). Higher nAb levels at BD-Day 366 were observed in participants who were pre-booster SARS-CoV-2 negative (3447.4 [95% CI: 2849.3, 4171.0]; n=96) than in those who were pre-booster SARS-CoV-2 positive (2034.8 [95% CI: 1688.2, 2452.6]; n=70).

**mRNA-1273 Alternate Primary Series Regimen (Study P204 Part 3, 6 Years Through 11 Years)**

The ensuing subsections present an overview of the immunogenicity results for the mRNA-1273 alternate primary series regimen (25 µg 2-dose primary series followed by Dose 3 of mRNA-1273 25 µg) in participants 6 years through 11 years of age (Part 3). Given that the number of participants who received at least 1 dose (N=90) in Part 3 was substantially smaller than the planned sample size (N=approximately 300), all the analyses of immunogenicity endpoints are descriptive.

The results are presented in the following order of sections.

- Primary immunogenicity analysis with nAb results following the mRNA-1273 25 µg 2-dose primary series and after Dose 3 of mRNA-1273 25 µg in Study P204 Part 3 participants.
- Long-term immunogenicity analyses demonstrating immune persistence at 6 months after Dose 3 of mRNA-1273 25 µg.

The primary analysis population for immunogenicity was the PPIS, which included participants selected for the Immunogenicity Subset (a subset of participants in the FAS with baseline [Day 1] SARS-CoV-2 status available and with both baseline and at least 1 post-injection antibody assessment for the analysis endpoint) who received planned doses of study vaccine per schedule, had baseline (Day 1) and Day 57 antibody assessment for the analysis endpoint, had no major protocol deviations that impacted key or critical data, and did not receive HAART if diagnosed with HIV.

**CO-PRIMARY ENDPOINTS: PRIMARY IMMUNOGENICITY ANALYSIS**

**Participants Who Received the 2-Dose Primary Series**

The GM values at Day 57 in Study P204 Part 3 (regardless of baseline serostatus) and Study P301 (young adults who were baseline seronegative) were 4368.6 (95% CI: 3339.6, 5714.6) and 1400.4 (95% CI: 1272.7, 1541.0), respectively. The GMR (P204 Part 3 versus P301) was 3.120 (95% CI: 2.347, 4.146) (Study P204 Final CSR Part 3 [6 years to 11 years] Table 13).

The SRR (relative to pre-Dose 1 values) against the SARS-CoV-2 strain on Day 57 in Study P204 Part 3 and Study P301 was 88.5% (95% CI: 77.8%, 95.3%) and 99.3% (95% CI: 97.6%, >99.9%), respectively. The SRR difference (P204 Part 3 versus P301) was -10.8% (95% CI: –21.2%, –4.9%) (Study P204 Final CSR Part 3 [6 years to 11 years] Table 15).

**Participants Who Received Dose 3**

The GM values at Dose 3 Day 29 in Study P204 Part 3 (regardless of baseline serostatus) and at Day 57 in Study P301 (young adults who were baseline seronegative) were 4616.6 (95% CI: 3669.4, 5808.3) and 1400.4 (95% CI: 1272.7, 1541.0), respectively. The GMR (P204 Part 3 versus P301) was 3.297 (95% CI: 2.577, 4.217) (Study P204 Final CSR Part 3 [6 years to 11 years] Table 14).

The SRR (relative to pre-Dose 1 values) against the SARS-CoV-2 strain on Dose 3 Day 29 in Study P204 Part 3 and on Day 57 in Study P301 was 90.0% (95% CI: 78.2%, 96.7%) and 99.3% (95% CI: 97.6%, >99.9%), respectively. The SRR difference (P204 Part 3 versus P301) was –9.3% (95% CI: –20.7%,  3.5%).

**Subgroup Analysis by Baseline/Pre-Dose 3 SARS-CoV-2 Status**

Immunogenicity was also assessed in participants without and with prior SARS-CoV-2 infection at baseline.

*Participants Who Received the 2-Dose Primary Series*

The baseline nAb GM levels were higher among SARS-CoV-2-positive participants at baseline (177.5 [95% CI: 111.2, 283.3]) than those who were SARS-CoV-2 negative at baseline (21.5 [95% CI: 2.6, 175.1]). The nAb GM value at Day 57 was 2140.6 (95% CI: 728.7, 6288.7) in the SARS-CoV-2-negative participants at baseline and 4592.9 (95% CI: 3470.7, 6077.9) in the SARS-CoV-2-positive participants at baseline. At Day 57, the GMR (P204 Part 3 versus P301) was 1.529 (95% CI: 0.671, 3.485) and the SRR was 100% (95% CI: 39.8%, 100.0%; N=4) in the SARS-CoV-2-negative participants at baseline. The GMR (P204 Part 3 versus P301) was 3.280 (95% CI: 2.558, 4.205) and the SRR was 87.7% (95% CI: 76.3%, 94.9%) in the SARS-CoV-2-positive participants at baseline.

*Participants Who Received Dose 3*

The pre-Dose 3 nAb GM levels were higher among SARS-CoV-2-positive participants at pre-Dose 3 (1902.0 [95% CI: 1279.2, 2827.9]) than those who were SARS-CoV-2 negative at pre-Dose 3 (1368.5 [95% CI: 482.3, 3882.9]). The nAb GM value at Dose 3 Day 29 was 6949.9 (95% CI: 1805.2, 26,756.6) in the SARS-CoV-2-negative participants at pre-Dose 3 and 4391.8 (95% CI: 3444.2, 5600.2) in the SARS-CoV-2-positive participants at pre-Dose 3. The GMR (Dose 3 Day 29 P204 Part 3 versus Day 57 P301) was 4.963 (95% CI: 2.361, 10.433) and the SRR was 100% (95% CI: 39.8%, 100.0%; N=4) in the SARS-CoV-2-negative participants at Dose 3 Day 29. The GMR (Dose 3 Day 29 P204 Part 3 versus Day 57 P301) was 3.136 (95% CI: 2.415, 4.073) and the SRR was 88.6% (95% CI: 75.4%, 96.2%) in the SARS-CoV-2-positive participants at Dose 3 Day 29.

Participants who were negative for SARS-CoV-2 prior to Dose 3 (N=5) experienced an increase in nAb levels compared with pre-Dose 3 values; however, the corresponding 95% CIs were wide because of the small sample size. Participants who were positive for SARS-CoV-2 prior to Dose 3 (N=45) had a similar level of increase in nAb levels.

**SECONDARY ENDPOINT: LONG-TERM IMMUNOGENICITY ANALYSES**

Long-term immunogenicity analysis was performed to assess the persistence of the immune response after Dose 3 of mRNA-1273 through Day 181 (6 months after Dose 3). Measurable nAb responses

persisted through 6 months (Day 181) after Dose 3 of mRNA-1273 and remained markedly elevated compared with pre-dose Day 1 values.

Long-term analyses of bAbs (VAC123) were also performed; results are presented in Study P204 Final CSR Part 3 (6 years to 11 years) (not presented here).

**ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS**

Primary Series Dosing Recommendations

In Part 1 of the study, for each age group, the dose level that was well tolerated and less reactogenic and expected to meet the prespecified success criteria for inference of effectiveness was advanced to Part 2. In the 6 years through 11 years age group, the 50 µg dose was selected as opposed to the 100 µg dose. For the 2 years through 5 years age group, after evaluation of a 50 µg dose of mRNA-1273 in Part 1, dose escalation to 100 µg dose was not pursued based on observed solicited ARs (post-Dose 1 of 50 µg in this age group and 100 µg dose in the 6 years through 11 years age group), in accordance with recommendations from the IST. The next lower dose level (25 µg) was found to be less reactogenic than 50 µg, and supported by the available immunogenicity results, the 25 µg dose was advanced to Part 2. Lastly, in the 6 months through 23 months age group, only one dose level (25 µg) was tested in Part 1 and found to have acceptable tolerability. Dose escalation to 50 µg was not pursued per IST recommendation after review of the reactogenicity profile of 50 µg in children 2 to 5 years.

The above-mentioned Part 1 doses were found to be safe and immunogenic after advancement to Part 2. The data from Part 2 supported worldwide authorizations of the mRNA-1273 vaccines for use in children 6 months through 11 years of age.

Part 3 explored a lower dose (25 µg) as an alternative primary series regimen in children 6 years through 11 years of age (2 IM injections, 28 days apart followed by a third 25 µg dose given at least 3 months and up to 5 months later). Results did not support the use of this alternative regimen as a primary series in this age group.

Booster Dosing Recommendations

The dosage level (10 or 25 µg) for optional BDs were lower than the dose chosen for the primary series for each age group, since the experience with adult boosters showed that a lower dose allowed for reductions in reactogenicity profile and dose sparing while still inducing a high level of neutralizing antibodies. An optional BD of 25 µg was evaluated in children 6 years through 11 years, and an optional BD of 10 µg was evaluated in children 6 months to <2 years and in children 2 to <6 years. These results supported the authorization of a single booster dose at the respective dose level with an updated vaccine formulation.

Current (2024-2025) Dosing Recommendations

Initial recommendations based on data from Study P204 included higher doses for the older children compared to younger children. Subsequently, given the increasing seroprevalence in the general population, dosing has been simplified and a single 25 µg dose is currently recommended for children 5 years through 11 years of age regardless of prior vaccination status. Given the lower seroprevalence in younger children, a 25 µg 2-dose primary series is recommended for previously unvaccinated children 6 months through 4 years of age while those who are previously vaccinated are recommended to receive a single 25 µg dose of an updated formulation.

***Assessor's comment:***

Initial recommendations based on data from Study P204 included 50 µg doses for the primary series regimen in children 6 – 11 years compared to younger children. Subsequently, given the increasing seroprevalence in the general population, dosing has been simplified and a single 25 µg dose is currently recommended for children 5 years through 11 years of age regardless of prior vaccination status. Given the lower seroprevalence in younger children, a 25 µg 2-dose primary series is recommended for previously unvaccinated children 6 months through 4 years of age while those who are previously vaccinated are recommended to receive a single 25 µg dose of a current variant-adapted formulation.

**PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS**

Overall, the long-term analyses of nAbs show persistence of immune response against D614G after Dose 2 of mRNA-1273 through 12 months after vaccination and after BD of mRNA-1273 through 6 months after vaccination (Part 1 and Part 2) and after Dose 3 of mRNA-1273 through 6 months after vaccination (Part 3).

Measurable nAb responses persisted through 12 months (Day 394) after Dose 2 of mRNA-1273 and remained markedly elevated compared with pre-dose Day 1 values in all age groups. mRNA-1273 BD maintained a persistent immunogenic effect for at least 6 months after dosing. Measurable nAb responses persisted through 6 months (Day 181) after Dose 3 of mRNA-1273 and remained markedly elevated compared with pre-dose Day 1 values.

## *2.3. Discussion*

The MAH submitted the final report from study mRNA-1273-P204 listed as a category 3 study in the RMP. This was an interventional Phase 2/3, 3-part, dose-escalation, open-label, age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in children 6 months through 11 years of age. Study P204 was conducted in order to infer effectiveness from the pivotal study P301.

The complete final analyses results were presented in the following CSRs:

| CSR Name | Primary/Booster | Study Part | Age Cohort |
|---|---|---|---|
| mRNA-1273-P204 Final CSR for Primary Series (6 to 11 years) | Primary Series (2-dose) | Parts 1 and 2 | 6 years to 11 years |
| mRNA-1273-P204 Final CSR for Primary Series (2 to 5 years) | Primary Series (2-dose) | Parts 1 and 2 | 2 years to 5 years |
| mRNA-1273-P204 Final CSR for Primary Series (6 to 23 months) | Primary Series (2-dose) | Parts 1 and 2 | 6 months to 23 months |
| mRNA-1273-P204 Final CSR for Booster Dose (6 to 11 years) | Booster | Part 2 | 6 years to 11 years |
| mRNA-1273-P204 Final CSR for Booster Dose (6 months to 5 years) | Booster | Part 2 | 6 months to 5 years |
| mRNA-1273-P204 Final CSR for Part 3 (6 to 11 years) (**this CSR**) | Alternative Primary Series Regimen | Part 3 | 6 years to 11 years |

Abbreviation: CSR=clinical study report.

Effectiveness of mRNA-1273 as a primary series in children aged 6 to 11 years was successfully inferred by bridging nAb responses based on GMR and SRR results observed in study P204 Part 2 to those observed in young adults in the pivotal P301 clinical efficacy study.

The non-inferiority endpoints of a primary series to infer effectiveness were met for both GMR and SRR for the 2 to 5 years age group as compared to the 18 to 25 years age group from P301.

Effectiveness of a primary series of mRNA-1273 against COVID-19 in children at ages 6 to 23 months was successfully inferred by bridging nAb responses (GMR and SRR) observed in study P204 to those observed in young adults in the pivotal P301 clinical efficacy study.

Long-term immunogenicity analysis was performed to assess the persistence of immune response after Dose 2 of mRNA-1273 through Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (12 months after Dose 2) in each age group. Overall, the long-term analyses of nAbs show persistence of immune response against SARS-CoV-2 D614G (ancestral strain) through 12 months after vaccination. Measurable nAb responses persisted through 12 months (Day 394) after Dose 2 of mRNA-1273 and remained elevated compared with pre-dose Day 1 values in all age groups. Persistence of nAb levels against ancestral SARS-CoV-2 was accompanied with the emergence of SARS-CoV-2 variants leading to breakthrough infections. Expectedly, participants who had an intercurrent SARS-CoV-2 infection had higher nAb levels than participants without intercurrent infection.

In the analysis of mRNA-1273 booster dose (BD), results from pre-booster SARS-CoV-2 negative participants in the age groups 6 to 11 years and 6 months to 5 years, respectively, met the non-inferiority criteria compared to results from the P301 young adult Primary Series.

These immunogenicity results laid the basis for the approval of mRNA-1273 in children and adolescents 6 months to 11 years of age.

Initial recommendations based on data from Study P204 included 50 µg doses for the primary series regimen in children 6 to 11 years compared to younger children. Subsequently, given the increasing seroprevalence in the general population, dosing has been simplified and a single 25 µg dose is currently recommended for children 5 years through 11 years of age regardless of prior vaccination status. Given the lower seroprevalence in younger children, a 25 µg 2-dose primary series is recommended for previously unvaccinated children 6 months through 4 years of age while those who are previously vaccinated are recommended to receive a single 25 µg dose of a current variant-adapted formulation.

The requested variation proposed no amendments to the Product Information.

# 3. Clinical Safety aspects

## *3.1. Methods – analysis of data submitted*

Data for safety are discussed in 4 parts with the analysis sets described in the below table:

- Study parts (1 and) 2:
    - Primary vaccination series (6m -11y of age)
    - Booster dose (6m -11y of age)
        - Booster dose (6y -11y of age)

- Study part 3:
    - Alternate primary vaccination scheme (6y -11y of age)

*Table 2 Analysis Populations (source: Table 2, summary clinical safety)*

| Analysis Population | Description |
|---|---|
| Solicited Safety Set | For Part 1, Part 2 and Part 3 (Primary Series):<br>All participants in the Safety Set who contributed any solicited AR data. This set was used for the analyses of solicited Ars.<br>In addition, for Part 1 and Part 2, this set was defined for each dose separately – First Injection Solicited Safety Set (all participants in the Solicited Safety Set who received the first dose) and Second Injection Solicited Safety Set (all participants in the Solicited Safety Set who received the second dose). |
| Safety Set | This set was used for analyses of safety data other than solicited Ars.<br>For Part 1 and Part 3:<br>All enrolled participants who received at least 1 dose.<br>For Part 2 (Primary Series):<br>All randomized participants who received at least 1 dose. |
| Safety Set (Part 2, Crossover Participants) | All participants from Part 2 placebo group in the Blinded Phase who crossed over and received mRNA-1273 in the Open-Label Phase. |
| Safety Set (Long-term Analysis) | All participants in the Safety Set (Part 2, Crossover Participants) for the placebo-mRNA-1273 group and Safety Set for the mRNA-1273 group. The Safety Set (Long-term Analysis) for the mRNA-1273 group was the same as the Safety Set in Part 1 and Part 2 Blinded Phase. |
| Solicited Safety Set (BD Analysis) | For Parts 1 and 2 Booster Phase:<br>All participants who received the BD and contributed any solicited AR data. This set was used for the analyses of solicited Ars following administration of the BD.<br>Note that, in Study P204 (Booster Phase), reactogenicity was only assessed for participants in the 6 years through 11 years age group who received the mRNA-1273 BD. |
| Safety Set (BD Analysis) | For Study P204 Parts 1 and 2 Booster Phase:<br>All participants who received the BD. This set was used for the analysis of all safety data, except the solicited Ars. |
| Solicited Safety Set (Third Dose Analysis) | For Study P204 Part 3:<br>All participants in the Safety Set in Part 3 who received Dose 3 and contributed any solicited AR data. |
| Safety Set (Third Dose Analysis) | For Study P204 Part 3:<br>All participants who received Dose 3 in Part 3. This set was used for the analysis of all safety data, except the solicited Ars. |

Abbreviations: AR = adverse reaction; BD = booster dose; mRNA = messenger ribonucleic acid.
Note: participants were analyzed according to the treatment actually received.

**Solicited Adverse Reactions**

Solicited ARs were assessed using a prespecified list of solicited local and systemic AR terms that were reported by participants daily via eDiary during the 7 days following each dose (ie, the day of dosing [primary series or BD/Dose 3] and 6 subsequent days). Solicited ARs that persisted beyond Day 7 were recorded until resolution or until the next dose, if applicable.

Severity grading (Grade 0 through Grade 4) of solicited local and systemic ARs occurred automatically based on participant entry into the eDiary according to the grading scales presented in Table 3, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Two versions of these scales and selection of solicited systemic AEs were used in the studies: one for participants 37 months of age and older and a modified, age-appropriate scale for participants 6 months through 36 months of age.

Table 3 Solicited ARs and Grading Scales Used in Study P204 (source: Table 3, summary clinical safety)

| | Age 37 Months Through 11 Years[a] | | | | | Age 6 Months Through 36 Months[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Reaction** | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4[b]** | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4[b]** |
| **Local AR** | | | | | | | | | | |
| Injection site pain/ tenderness | None | Does not interfere with activity | Interferes with activity | Prevents daily activity | Requires ER Visit[c] or hospitalization | None | Mild discomfort to touch or some pain but no interference with normal daily activities | Cries when limb is moved/ refuses to move limb or pain interferes with normal daily activities | Significant pain at rest or pain prevents normal daily activities | Requires ER Visit[c] or hospitalization |
| Injection site erythema (redness) | <25 mm/ <2.5 cm | 25-50 mm/ 2.5-5 cm | 51-100 mm/ 5.1-10 cm | >100 mm/ >10 cm | Necrosis or exfoliative dermatitis | <5 mm/ <0.5 cm | 5-20 mm/ 0.5-2 cm | >20-50 mm/ >2-5 cm | >50 mm/ >5 cm | Necrosis or exfoliative dermatitis |
| Injection site swelling/ induration (hardness) | <25 mm/ <2.5 cm | 25-50 mm/ 2.5-5 cm | 51-100 mm/ 5.1-10 cm | >100 mm/ >10 cm | Necrosis | <5 mm/ <0.5 cm | 5-20 mm/ 0.5-2 cm | >20-50 mm/ >2-5 cm | >50 mm/ >5 cm | Necrosis |
| Axillary (underarm or groin) swelling or tenderness ipsilateral to the side of injection | None | No interference with activity | Some interference with activity | Prevents daily activity | Requires ER Visit[c] or hospitalization | None | Some swelling or tenderness but no interference with normal daily activities | Swelling or tenderness that interferes with normal daily activities | Swelling or tenderness that prevents normal daily activities | Requires ER Visit[c] or hospitalization |
| **Systemic AR** | | | | | | | | | | |
| Headache | None | No interference with activity | Some interference with activity | Significant; Prevents daily activity | Requires ER Visit[c] or hospitalization | NA | | | | |
| Fatigue | None | No interference with activity | Some interference with activity | Significant; Prevents daily activity | Requires ER Visit[c] or hospitalization | NA | | | | |
| Myalgia (muscle aches all over body) | None | No interference with activity | Some interference with activity | Significant; Prevents daily activity | Requires ER Visit[c] or hospitalization | NA | | | | |

| Reaction | Age 37 Months Through 11 Years[a] | | | | | Age 6 Months Through 36 Months[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4[b] | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4[b] |
| Arthralgia (joint aches in several joints) | None | No interference with activity | Some interference with activity | Significant; Prevents daily activity | Requires ER Visit[c] or hospitalization | NA | | | | |
| Nausea/ vomiting | None | No interference with activity or 1-2 episodes/ 24 hours | Some interference with activity or >2 episodes/ 24 hours | Prevents daily activity | Requires ER Visit[c] or hospitalization for hypotensive shock | NA | | | | |
| Chills | None | No interference with activity | Some interference with activity not requiring medical intervention | Prevents daily activity and requires medical intervention | Requires ER Visit[c] or hospitalization | NA | | | | |
| Fever | <38.0°C <100.4°F | 38.0°C–38.4°C 100.4°F–101.1°F | 38.5°C–38.9°C 101.2°F–102.0°F | 39.0°C–40.0°C 102.1°F–104.0°F | >40.0°C >104.0°F | <38.0°C | 38.0°C–38.4°C 100.4°F–101.1°F | 38.5°C–39.5°C 101.2°F–103.1°F | 39.6°C–40.0°C 103.2°F–104.0°F | >40.0°C >104.0°F |
| Irritability/ crying | NA | | | | | None | Lasting <1 hour or easily consolable | Lasting 1-3 hours or requiring increased attention | Lasting >3 hours or inconsolable | Requires ER Visit[c] or hospitalization |
| Sleepiness | NA | | | | | None | Sleepier than usual or less interested in surroundings | Not interested in surroundings or sleeps through meals | Sleeps most of the time, hard to arouse | Inability to arouse |
| Loss of appetite | NA | | | | | None | Eating less than normal for 1-2 feeds/meals | Missed 1-2 feeds/meals completely | Missed >2 feeds/meals completely or refuses most feeds/meals | Requires ER Visit[c] or hospitalization |

Abbreviations: AR = adverse reaction; eCRF = electronic case report form; ER = emergency room; NA = not applicable.

Notes: The grading scales presented for "Age 37 months through 11 years" were applicable for Study P204 participants 37 months through 11 years of age and Study P306 participants 37 months through 5 years of age. The grading scales presented for "Age 6 months through 36 months" were applicable for Study P204 participants 6 months through 36 months of age.

a. Age at the time of enrollment determined the scale was to be used.

b. Grading for Grade 4 events per Investigator assessment (with exception of fever).

c. ER Visit included urgent care visit.

Source: Guidance for Industry – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

**Unsolicited Adverse Events**

An unsolicited AE was any AE reported by the participant that was not specified as a solicited AR in the study protocol or was specified as a solicited AR but started outside the protocol-defined period for reporting solicited ARs (ie, with onset after Day 7 of dosing).

Severity (mild, moderate, or severe) and causality (related or not related) of unsolicited AEs were summarised per the Investigator's assessment according to the guidelines for these assessments prespecified in the study protocols.

Unsolicited AEs were collected up to 28 days after each dose (ie, the day of dosing and 27 subsequent days). SAEs (including deaths), MAAEs, AESIs, unsolicited AEs leading to study vaccine discontinuation (as applicable), and/or study participation discontinuation were collected up to the end of the study.

**Serious Adverse Events**

An AE (including an AR) was considered an SAE if, in the view of either the investigator or Sponsor, it led to any of the following outcomes: resulted in death, was life-threating, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant incapacity

or substantial disruption of the ability to conduct normal life functions, or was a congenital anomaly/birth defect, or any medically important event.

Serious AEs were collected from Day 1 and throughout available follow-up. Solicited ARs that met the criteria for seriousness, were also reported as an SAE.

**Medically Attended Adverse Events**

An MAAE was defined as any unsolicited AE that led to an unscheduled visit to an HCP. This included visits to a study site for unscheduled assessments (eg, abnormal laboratory test result, evaluation of an illness, etc), and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators reviewed unsolicited AEs for the occurrence of any MAAE.

Participants with suspected COVID-19 were required per protocol to visit the study site for evaluation. Per protocol, all confirmed COVID-19 cases (as well as any other AEs associated with an illness visit) after the administration of study vaccine were recorded as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and were reported immediately to the Sponsor.

The data presented in this SCS represent results from an analysis conducted per FDA request, where all COVID-19-related events were to be treated as clinical endpoints and not reported as unsolicited AEs. Therefore, re-mapping was performed, treating any AE terms containing "COVID" or "SARS-CoV-2" as clinical events in datasets and in analysis, instead of AEs.

**Adverse Events of Special Interest**

An AESI was an unsolicited AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the Investigator to the Sponsor, and documentation in the form of a case narrative, was required. Such events may have required further investigation to characterize and understand them.

Multisystem Inflammatory Syndrome in Children

Investigators were instructed to report clinical signs/symptoms consistent with the CDC case definition of MIS-C (CDC 2024) as an AESI. MIS-C was also to be considered in any pediatric death with evidence of SARS-CoV-2 infection as well as participants fulfilling full or partial criteria for Kawasaki's disease if meeting the case definition for MIS-C.

Protocol-Defined Adverse Events of Special Interest

In addition to designation of MIS-C as an AESI, other AESIs selected were medical concepts that may be related to COVID-19 or were of interest in COVID-19 vaccine safety surveillance. A full list of the AESIs assessed for Study P204 is provided in the study protocol .

Programmed SMQs

All reported unsolicited AEs (regardless of Investigator's assessment as AESI) were queried using MedDRA SMQs (narrow and broad scope) to identify AESIs. The SMQs selected represent medical events that were assessed by global experts and regulatory agencies as hypothetically relevant to the COVID-19 vaccines. The SMQs for Study P204 included Anaphylactic reaction, Angioedema, Arthritis, Convulsions, Demyelination, Hypersensitivity, Peripheral neuropathy, Vasculitis, Central nervous system vascular disorders, Embolic and thrombotic events, Hearing and vestibular disorders, Cardiomyopathy, Hematopoietic cytopenia, Ischemic heart disease, Cardiac failure, and Cardiac arrhythmias. The SMQs of Cardiomyopathy and Hypersensitivity were critically reviewed for potential myocarditis and/or pericarditis and anaphylaxis events, respectively (see below).

Myocarditis and Pericarditis

Investigators were instructed to report any cases of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis as AESIs due to the previously-identified safety signal of an association between myocarditis/pericarditis and COVID-19 mRNA vaccines, particularly in adolescents and young adults (real-world use data). In order to enhance sensitivity for identifying cases of myocarditis/pericarditis after the safety signal emerged, the safety call script was revised to specifically solicit symptoms suggestive of myocarditis and/or pericarditis at prespecified timepoints. Any cases of myocarditis, pericarditis, or myopericarditis reported were to be adjudicated by a CEAC, made up of pediatric and adult cardiologists, to determine if the event met CDC case definition of probable or confirmed myocarditis or pericarditis events, or as "not a charter-defined case.

Additionally, supplemental measures to search for unrecognized myocarditis/pericarditis cases were employed. The safety dataset was interrogated for unsolicited AEs compatible with signs, symptoms, laboratory investigations, or procedural findings that might indicate potential cases. Two overlapping approaches were used to interrogate all events using: (1) The narrow and broad Cardiomyopathy SMQ, and (2) analysis of PTs reported and potentially indicative of myocarditis and pericarditis using a customized MedDRA query (CMQ) (based on the CDC working case definition) (Gargano et al 2021).

Any potential myocarditis and/or pericarditis cases identified by these reviews would also be adjudicated by the CEAC. Reports of chest pain and other nonspecific symptoms were not sent for adjudication if there was sufficient supporting information (eg, ECG, troponin or other test results not indicative of myocarditis/pericarditis).

Of note, since specific symptoms for myocarditis and pericarditis were solicited as part of safety calls and follow up, events such as chest pain and dyspnea were sometimes reported as AESIs even though not meeting protocol-defined AESI criteria. This enhanced collection may also have introduced some bias in reporting practices around these events.

Anaphylaxis

Investigators were instructed to report events of anaphylaxis as an AESI. The narrow and broad SMQ for Hypersensitivity was used to identify events of hypersensitivity, including anaphylaxis, which were subsequently reviewed.

**Overall Extent of Exposure and Duration of Follow-Up**

**Extent of Exposure**

Over 10,000 children, 6 months through 11 years of age participated in Study P204. Inclusion/exclusion criteria were designed to largely mimic the population expected to receive vaccine in the real world, ie, healthy children as well as children with medically stable underlying diseases were eligible to participate in the studies.

*Table 4 Summary of Vaccine Exposure (Primary Series and BD/Dose 3) - Study P204 (source: Table 4, summary clinical safety)*

| | Study Part | Age Group | Study Vaccine | Dose (µg) | N | Safety Set | |
|---|---|---|---|---|---|---|---|
| | | | | | | Received First Dose n (%) | Received Second Dose n (%) |
| **2-dose primary series** | | | | | | | |
| mRNA-1273 Primary Series | Part 1[a] | 6 years – 11 years | mRNA-1273 | 50 | 380 | 380 (100.0) | 379 (99.7) |
| | | | | 100 | 371 | 371 (100.0) | 371 (100.0) |
| | | 2 years – 5 years | | 25 | 69 | 69 (100.0) | 69 (100.0) |
| | | | | 50 | 155 | 155 (100.0) | 155 (100.0) |
| | | 6 months – 23 months | | 25 | 150 | 150 (100.0) | 150 (100.0) |
| | Part 2[b] | 6 years – 11 years | mRNA-1273 | 50 | 3007 | 3007 (100.0) | 2997 (99.7) |
| | | | Placebo | - | 995 | 995 (100.0) | 972 (97.7) |
| | | | Placebo-mRNA-1273[c] | 50 | 701 | 701 (100.0) | 697 (99.4) |
| | | 2 years – 5 years | mRNA-1273 | 25 | 3031 | 3031 (100.0) | 3007 (99.2) |
| | | | Placebo | - | 1007 | 1007 (100.0) | 984 (97.7) |
| | | | Placebo-mRNA-1273[c] | 25 | 640 | 640 (100.0) | 615 (96.1) |
| | | 6 months – 23 months | mRNA-1273 | 25 | 1994 | 1994 (100.0) | 1980 (99.3) |
| | | | Placebo | - | 666 | 666 (100.0) | 648 (97.3) |
| | | | Placebo-mRNA-1273[c] | 25 | 444 | 444 (100.0) | 421 (94.8) |

| | Study Part | Age Group | Study Vaccine | Dose (µg) | N | Safety Set | |
|---|---|---|---|---|---|---|---|
| | | | | | | Received First Dose n (%) | Received Second Dose n (%) |
| | Part 3[d] | 6 years – 11 years | mRNA-1273 | 25 | 90 | 90 (100.0) | 84 (93.3) |
| Overall mRNA-1273 exposure (primary series; at least 1 dose at any dose level)[e] | | | | | | 11032 | |
| **BD/Dose 3** | | | | | | | |
| | Study | Age Group | Study Vaccine | Dose (µg) | N | Received BD/Dose 3 (Safety Set [BD/Third Dose Analysis]) n (%) | |
| mRNA-1273 BD/Dose 3 | Part 1 + Part 2 | 6 years – 11 years | mRNA-1273 | 25 | 2519[f] | 2519 (100) | |
| | Part 1 | 6 years – 11 years | mRNA-1273 | 25 | 247[g] | 247 (100) | |
| | Part 1 | 6 months – 5 years | mRNA-1273 | 10 | 212[h] | 212 (100) | |
| | Part 2 | 6 months – 5 years | mRNA-1273 | 25 | 42[i] | 42 (100) | |
| | Part 1 | 6 months – 5 years | mRNA-1273 | 25 | 47[j] | 47 (100) | |
| | Part 3[d] | 6 years – 11 years | mRNA-1273 | 25 | 70 | 70 (100) | |
| mRNA-1273.214 BD | Part 1 + Part 2 | 6 years – 11 years | mRNA-1273.214 | 25 | 184[k] | 184 (100) | |
| | Part 2 | 6 months – 5 years | mRNA-1273.214 | 10 | 2766[l] | 2766 (100) | |
| | Part 2 | 6 months – 5 years | mRNA-1273.214 | 25 | 28[l] | 28 (100) | |
| | Part 1 | 6 months – 5 years | mRNA-1273.214 | 10 | 5[l] | 5 (100) | |
| Overall mRNA-1273 BD/Dose 3 exposure (at any dose level)[m] | | | | | | 3137 | |
| Overall mRNA-1273.214 BD exposure (at any dose level)[n] | | | | | | 2983 | |

Abbreviations: BD = booster dose; COVID-19 = coronavirus disease 2019; EUA = Emergency Use Authorization; mRNA = messenger ribonucleic acid.

[d] Part 1 was an Open-Label dose-finding phase.

Part 2 initiated with a Blinded Phase wherein participants within each age group were randomised to receive mRNA-1273 (at the dose selected based on safety, reactogenicity and immunogenicity data from Part 1) or placebo as a 2-dose primary series. The doses of the mRNA-1273 2-dose primary series selected for evaluation in Part 2 were 50 µg for participants in the 6 years through 11 years age group and 25 µg each for participants in the 2 years through 5 years and 6 months through 23 months age groups.

Following study unblinding (due to the availability of a nonstudy COVID-19 vaccine under EUA), participants who received placebo during the Blinded Phase of the study were offered to receive mRNA-1273 in the Open-Label Phase. These do not represent additional participants enrolled in the study.

[d] Part 3 was an Open-Label alternative dosing assessment in the 6 years through 11 years age group. mRNA-1273 25 µg was administered as 3 injections, approximately 28 days apart for the Dose 1 and Dose 2 followed by Dose 3 at least 3 months and up to 5 months after receipt of Dose 2.

[e] Includes all participants from Part 1, Part 2 and Part 3 who received at least 1 dose of mRNA-1273 in the primary series, irrespective of dose level and age group.

[f] Includes Part 1 and Part 2 participants 6 years through 11 years of age who received the mRNA-1273 50 µg 2-dose primary series followed by mRNA-1273 25 µg BD.

[g] Includes Part 1 participants 6 years through 11 years of age who received the mRNA-1273 100 µg 2-dose primary series followed by the mRNA-1273 25 µg BD.

[h] Includes Part 1 participants 6 months through 5 years of age who received the mRNA-1273 10 µg BD.

[i] Includes Part 2 participants 6 months through 5 years of age who received the mRNA-1273 25 µg BD.

[j] Includes Part 1 participants 6 months through 5 years of age who received the mRNA-1273 25 µg BD.

Includes Part 1 and Part 2 participants 6 years through 11 years of age (N=184) who received the mRNA-1273 primary series followed by the mRNA-1273.214 BD. Of these, 181 participants received the 25 µg BD of mRNA-1273.214, and 3 participants received the 10 µg BD of mRNA-1273.214 instead of the 25 µg BD in error. Together, these 184 participants were assessed as part of the mRNA-1273.214 25 µg BD analysis in participants 6 years through 11 years of age.
Includes Part 2 participants 6 months through 5 years of age (N=2766) who received the mRNA-1273 25 µg primary series followed by the mRNA-1273.214 BD. Of these, 2760 participants received the 10 µg BD of mRNA-1273.214, and 6 participants received a 5 µg BD of mRNA-1273.214 instead of the 10 µg BD in error. Together, these 2766 participants were assessed as part of the mRNA-1273.214 10 µg BD analysis in Part 2 participants 6 months through 5 years of age. In addition to these 2766 participants who received the BD, 5 Part 1 participants received mRNA-1273.214 10 µg BD and 28 Part 2 participants received a 25 µg BD of mRNA-1273.214 instead of the 10 µg BD.
Includes all participants from Part 1, Part 2 and Part 3 who received the mRNA-1273 BD, irrespective of dose level and age group.
Includes all participants who received the mRNA-1273.214 BD, irrespective of dose level and age group.

**Demographic and Other Characteristics of the Study Population**

In Study P204, age cohort-based enrollment was implemented (6 years through 11 years, 2 years through 5 years, and 6 months through 23 months).

Eligible children were generally healthy or had stable chronic conditions (excluding certain conditions that could impact study endpoint assessment[s]). Children meeting the study protocol criteria for history of SARS-CoV-2 infection and those with known hypersensitivity to study vaccine (mRNA-1273 or mRNA-1273.214) components were excluded. Children who had received an investigational or approved SARS-CoV-2-related vaccine were excluded from receiving the primary series.

## *3.2. Results*

**Solicited AEs**

Overall, the reactogenicity profile of children 6 months through 11 years of age was broadly consistent with the known safety profile of mRNA-1273. Reactogenicity consisted primarily of solicited ARs with Grade 1 or 2 in severity occurring within 1 to 2 days after vaccination, and typically resolving in 1 to 3 days. Grade 3 solicited ARs occurred less frequently. Few Grade 4 solicited ARs (in ≤0.3% of participants by treatment group and all of which were fever events) were reported.

**Primary Series**

Of the youngest age cohort (2-23m of age) most showed pain and irritability as the solicited AEs. 6 cases of grade 4 fever were reported with 4 cases not attributable to underlying infections.

In the group of 2y-5y olds a similar picture was seen, here, all 4 grade 4 fever cases are attributable to infections.

The group of 6-11y olds showed mainly pain and few systemic reactions. No grade 4 reactions were recorded.

**Booster dose**

Over 90% of subjects experienced at least on AR with pain and fatigue being the most frequent in the age group of 6-11y. The grade 4 fever events were attributable to concurrent Covid infections.

**Alternate primary series**

Most ARs were seen after the first dose and were mild with no Grade 4 reactions at all.

After Dose 1, the most frequently reported solicited ARs were injection site pain (61.8%), fatigue (31.1%), and headache (28.9%). Solicited ARs after Dose 1 were mainly Grade 1 or Grade 2 in severity. Grade 3 solicited ARs were reported in 6.7% of participants with nausea/vomiting (3.3%) and

headache (2.2%) being the most frequently reported Grade 3 solicited ARs. No Grade 4 solicited ARs were reported. Fever (≥38ºC) was reported by 5.7% of participants overall. Grade 3 fever was reported by 1.1% participants.

After Dose 2, the most frequently reported solicited ARs were injection site pain (54.8%), headache (28.6%), and fatigue (26.2%). Solicited ARs after Dose 1 were mainly Grade 1 or Grade 2 in severity. The only Grade 3 solicited AR reported was fever (2.4%). No Grade 4 solicited ARs were reported.

After Dose 3, the most frequently reported solicited ARs were injection site pain (46.4%), fatigue (21.4%), and headache (17.9%). No Grade 3 or Grade 4 solicited ARs were reported. Any fever (≥38ºC) was reported by 5.6% of participants.

**Unsolicited AEs**

**Primary Series**

Across the 3 age groups, injection site erythema was the most frequently reported unsolicited AE assessed as related to study vaccine. The frequency of this event was highest in the older age cohorts of 6-11y (6,3%) and diminished in the lower age groups (1,3% in 2-5y, 1% on 2-23m of age).

**Booster dose**

6-11y of age:

The most frequently reported events in this category were abdominal pain, abdominal pain upper, urticaria, arthralgia, and fatigue, (3 [0.1%] participants each). Of the events with PTs synonymous or similar to solicited ARs, only 1 event (arthralgia) occurred within 7 days after the BD and was reported as an AE.

6-23m of age:

The events were primarily infection-related events, including common respiratory tract infections. 9 of those were considered related to the vaccination according to the investigator.

**Alternate primary series**

Overall, 3.3% of participants reported unsolicited AEs assessed as related to study vaccine by the Investigator during the first two doses. There are no related unsolicited AEs reported for the third dose.

**SAEs**

No death was reported as relatable to the vaccine.

**Primary Series**

One case of febrile convulsions is possibly attributable to the vaccination although a few days later a roseola was also diagnosed. This combination could have caused the SAE.

*The participant experienced fever (103.1°F; reported as an unsolicited AE of pyrexia) approximately 6 hours after receiving Dose 1, which persisted into the next day, increasing to 104°F. The parents noted the infant demonstrated unusual crying and mildly depressed mental status, but no seizure activity was witnessed. The participant was taken to the ED where febrile seizure was suspected. The participant was discharged the following day on no medications. The Investigator assessed the events of pyrexia and febrile seizure as related to mRNA-1273. Three days later, a fine maculopapular rash was noted on the infant's trunk after the participant had defervesced. The short time to onset of the fever and the appearance of the rash after several days of high fever provide an alternate explanation suggestive of a viral illness (roseola). The infant sustained another brief febrile seizure 50 days after*

*Dose 1; the participant's temperature immediately after was 102.9°F. The event was witnessed by a parent, did not require medication, and the participant subsequently received Dose 2 without incident.*

**Booster dose**

No related severe adverse reactions were reported in either age group.

**Alternate primary series**

No SAEs reported in this group.

**AESIs**

There were no cases of myocarditis or pericarditis reported

**Primary Series**

Four AESI as listed in the study report considered related to the vaccinations are recorded during the study.

- Erythema multiforme: A 3-year-old participant in the mRNA-1273 group experienced mild erythema multiforme (verbatim term: erythema multiforme [bilateral arms]) 3 days after Dose 2, which resolved the next day. There were no other symptoms, and no treatment was given.
- Chest pain: A 4-year-old participant in the mRNA-1273 group experienced mild chest pain (verbatim term: chest pain [chest pain type unknown]) 5 days after Dose 2, which resolved within 30 minutes. An ECG and high-sensitivity troponin test performed showed normal results. No treatment was given.
- Henoch-Schönlein purpura: A 3-year-old participant in the placebo group experienced severe Henoch-Schönlein purpura 3 days after Dose 2, which resolved 7 days later. The individual was treated with prednisolone.
- A 10-year-old participant with a medical history of asthma developed severe urticaria (verbatim term: worsening of hives) 18 days after Dose 2 of mRNA-1273. This AE followed an initial unsolicited AE of moderate urticaria (verbatim term: hives located all over the body) with onset 11 days after Dose 1. The event remained ongoing through Dose 2 and was considered resolved when the event of severe urticaria was reported (duration of 34 days). Treatment for the severe urticaria included prednisone, topical mometasone, and levocetirizine. The severe urticaria resolved after 6 days and was assessed as related to mRNA-1273 by the Investigator.

**Booster dose**

2 cases of arthralgia and 3 cases of urticaria attributable to the vaccination were seen and medically attended in the age group of 6-11y of age.

**Alternate primary series**

No case attributable to the vaccination was recorded.

## *3.3. Discussion*

The spectrum of safety data generated during this study is as known. No new safety issues are seen and no cases of myocarditis/pericarditis is recorded.