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BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA) Supplement
STN	125752/276
CBER Received Date	January 07, 2025
PDUFA Goal Date	July 09, 2025
Division / Office	DCTR / OVRR
Priority Review	Yes
Reviewer Names	Alaina Halbach, MD Clinical Reviewer CRB3, DCTR, OVRR, CBER Robin Wisch, MD Clinical Reviewer CRB3, DCTR, OVRR, CBER
Review Completion Date	July 9, 2025
Supervisory Concurrence	Mark Connelly MD Team Leader, Clinical Review Branch-3 DCTR, OVRR, CBER Anuja Rastogi, MD, MHS Branch Chief, Clinical Review Branch-3, DCTR, OVRR, CBER
Applicant	Moderna TX, Inc.
Established Name	COVID-19 Vaccine, mRNA
Trade Name	SPIKEVAX
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Refer to United States Prescribing Information
Dosage Form and Route of Administration	Suspension for intramuscular injection (IM)
Dosing Regimen	Refer to United States Prescribing Information
Applicant Proposed Indication and Intended Population	Active immunization for the prevention of COVID-19 disease caused by SARS- CoV-2 virus for the ages 6 months and older
Orphan Designated	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
AU	arbitrary unit
bAb	binding antibody
BD	booster dose
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac External Adjudication Committee
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	computed tomography
DVRPA	Division of Vaccines and Related Products Applications
e-diary	electronic diary
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEG	electroencephalogram
EOS	end of the study
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GM	geometric mean
GMC	geometric mean concentration
GMT	geometric mean titer
HSP	Henoch-Schönlein purpura
IA	interim analysis
IM	intramuscular
IMV	invasive mechanical ventilation
IND	Investigational New Drug
IP	investigational product
IR	Information Request (by FDA)
KD	Kawasaki disease
LB	lower bound
LFTs	liver function tests
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MRI	magnetic resonance imaging
mRNA	messenger RNA
mRNA-1273	refers to the investigational product prior to authorization or approval
MSD	MesoScale Discovery
NAAT	nucleic acid amplification-based test
nAb	neutralizing antibody

NI	noninferiority
NP	nasopharyngeal
PMR	postmarketing requirement
PP	Per Protocol
PPIS	Per Protocol Immunogenicity Set
PREA	Pediatric Research Equity Act
PsVNA	pseudotyped virus neutralization assay
PT	Preferred Term
RT-PCR	reverse transcription-polymerase chain reaction
S-2P	prefusion stabilized spike protein nucleoside sequence modified to introduce 2 proline residues
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sBLA	supplemental Biologics License Application
SMQ	Standard MedDRA Query
SOC	System Organ Class
SPIKEVAX	Any formulation of the approved product, Spikevax, irrespective of strain composition or valency
SRR	seroresponse rates
STN	Submission Tracking Number
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink

1. EXECUTIVE SUMMARY

On January 7, 2025, ModernaTX, Inc. (the Applicant) submitted a supplemental Biologics License Application (sBLA) to the United States (U.S.) Food and Drug Administration (FDA) to support licensure of Spikevax (25µg) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 6 months through 11 years of age. Moderna COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Spikevax, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 through 11 years of age, two-dose regimen in those individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, and a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with Moderna COVID-19 Vaccine

Spikevax is a nucleoside-modified mRNA vaccine encoding for pre-fusion stabilized SARS-CoV-2 spike (S) glycoprotein, encapsulated in lipid particles. It is currently licensed for use as a single 50µg dose for individuals 12 years of age and older.

Data from 2 multi-part clinical studies were submitted in support of the sBLA. Study mRNA-1273-P204 (P204) evaluated a 2-dose series of the original monovalent formulation of Spikevax (mRNA-1273) in COVID-19 vaccine-naïve participants 6 months – 11 years of age (Part 1 [open label dose-finding] and Part 2 [blinded, saline placebo comparator]) and a single dose of either mRNA-1273 (6 years – 11 years) or a bivalent vaccine (Original and Omicron BA.1) (mRNA-1273.214, 6 months – 5 years) following the 2-dose series in Part 1/Part 2 (open label Booster Phase). Study mRNA-1273-P306 (P306) was an open label study that evaluated a 2-dose series of mRNA-1273.214 in COVID-19 vaccine-naïve participants who were 6 months – 5 years of age (Part 1), a single dose of mRNA-1273.214 in COVID-19 vaccine-experienced participants 6 months – 5 years of age (Part 2), and either a single dose (2 years – 4 years) or 2 doses (6 months – 23 months) of the monovalent XBB.1.5 formulation of Spikevax (mRNA-1273.815, Part 4).

Effectiveness

The primary results supporting the effectiveness of Spikevax came from

- Ages 6 years through 11 years
  - COVID-19 vaccine-naïve:
    - P204 Part 2 blinded phase (N= 311)
      The primary effectiveness objective was to demonstrate the noninferiority of the neutralizing antibody (nAb) responses following 2 doses of mRNA-1273 measured with an original strain (D614G) pseudovirus neutralization assay (PsVNA) as compared with the nAb responses following 2 doses of mRNA-1273 in young adults (18 years – 25 years old) for whom clinical efficacy was demonstrated in Study P301.

  - COVID-19 vaccine-experienced:
    - P204 Booster Phase (N= 114)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses following a single dose of mRNA-1273 measured with an original strain (D614G) PsVNA as compared with the nAb responses following 2 doses of mRNA-1273 in young adults (18 years – 25 years old) for whom clinical efficacy was demonstrated in Study P301.

- Ages 2 years through 5 years
  - COVID-19 vaccine-naïve:
    - P204 Part 2 blinded phase (N= 304)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses following 2 doses of mRNA-1273 measured with an original strain (D614G) PsVNA as compared with the nAb responses following 2 doses of mRNA-1273 in young adults (18 years – 25 years old) for whom clinical efficacy was demonstrated in Study P301.

    - P306 Part 4 (N= 149)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses measured with an XBB.1.5 PsVNA following a single dose of mRNA-1273.815 in participants 2 years – 4 years of age who were SARS-CoV-2 positive at baseline as compared with the nAb responses measured with the same PsVNA following 2 doses of mRNA-1273.815 in participants 6 months – 23 months of age who were SARS-CoV-2 negative at baseline.

  - COVID-19 vaccine-experienced:
    - P306 Part 2 (N= 425)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses following a single dose of mRNA-1273.214 measured with an original strain (D614G) PsVNA and superiority of the nAb responses measured with an Omicron BA.1 PsVNA as compared with the nAb responses following 2 doses of mRNA-1273 in participants in the same age group in P204.

- Ages 6 months – 23 months
  - COVID-19 vaccine-naïve:
    - P204 Part 2 blinded phase (N= 286)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses following 2 doses of mRNA-1273 measured with an original strain (D614G) pseudovirus neutralization assay (PsVNA) as compared with the nAb responses following 2 doses of mRNA-1273 in young adults (18 years – 25 years old) for whom clinical efficacy was demonstrated in Study P301.

    - P306 Part 4 (N= 399)
      nAb responses as described in the P306 Part 4 section of the 2 years – 4 years age group above.

  - COVID-19 vaccine-experienced:
    - P306 Part 2 (N= 114)
      The primary effectiveness objective was to demonstrate the noninferiority of the nAb responses following a single dose of mRNA-1273.214 measured with an original strain (D614G) PsVNA and superiority of the nAb responses measured with an Omicron BA.1 PsVNA as compared with the

nAb responses following 2 doses of mRNA-1273 in participants in the same age group in P204.

All study parts met their primary effectiveness objectives for all age groups. Descriptive endpoints evaluated the incidence of COVID-19 14 days following the 2nd dose of mRNA-1273 as compared with placebo in Study P204 Part 2.

Safety
The overall safety database supporting the safety of Spikevax in individuals 6 months through 11 years included 11,931 vaccinated participants (4,459 participants 6 years through – 11 years of age; 4,355 participants 2 years through 5 years of age; and 3,117 participants 6 months through 23 months of age). In the clinical studies submitted to this sBLA, across all age groups, local and/or systemic solicited adverse reactions (ARs) following vaccination were generally mild to moderate and of 1 – 2 days in duration. The most common solicited local AR was pain at the injection site. The most common solicited systemic ARs were irritability/crying, fatigue, headache, and sleepiness.

There were no cases of myocarditis or pericarditis reported in the studies submitted to this sBLA. Two non-serious unsolicited events of alopecia areata and serum sickness-like reaction, two adverse events of special interest (AESIs) of erythema multiforme (EM) and Henoch-Schönlein purpura (HSP), and two serious adverse events (SAEs) of pyrexia and febrile convulsions were assessed as related to the study doses by investigators and are recommended for inclusion in the USPI. There were no other safety concerns identified which are not already captured in the Spikevax prescribing information. No new safety PMR studies are recommended.

Conclusion
Substantial evidence of Spikevax vaccine effectiveness in children 6 months through 11 years of age was supported by the demonstration of noninferior immunogenicity of Spikevax (Original monovalent) and noninferior and superior immunogenicity of a bivalent vaccine (Original and Omicron BA.1) compared with Spikevax (Original monovalent) in young adults in Study P301 or in children of the same age group in Study P204. Safety data from studies P204 and P306 suggest that Spikevax in children under 12 years of age has a similar safety profile compared with Spikevax in adolescents and young adults (previously approved, safety data described in the USPI) absent evidence of increased risk of myocarditis/pericarditis in children under 12 years of age following vaccination. The package insert was updated with six new possibly related events; alopecia areata, serum sickness-like reaction, erythema multiforme, HSP, pyrexia, and febrile convulsions, all of which have either infection or vaccination as known risk factors. Therefore, the available data submitted to this application support FDA assessment of a favorable benefit-risk of Spikevax in children 6 months through 11 years of age for the proposed indication.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

Effectiveness
Subpopulation analyses of vaccine effectiveness did not suggest meaningful differences in vaccine responses by sex, racial and ethnic groups, although analyses were limited by small numbers of participants in some subgroups.

Safety
In safety analyses, reported rates of some solicited local and systemic adverse reactions (ARs) were higher among participants who had evidence of prior SARS-CoV-2 infection at baseline compared with those who did not, however these differences varied by age and interpretation are limited by small sample sizes in some studies. Other differences between the age groups in overall rates and types of unsolicited AEs and serious adverse events (SAEs) largely reflected differences in underlying disease epidemiology between the age groups. No clinically meaningful differences in the occurrence of unsolicited AEs or SAEs were observed by sex, race, or ethnicity subgroups; however, interpretation is limited by small sample sizes in some subgroups.

1.2 Patient Experience Data

No patient experience data were submitted in this sBLA.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. As of June 30, 2025, SARS-CoV-2 infection has resulted in over 778 million cases of COVID-19 and over 7 million deaths worldwide (WHO, 2025). Disease symptoms vary. Many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older and individuals with certain co-morbid conditions (CDC, 2025a), may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most individuals with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2025b), and in rare instances, children may experience a serious medical condition associated with COVID-19 called Multisystem Inflammatory Syndrome in Children (MIS-C) (CDC, 2025c).

In the U.S., more than 1.2 million deaths from COVID-19 have been reported to the CDC (CDC, 2025d), with a cumulative COVID-19-associated hospitalization rate of 76.5 per 100,000 people for the 2024-2025 season, as of June 21, 2025 (CDC, 2025d). While individuals 65 years of age and older accounted for the majority of COVID-19 associated hospitalizations and death at the end of the 2024-2025 season (317.4 per 100,000 people) (CDC, 2025d and CDC, 2025e) and individuals 5 through17 years of age have the lowest hospitalization rate at 5.9 per 100,000 people, (CDC, 2025d), infants and children 0 through4 years of age had a comparatively higher hospitalization rate of 41.4 per 100,000 people, with the highest rates in individuals 6 through23 months of age (100 per 100,000 people) and infants less than 6 months of age (268 per 100,000 people) (CDC 2025e). The hospitalization rate for the 6-month through 23-month-old age group was similar to the hospitalization rate for adults 50 through 64 years of age, however, unlike these adults, 94% of whom had at least one underlying medical condition that put them at increased risk for severe COVID-19, only 46% of infants and children 6 months-23 months of age had any underlying medical condition (CDC, 2025e). Since the start of the pandemic, surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public

health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses.

The SARS-CoV-2 Omicron variant has evolved into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome, leading to successive waves across the globe. In June 2023, XBB sublineages dominated, both in the U.S. and globally and accounted for >95% of the circulating virus variants in the U.S (CDC, 2025f). In June 2024, an increase in the prevalence of KP.2 sublineage led FDA to advise the manufacturers of the licensed and authorized COVID-19 vaccines that the preferred JN.1-lineage for COVID-19 vaccines (2024-2025 Formula) is KP.2, if feasible (Updated COVID-19 Vaccines for Use in the United States Beginning in Fall 2024 | FDA). On May 22, 2025, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States. The committee unanimously voted to recommend a monovalent JN.1-lineage vaccine composition. Based on the totality of the evidence, FDA has advised the manufacturers of the approved COVID-19 vaccines that to more closely match currently circulating SARS-CoV-2 viruses, the COVID-19 vaccines for use in the United States beginning in fall 2025 should be monovalent JN.1-lineage-based COVID-19 vaccines (2025-2026 Formula), preferentially using the LP.8.1 strain (COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025 | FDA).

Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, SARS-CoV-2 evolution is complex and remains unpredictable. Intrinsic viral factors, e.g., mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals. Thus far, the impressive plasticity, especially in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

FDA-approved Therapies for COVID-19

Antivirals:
Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), who are either hospitalized, or not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Immune modulators:
Olumiant (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra (Tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Pharmacological Products for Pre-exposure Prophylaxis of COVID-19, Post-exposure Prophylaxis and/or Treatment of COVID-19 Authorized for Emergency Use

Antivirals:
Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults and authorized for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 through 17 years of age and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults 18 years of age and older with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies:
Pemgarda (pemivibart) is authorized for preexposure prophylaxis for individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2; and who have moderate-to-severe immune compromise due to a medical condition or due to taking immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination.

Immune modulators:
Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 years to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Tocilizumab is authorized for the treatment of COVID-19 in hospitalized pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma:
COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

2.3 Safety and Efficacy of Pharmacologically Related Products

mNexspike (2024-2025 Formula)
mNexspike (COVID-19 Vaccine, mRNA), manufactured by Moderna, is indicated for the active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals who have been previously vaccinated with any COVID-19 vaccine and are 65 years of age and older or 12 through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. mNexspike (2024-2025 Formula) contains nucleoside-modified mRNA encoding the N-terminal domain (NTD) and receptor binding domain (RBD) of the S protein of the SARS-CoV-2 Omicron variant JN.1, encapsulated in lipid particles. For additional information on dosing and schedule, please refer to the mNexspike Package Insert. Safety and effectiveness data supporting approval of mNexspike are documented in the Summary Basis of Regulatory Action.

Comirnaty and Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula)
Comirnaty (COVID-19 Vaccine, mRNA) manufactured by Pfizer for BioNTech, is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty (2024-2025 Formula) contains nucleoside-modified messenger RNA (modRNA) encoding the viral Spike (S) glycoprotein of the SARS-CoV-2 Omicron variant lineage KP.2 that is formulated in lipid particles. Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Comirnaty, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 through 11 years of age, three-dose regimen in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, 2-dose regimen if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer BioNTech COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Comirnaty and authorization of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are documented in the BLA clinical review memorandum and EUA decision memorandum, respectively.

Nuvaxovid and Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)
Nuvaxovid (COVID-19 Vaccine, Adjuvanted) manufactured by Novavax, Inc. is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults 65 years and older, and for individuals 12 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Nuvaxovid (2024-2025 Formula) contains recombinant S protein of the SARS-CoV-2 Omicron variant JN.1 and Matrix-M adjuvant. Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Nuvaxovid, is authorized under EUA for administration of a single-dose regimen at least 2 months after receipt of the last previous dose of COVID-19 vaccine to individuals 12 years of age and older previously vaccinated with any COVID-19 Vaccine. In individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, Novavax COVID-19 Vaccine (2024-2025 Formula), Adjuvanted is

authorized under EUA for administration as a 2-dose regimen. Individuals with certain kinds of immunocompromise 12 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Nuvaxovid and authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) are documented in the BLA clinical review memorandum and EUA decision memorandum, respectively.

2.4 Previous Human Experience with the Product

Moderna COVID-19 Vaccine (Original monovalent) was authorized under EUA on December 18, 2020, and subsequently approved under the trade name Spikevax on January 31, 2022. Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized under EUA on August 31, 2022. On September 11, 2023, Spikevax (2023-2024 Formula, XBB.1.5 monovalent-based) was approved for use in individuals ≥12 years of age and was authorized under EUA as Moderna COVID-19 Vaccine (2023-2024 Formula, monovalent XBB1.5-based) for use in individuals 6 months through 11 years of age. On August 22, 2024, Spikevax (2024-2025 Formula, KP.2-based) was approved for use in individuals 12 years of age and older and Moderna COVID-19 Vaccine (2024-2025 Formula, [KP.2 monovalent-based) a was authorized for individuals 6 months through 11 years of age. As of December 2022, Spikevax was approved in 88 countries and Moderna COVID-19 Vaccine (inclusive of all formulations) has been used in 92 countries. In the U.S., over 340 million doses of Moderna COVID-19 vaccines have been administered as of September 2024 (STN#125752/276 Clinical Overview).

2.5 Summary of Regulatory Activities Related to the Submission

Major sBLA-associated regulatory activities:

- October-December 2023: Pre-sBLA meeting and follow-up; multiple communications were issued to Moderna related to the proposed pediatric sBLA submission and specifically on the data required to support the proposed dosing posology.
- March 22, 2024: Written response provided to Moderna regarding pediatric sBLA follow-up questions stating the CBER expectation that Moderna obtain study data from P306 Part 4 prior to submission of the sBLA.
- September 12, 2024: Written response provided to Moderna with CBER agreement that Study mRNA-1273-P306 Part 4 clinical study report and clinical overview addendum will be submitted in first Quarter 2025 during review of this pediatric sBLA.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The studies submitted to this sBLA were conducted in accordance with the International Council on Harmonization's Good Clinical Practice guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR 50.25.

Bioresearch monitoring (BIMO) inspections were issued for 2 clinical study sites. The inspections did not reveal substantive issues that would impact the integrity of the clinical data submitted in this application. Please see BIMO review memorandum for additional details.

3.3 Financial Disclosures

Table 1: Financial disclosures in Studies P204 and P306

Studies P204 and P306
Was a list of clinical investigators provided? ☒ Yes ☐ No
Total number of investigators identified: 135 (88 for P204, 47 for P306)
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 The site investigator for a single site in Study P204 site (70 participants enrolled, 0.59% of the total population) reported a (b) (4) grant from Moderna (b) (4)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Source: FDA generated table. Adapted from STN#125752/276

Clinical Reviewer Comment:
After review of the information submitted in Form FDA 3455, this reviewer has determined that the awarded grant is unlikely to impact the clinical data quality for the following reasons: 1) the site enrolled only 0.59% of the total number of participants enrolled in the study; 2) the grant occurred after enrollment at the study site had closed and was unrelated to COVID-19 vaccination outcomes; and 3) the study followed appropriate Good Clinical Practices, including blinding procedures and use of an independent Data Monitoring Committee..

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

CBER product reviewer reviewed the manufacturing process development, in-process testing, release, and stability testing in support of licensure. The Spikevax (Original monovalent) Drug Substance (DS) and Drug Product (DP) manufacturing process and controls were approved under the original BLA. This sBLA reviews the chemistry, manufacturing, and controls changes information pertinent to manufacturing of the 25µg pre-filled syringe formulation of Spikevax (2024-2025 Formula). Facility information provided in the sBLA was reviewed and found to be sufficient and acceptable.

4.2 Assay Validation

CBER assay and statistical reviewers reviewed the clinical assays (serology and molecular) and found them to be adequate to support licensure.

4.3 Nonclinical Pharmacology/Toxicology

The CBER toxicology reviewer did not identify any safety issues based on the submitted preclinical studies that would impact the conclusions of the clinical review. Please see CBER toxicology review memorandum for further details.

4.4 Mechanism of Action

The nucleoside-modified mRNA in SPIKEVAX is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

4.5 Statistical

CBER statistical reviewers confirmed the key statistical analyses for safety, immunogenicity, and efficacy and found no major statistical issues that would impact the interpretation of the data and conclusions.

4.6 Pharmacovigilance

Moderna is conducting safety-related post-authorization/postmarketing studies for Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Moderna has a pharmacovigilance plan (version 10.1) to monitor safety concerns that could be associated with the Spikevax (2024-2025 Formula). The plan includes the following safety concerns:

- Important Identified Risks: Anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease
- Missing Information: Use in pregnancy and while breast-feeding, long-term safety, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities, and use in subjects with autoimmune or inflammatory disorders

The Applicant will perform routine and enhanced pharmacovigilance in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). Please see Pharmacovigilance review memorandum for further details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

At the January 26, 2023, VRBPAC meeting, the committee discussed harmonization of the strain composition for primary series and booster doses, simplification of the immunization schedule, and periodic updates of COVID-19 vaccine strain composition. Following this meeting, FDA identified evidentiary gaps and the comprehensive data package needed to address those evidentiary gaps to support a simplification of vaccine composition and immunizations schedule. Evidence suggests that a combination of SARS-CoV-2 infection and vaccination confers significant protection, particularly against severe COVID-19 and hospital admissions. According to CDC, the seroprevalence of SARS-CoV-2 in 2023 was estimated to be 98% in people 16 years of age and older (CDC, 2023). Similarly, among adolescents 12 through 17 years old, children 5 through 11 years old, and 0 through 4 years old, the seroprevalence of SARS-CoV-2 was estimated to be approximately 99%, 97%, and 90%, respectively (CDC, 2022). Based on the substantial evidence that supported the use of single 50 mcg dose of Spikevax in individuals 12 years of age and older irrespective of their prior COVID-19 vaccination status, FDA approved a single dose (50 µg) of Spikevax in individuals 12 years of

age and older in September 2023. FDA additionally sought evidence from the Applicant of the safety and effectiveness of a single dose (25 µg) of Spikevax in children 2 years through 12 years of age, irrespective of COVID-19 vaccination status, and 2 doses in children 6 months through 23 months of age who are less likely have prior exposure to SARS-CoV-2 and therefore less likely to have underlying immunity. These pediatric data were submitted to this sBLA and are summarized below:

Effectiveness of a single dose (25 µg) of Spikevax in children 2 years through 11 years of age, irrespective of prior COVID-19 vaccination status, and in COVID-19 vaccine-experienced infants and children 6 months through 23 months of age, and of a 2-dose series (25 µg) of Spikevax in COVID-19 vaccine-naïve infants and children 6 months through 23 months of age is based on:

- Immunogenicity and Efficacy of 2 doses (50 µg for children 6 through 11 years of age or 25 µg for infants and children 6 months through 5 years of age) of Spikevax (Original monovalent) in COVID-19 vaccine-naïve infants and children 6 months through 11 years of age (Study P204 Part 2).
- Immunogenicity of a single dose of (25 µg) of Spikevax (XBB.1.5 monovalent) in vaccine-naïve children 2 years through 4 years of age and 2 doses (25 µg) of Spikevax (XBB.1.5 monovalent) in vaccine-naïve infants and children 6 months through 23 months of age (Study P306 Part 4).
- Immunogenicity of a single 25 µg dose of Spikevax (Original monovalent) in vaccine-experienced children 6 years through 11 years of age (Study P204 Part Booster)
- Immunogenicity of a single 10 µg dose of a bivalent vaccine (Original and Omicron BA.1) in vaccine-experienced children 6 months through 5 years of age (Study P306 Part 2).

Safety of either a single dose (25 µg) or 2 doses (25 µg) of Spikevax including Spikevax (2024-2025 Formula) in individuals 6 months through 11 year of age is based on the above studies as well as the following:

- Safety of a single dose (10 µg) of Spikevax (Original monovalent) in vaccine-experienced children 6 months through 5 years of age (Study P204 Part 2).
- Safety of a 2-dose series (25 µg) of a bivalent vaccine (Original and Omicron BA.1) in COVID-19 vaccine-naïve infants and children 6 months through 5 years of age (Study P306 Part 1).

Study P204 Part 1 was a dose-finding study with limited contribution to the overall safety and effectiveness assessment; therefore, their results will not be discussed in detail in this sBLA clinical review. Study P204 Part 3 assessed the effectiveness of a third dose of Spikevax administered 3-5 months after the second dose. As these data are not in scope for this sBLA, the results will not be discussed in this clinical review. Study P306 Part 3 is ongoing and is evaluating the effectiveness of a single 25 µg dose of Spikevax (XBB.1.5 monovalent) at least 4 months after the last receipt of a COVID-19 vaccine in participants 6 months through 5 years of age. As the data from this study are not yet final and are redundant with those submitted from P306 Part 2, these results will not be discussed in this clinical review.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following STN 125752/276 Amendments were reviewed in support of this application:

Table 2. Amendments to sBLA 125752/276

Amendment Number	Date Received	Description
1	January 29, 2025	Study P306 Part 4 Topline results
3	February 12, 2025	Updated draft labeling
5	March 13, 2025	Response to IR re: Labeling and cross reference clarification
6	March 14, 2025	Efficacy supplement re: P306 Part 4 final clinical study report
7	March 18, 2025	Response to IR re: Study P306 Part 3
8	March 28, 2025	Response to IR re: Cumulative myocarditis and pericarditis data
9	April 11, 2025	Response to IR re: Consolidated USPI
11	April 15, 2025	Response to IR re: Submission of agreed PSP
12	April 23, 2025	Response to IR re: Shell tables
13	April 28, 2025	Updated financial disclosure information
14	June 12, 2025	Response to IR re: Safety data studies P204 and P306
16	June 16, 2025	Response to IR re: Safety data studies P204 and P306
17	June 16, 2025	Response to IR re: Safety tables study P204 Booster Phase
19	June 17, 2025	Response to IR re: Updated draft labeling with reorganization
20	June 20, 2025	Response to IR re: Updated draft labeling with updated indication
21	June 25, 2025	Response to IR re: Safety data studies P204 and P306
22	June 26, 2025	Response to IR re: Safety data studies P204 and P306
23	June 26, 2025	Response to IR re: Vaccine effectiveness data in participants with at least one condition that puts them at high risk
24	June 27, 2025	Response to IR re: Safety data studies P204 and P306
26	June 30, 2025	Response to IR re: Safety data for study P204
27	July 1, 2025	Response to IR re: Safety data for study P204
28	July 7, 2025	Updated draft labeling
29	July 8, 2025	Updated draft labeling
30	July 9, 2025	Updated draft labeling
31	July 9, 2025	Updated draft labeling

Source: FDA-generated table from amendments to STN#125752/276. IR = information request

The information submitted with the above listed amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

5.3 Overview of Clinical Studies

Clinical studies submitted to support the safety and effectiveness of Spikevax are summarized in Table 3 below. In these studies, participants received a single dose, a 2-dose series one month apart, and an additional single dose referred to as a "booster dose."

Table 3. Clinical Trials Submitted in Support of Effectiveness and Safety Determinations of Spikevax in Infants and Children 6 Months Through 11 Years of Age

Study Number Blinding Purpose	Participants Vaccinated (N)	COVID-19 Vaccination Status	Formulation	Number of Doses	Dose Levels Assessed
P204 **NCT04796896**	--	--	--	--	--
P204 *Part 1* Open Label* Dose-finding, Safety	1,125 Total <u>6y - 11y</u> 371 (100µg) 380 (50µg) <u>2y - 5y</u> 155 (50µg) 69 (25µg) <u>6m - 23m</u> 150 (25µg)	Naïve	mRNA-1273 [a]	2 doses	100 µg 50 µg 25 µg
P204 *Part 2* Blinded, Randomized, Placebo-controlled Safety, Immunogenicity, Efficacy (descriptive)	8,032 in Blinded Phase <u>6y - 11y</u> 3007 (50µg) <u>2y - 5y</u> 3031 (25µg) <u>6m - 23m</u> 1994 (25µg)	Naïve	mRNA-1273 [a]	2 doses	50 µg 25 µg
P204 *Part 2* Open Label/ Cross-Over* Safety, Immunogenicity, Efficacy (descriptive)	1,785 in Cross-Over Phase <u>6y - 11y</u> 701 (50µg) <u>2y - 5y</u> 640 (25µg) <u>6m - 23m</u> 444 (25µg)	Naïve	mRNA-1273 [a]	2 doses	50 µg 25 µg

Study Number Blinding Purpose	Participants Vaccinated (N)	COVID-19 Vaccination Status	Formulation	Number of Doses	Dose Levels Assessed
P204 *Booster Part* Open Label Safety, Immunogenicity	5,770 Total <u>6y - 11 y</u> 2519 (25µg monovalent) 184 (25µg bivalent) <u>6m - 5 y</u> 301 (10µg monovalent) 2766 (10µg bivalent)	Experienced	mRNA-1273[a] mRNA-1273.214 [b]	Single dose	25 µg 10 µg
P306 NCT05436834	--	--	--	--	--
P306 *Part 1* Open Label* Safety, Immunogenicity	391 Total <u>2y - 5y</u> 261 (25µg) <u>6m - 23m</u> 130 (25µg)	Naïve	mRNA-1273.214 [b]	2 doses	25 µg
P306 *Part 2* Open Label Safety, Immunogenicity	539 Total <u>2y - 5y</u> 425 (10µg) <u>6m - 23m</u> 114 (10µg)	Experienced	mRNA-1273.214 [b]	Single dose	10 µg
P306 *Part 4* Open Label Safety, Immunogenicity	598 Total <u>2y - 4y</u> 199 (25µg) <u>6m - 23m</u> 399 (25µg)	Naïve	mRNA-1273.815 [c]	Single dose (2y – 4y) 2 doses (6m – 23m)	25 µg

Source: STN#125752/276. FDA-generated table
Abbreviations: m = month; N= total number of vaccinated participants; NCT = national clinical trial; y = year
* Data from participants in these study parts included only MAAEs, AESIs, SAEs, deaths, and AEs leading to discontinuation..
a. mRNA-1273= monovalent, original strain (Wuhan-Hu-1)
b. mRNA-1273.214 = bivalent, 1:1 ratio of original strain and Omicron BA.1.529
c. mRNA- 1273.815 = monovalent, Omicron XBB.1.5

Table 4 summarizes the vaccine composition, study dates, and SARS-CoV-2 variants that were predominant at the time of the study.

Table 4. Study Dates, Predominant SARS-CoV-2 Variant and Vaccine Characteristics for Studies Submitted with sBLA125752/276

Study NCT# ***Part*** **Design** **Doses**	**Age,[a]** **Vaccine Status,[b]** **and Study Period**	**Vaccine** **Valency** **Strain(s)**	**Prevalent circulating** **SARS-CoV-2 variant[c]**
P204 **NCT04796896**	-	-	-
Part 1 Open label 2 doses	6m-11y Naïve 3/2021 - 11/2021	mRNA-1273 monovalent Original (Wuhan-Hu-1)	Alpha (B.1.1.7) Delta (B.1.617.2)
Part 2 Blinded 2 doses	6y-11y Naïve 8/2021 - 11/2021	mRNA-1273 monovalent Original (Wuhan-Hu-1)	Delta (B.1.617.2)
Part 2 Blinded 2 doses	6m-5y Naïve 10/2021 - 6/2022	mRNA-1273 monovalent Original (Wuhan-Hu-1)	Delta (B.1.617.2) Omicron (B.1.1.529, BA.1.1, BA.2, BA.5)
Part 2 Open label[c] 2 doses	6m-11y Naïve Q4 2021 to 2022	mRNA-1273 monovalent Original (Wuhan-Hu-1)	Delta (B.1.617.2) Omicron (B.1.1.529, BA.1.1, BA.2, BA.5)
Booster Part Open label Single dose	6m-11y Experienced[d] 3/2022 to 3/2024	mRNA-1273 monovalent Original (Wuhan-Hu-1) mRNA-1273.214 bivalent Original + BA.1	Omicron (BA.1.1, BA.2, BA.5, XBB, JN.1)
P306 **NCT05436834**	-	-	-
Part 1 Open label 2 doses	6m-5y Naïve 6/2022 to 6/2024	mRNA-1273.214 bivalent Original + BA.1	Omicron (BA.5, XBB, JN.1)
Part 2 Open label Single dose	6m-5y Experienced[e] 6/2022 to 3/2023	mRNA-1273.214 bivalent Original + BA.1	Omicron (BA.5, XBB)
Part 4 Open label Single dose	2y – 4y Naïve 3/2024 to 10/2024	mRNA-1273.815 monovalent XBB.1.5	Omicron JN.1, KP.3.1.1)

Study NCT# ***Part*** **Design** **Doses**	**Age,[a]** **Vaccine Status,[b]** **and Study Period**	**Vaccine** **Valency** **Strain(s)**	**Prevalent circulating** **SARS-CoV-2 variant[c]**
Part 4 Open label 2 doses	6m – 23m Naïve 3/2024 to 1/2025	mRNA-1273.815 monovalent XBB.1.5	Omicron (JN.1, KP.3.1.1, XEC)

Source: FDA generated table from STN#125752/276, Study P204 and P306 CSRs and Response to IR sent June 5, 2025
Abbreviations: # = number, COVID-19 = , SARS-CoV-2 = , m = month, NCT = national clinical trial; Q4 = fourth quarter; y = year
a. Age of participants at time of enrollment in months (m), years (y)
b. COVID-19 vaccine status at study enrollment. Vaccine-experienced participants had previously received Spikevax.
c. SARS-CoV-2 variant predominantly circulating
c. P204 blinded phase was followed by an open label cross-over phase in which placebo recipients in the blinded phase received a 2-dose series of mRNA-1273
d. Participants had previously received 2 doses of mRNA-1273 in Study P204 Part 1 or Part 2
e. Participants had previously received 2 doses of mRNA-1273 in P204

Clinical Reviewer Comment:
During the conduct of Study P204 Part 2 (blinded phase), there was a mismatch between vaccine antigen (Original Wuhan-Hu-1 strain) and predominant circulating SARS-CoV-2 variant (Delta and Omicron strains) in the younger pediatric age cohorts (6m through 23m and 2y through 5y) due to rapid emergence of variants during the pandemic (see section 6.1.11.1).

5.4 Literature Reviewed

Centers for Disease Control and Prevention (CDC). 2025a. Underlying Medical Conditions Associated with Higher Risk for Severe COVID 19: Information for Healthcare Professionals. Website updated 2/6/2025. Accessed 6/30/2025. https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

Centers for Disease Control and Prevention (CDC). 2025b. Post-COVID Conditions: Overview for Healthcare Providers. Website updated 2/3/2025. Accessed 6/30/2025. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html.

Centers for Disease Control and Prevention (CDC). 2025c. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Website updated 6/4/2025. Accessed 6/30/2025. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance.

Centers for Disease Control and Prevention (CDC). 2025d. COVID Data Tracker [database on the Internet]. Atlanta, GA: U.S. Department of Health and Human Services. Accessed 6/30/2025. https://covid.cdc.gov/covid-data-tracker.

Centers for Disease Control and Prevention (CDC). 2025e. Current Epidemiology of COVID-19. Presentation for the Advisory Committee on Immunization Practices (ACIP). June 25, 2025. https://www.cdc.gov/acip/downloads/slides-2025-06-25-26/04-Meyer-COVID-508.pdf

Centers for Disease Control and Prevention (CDC). 2025f. Summary of Variant Surveillance. Accessed 6/30/2025. https://covid.cdc.gov/covid-data-tracker/#variant-summary.

Centers for Disease Control and Prevention (CDC). 2023. 2022-2023 Nationwide COVID-19 Infection- and Vaccination-Induced Antibody Seroprevalence (Blood donations). Accessed 6/30/2025. CDC COVID Data Tracker: 2022-2023 Nationwide Blood Donor Seroprevalence https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022

Centers for Disease Control and Prevention (CDC). 2022. Nationwide Commercial Lab Pediatric Antibody Seroprevalence. Accessed 6/30/2025. https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence.

Hafsi W, Badri T. Erythema Multiforme. [Updated 2024 Oct 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470259

Havers, FP. (2024) COVID-19-Associated Hospitalizations Among Children and Adults COVID-NET. ACIP Meeting June 2024. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/02-COVID-Havers-508.pdf.

Ma KC, Shirk P, Lambrou AS, et al. Genomic Surveillance for SARS-CoV-2 Variants: Circulation of Omicron Lineages — United States, January 2022–May 2023. MMWR Morb Mortal Wkly Rep 2023;72:651–656. doi: 10.15585/mmwr.mm7224a2.

Oaks RJ, Cindass R. Silver Sulfadiazine. [Updated 2023 Jan 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556054/

World Health Organization. (2025) Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed May 12, 2025.

6. Discussion of Individual Studies/Clinical Trials

Safety and immunogenicity data from Studies mRNA-1273-P204 (P204) and mRNA-1273-P306 (P306) supported the safety and effectiveness of Spikevax in children 6 months through 11 years of age.

6.1 Study mRNA-1273-P204

NCT04796896: "A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age"

Study Overview: P204 was a combined Phase 2 and Phase 3 study designed to evaluate the safety and effectiveness of a 2-dose series of the original monovalent formulation of Spikevax (hereafter referred to as mRNA-1273) and a single dose (3rd dose) of either mRNA-1273 or mRNA-1273.214, a bivalent vaccine (Original + Omicron B.1.1.539 [also referred to as the BA.1 sublineage]), in children 6 months through 11 years of age. The study enrolled a total of 11,825 participants across Part 1 and Part 2. It was conducted at 88 centers in the U.S. and Canada. The study was conducted from March 15, 2021, up to database lock on May 17, 2024.

6.1.1 Objectives

Clinical Reviewer Comment:
Only key study objectives/endpoints relevant to the analyses to support the proposed USPI dosing/administration regimen with this sBLA are reviewed. Immunogenicity and safety objectives have been presented together for 2-dose series in vaccine-naïve individuals and single dose in vaccine-experienced individuals, respectively.

6.1.1.1 Immunogenicity Objectives

Primary Objectives/Endpoints:
All study endpoints were evaluated by age group: 6 -11 years, 2-5 years, and 6-23 months.

Vaccine-naïve, 6 months – 11 years, mRNA-1273 (Parts 1 and 2)
To infer the efficacy of mRNA-1273 (25, 50, and 100 µg) administered as 2 doses 28 days apart based on immunogenicity assessed by neutralizing antibody (nAb) responses in 3 age groups

- *Hypothesis #1:* Noninferiority of nAb in terms of geometric mean titer or concentration ratio (GMT or GMC ratio) against the D614G strain 28 days after 2 doses of mRNA-1273 in COVID-19 vaccine-naïve infants and children in Study P204 Part 2 compared with those obtained 28 days after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants (18-25 years of age) in Study P301.
    - **Success criterion**: The GMT or GMC ratio (infants and children post-Dose 2/young adults post-Dose 2) is noninferior if the LB of the 2-sided 95% CI is >0.667 and the point estimate is ≥0.8.

- *Hypothesis #2*: Noninferiority of nAb in terms of seroresponse rates (SRR) against the D614G strain 28 days after 2 doses of mRNA-1273 in COVID-19 vaccine-naïve infants and children in Study P204 Part 2 compared with those obtained 28 days after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants in Study P301.
    - **Success criterion**: The SRR[1] is noninferior if the LB of the 2-sided 95% CI for difference in SRR percentage (infants and children post-Dose 2 - young adults post-Dose 2) is >-10% and the point estimate is ≥-5%.

Vaccine-experienced, 6 months – 11 years, mRNA-1273 (Booster Part) To infer effectiveness of the mRNA-1273 booster dose by establishing noninferiority of nAb response after the booster dose compared with after 2 doses in adult mRNA-1273 recipients in the clinical endpoint efficacy trial (Study P301)

- *Hypothesis #3:* The geometric mean titer or concentration value of post-booster nAb in Study P204 compared with after 2 doses (post-Dose 2) in adults (18-25 years) in Study P301
    - **Success criterion**: The GMT or GMC ratio (infants and children post-Dose 2/young adults post-Dose 2) is noninferior if the LB of the 2-sided 95% CI >0.667 and the point estimate is ≥0.8.

- *Hypothesis #4:* The seroresponse rate of post-booster from baseline (pre-Dose 1 of 2-dose series) compared with after 2 doses (post-Dose 2) from baseline (pre-Dose 1 of 2-dose series) in the adults (18-25 years) in Study P301.

[1] Seroresponse is defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ

- **Success criterion**: The SRR[1] percentage is noninferior if the LB of the 2-sided 95% CI (infants and children post-dose 2 - young adults post-dose 2) is >-10% and the SRR percentage point estimate is ≥-5%.

Clinical Reviewer Comment:
Immunogenicity objectives associated with the mRNA-1273.214 when administered as single dose (booster) in vaccine experienced individuals were not included in the study design for this part of Study P204.

6.1.1.2. Safety Objectives

Primary Objectives: To evaluate the safety and reactogenicity of:

- 2 doses of mRNA-1273 administered 28 days apart in 3 age groups (6 months through 23 months, 2 years through 5 years, 6 years through 11 years) at two dose levels (25µg: 6 months – 5 years and 50µg: 6 years – 11 years).
- A single dose of mRNA-1273 (25µg, 6 years through 11 years) or mRNA-1273.214 (10µg, 6 months through 5 years) following completion of a 2-dose series of mRNA-1273

Endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection.
- Unsolicited adverse events (AEs) through 28 days after each injection.
- Medically attended adverse events (MAAEs) through the entire study period.
- Serious adverse events (SAEs) through the entire study period.
- Adverse events of special interest (AESIs), including multisystem inflammatory syndrome in children (MIS-C) and myocarditis and/or pericarditis, through the entire study period.

6.1.2 Design Overview

Study P204 was a Phase 2/3, three-part study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in healthy infants and children, in 3 age groups (6 through 11 years, 2 through 5 years, and 6 through 23 months). An optional booster phase was also included in the study design.

Part 1 of the study was an open-label part which evaluated the safety and reactogenicity of 2 doses of mRNA-1273 administered 28 days apart. The dose levels varied by age: 6 years through 11 years: 50 µg or 100 µg; 2 years through 5 years: 25 µg or 50 µg; and 6 months through 23 months: 25 µg. The study was designed with a dose escalation and age de-escalation strategy to select the dose for each age group. Each age group began dosing with the lowest dose planned for that group and dose-escalation/age de-escalation progressed only after confirming the safety of a prior dose level or age group. Dose levels that were less tolerated in older age groups were not administered to any younger age groups.

Clinical Reviewer Comment:
Selection of the dose levels for evaluation was based on data from Part 1 of Study P204. The dose levels selected for evaluation in Part 2 of the study consisted of a 50 µg dose for the 6 through 11 years age group and a 25 µg dose for the 6 months through 5 years age group. Dose selection was based on the Applicant's review of safety and immunogenicity data in a total of 1,125 participants enrolled in Part 1.

Part 2 of the study was a randomized, observer-blind, placebo-controlled phase that evaluated the effectiveness of a 2-dose series of mRNA-1273 (50µg each) in children 6 through 11 years and a 2-dose series at 25 µg each in infants and children 6 months through 5 years. In this phase of the study, the availability of any COVID-19 vaccine authorized under EUA triggered eligibility for unblinding and optional crossover vaccination for placebo recipients to receive mRNA-1273 in any age group. If a placebo recipient elected to receive a non-study COVID-19 vaccine, they were withdrawn from the study.

Following Parts 1 and 2, unblinded participants were offered an additional single dose of either mRNA-1273 or a bivalent Original + Omicron BA.1 formulation of the vaccine (mRNA-1273.214) in an optional Booster phase of the study.

Part 3 of the study was an open-label, alternative dosage/regimen (3-dose series, 25 µg dosage) assessment in approximately 300 participants 6 through 11 years of age that was not pursued in mRNA-1273 clinical development plan and does not reflect the proposed USPI dosage/administration for this age cohort.

6.1.3 Population

Study P204 enrolled children 6 months through 11 years of age who were in good health without any protocol-specified exclusionary pre-existing conditions that could affect study endpoint assessment or compromise participant safety. Stable chronic medical conditions were allowed if well controlled. For children 6 months to <12 months, there was an additional inclusion criterion of full-term birth (≥37 weeks gestation) with a minimum birth weight of 2.5 kg.

6.1.4 Study Treatments or Agents Mandated by the Protocol

P204 dosage levels and formulations varied by participant age and study part:

1. mRNA-1273 (10, 25, 50, and 100 µg): a lipid nanoparticle (LNP) dispersion of an mRNA that encodes for the prefusion stabilized spike protein (nucleoside sequence modified to introduce 2 proline residues [S-2P]) of SARS-CoV-2 (Original [Wuhan-Hu-1] strain) supplied as a sterile liquid for injection
    - 2-dose series in vaccine-naïve individuals (Parts 1 and 2)
        - 6 through 11 years: 0.5 mL containing 50 µg or 100 µg mRNA-1273
        - 2 through 5 years: 0.5 mL containing 25 µg or 50 µg mRNA-1273
        - 6 through 23 months: 0.5 mL containing 25 µg mRNA-1273
    - Single dose in vaccine-experienced individuals
        - 6 through 11 years: 0.5 mL containing 25 µg mRNA-1273
        - 6 months through 5 years: 0.5 mL containing 10 µg or 25 µg mRNA-1273
    - Lots:
        - 7006121001, 7006121002, 7006121003, 7008121001, 7008121002, 7010222002, and 7010222004

2. mRNA-1273.214 (10 and 25 µg): a bivalent vaccine that contains mRNA encoding for the S-2P of the SARS-CoV-2 Omicron variant BA.1 and the SARS-CoV-2 Original strain, co-formulated at a 1:1 ratio and encapsulated in LNPs, supplied as a sterile liquid for injection
    - Single dose in vaccine-experienced individuals

        - 6 through 11 years: 0.2 or 0.25 mL containing 25 µg mRNA-1273.214
        - 6 months through 5 years: 0.2 or 0.25 mL containing 10 µg or 25 µg mRNA-1273.214
    - Lots:
        - 8523300104, 8523300105, 8523300106, 8523300108, 8523800101, 7016322001

3. Placebo: 0.5 mL of 0.9% sodium chloride (2-dose series, Part 2 blinded part only)
    - Lots: 10097DK, 14251DK, 13088DK, 13091DK, 14001DK, 15110DK, 21077DK, 21101DK, 21102DK, EE7938, EG1869, EK9712, and EK9713

6.1.5 Directions for Use

Intramuscular injection into the deltoid muscle, or anterolateral thigh.

6.1.6 Sites and Centers

Study P204 was conducted in 88 study sites in the U.S. and Canada.

6.1.7 Surveillance/Monitoring

Study oversight included Institutional Review Board/Independent Ethics Committee review and approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents.

An Internal Safety Team (IST) reviewed safety data throughout Part 1 and recommended whether dose-escalation and age de-escalation were appropriate. The IST was also responsible for escalating any safety concerns to the Data Safety Monitoring Board (DSMB).

A DSMB composed of external independent consultants with relevant expertise reviewed cumulative Part 1 safety data at the selected dose level before enrollment began in Part 2 and assessed safety throughout Part 2 of the study. The DSMB held regular meetings to evaluate the safety of Part 2 of the study and had the authority to convene on an ad hoc basis if safety concerns developed. Additionally, the DSMB reviewed all available unblinded study data (as applicable) to help adjudicate any potential safety concerns.

All potential cases of myocarditis and pericarditis, as identified by the investigator or Applicant, were to be reviewed by an independent Cardiac Event Adjudication Committee (CEAC) to determine whether the case met the CDC criteria (Appendix C) for confirmed or probable myocarditis or pericarditis. The independent CEAC was composed of composed of at least three physicians (inclusive of the Chair) with expertise in pediatric and adult cardiology and were independent of the Applicant.

Safety Assessments
2-dose series in vaccine-naïve (all ages); single dose in vaccine-experienced (6 years – 11 years)

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following each vaccination (starting on the day of vaccination and followed by 6

subsequent days). Solicited ARs were recorded using electronic diaries (e-diaries) according to age group as follows:

- 37 months to <12 years
  - Solicited local ARs: injection site pain; injection site erythema/redness; injection site swelling/induration (hardness); and axillary (underarm) swelling or tenderness ipsilateral to the side of injection
  - Solicited systemic ARs: headache; fatigue; myalgia (muscle aches all over body); arthralgia (joint aches in several joints); nausea/vomiting; chills; and fever
- 6 months to ≤36 months
  - Solicited local ARs: injection site pain/tenderness; injection site erythema (redness); injection site swelling/induration (hardness); and groin or underarm swelling or tenderness ipsilateral to the side of injection
  - Solicited systemic ARs: fever, irritability/crying; sleepiness; and loss of appetite

2-dose series in vaccine-naïve (all ages); single dose in vaccine-experienced (all ages)

1) Unsolicited adverse events (AEs) observed or reported during the 28 days following each vaccination (starting the day of vaccination and followed by 27 subsequent days).
2) AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
3) Medically-attended adverse events (MAAEs) from first dose on Day 1 through the entire study period.
4) Serious adverse events (SAEs) from first dose on Day 1 through the entire study period.
5) Adverse events of special interest (AESIs) through the entire study period.
   a. Protocol-specified AESIs included the following medical concepts that may be related to COVID-19: anosmia/ageusia; subacute thyroiditis; acute pancreatitis; appendicitis; rhabdomyolysis; acute respiratory distress syndrome (ARDS); coagulation disorders; acute cardiovascular injury; acute kidney injury; acute liver injury; dermatologic findings; multisystem inflammatory disorders; thrombocytopenia; acute aseptic arthritis; new onset of or worsening of neurologic disease; anaphylaxis; and other syndromes (i.e., fibromyalgia, postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome, myalgic encephalomyelitis, post-viral fatigue syndrome, and myasthenia gravis)
6) Assessments for SARS-CoV-2 infection from Day 1 through study completion
7) Vital sign measurements.
8) Physical examination findings.
9) Details of all pregnancies in female participants from the time of Dose 1 until the end of their participation in the study.

Parents/legal authorized representatives (LARs) recorded solicited ARs in the e-diary daily for 7 days following each vaccination. The e-diary was also used every 4 weeks, starting at Day 71 through Day 183 and at Day 223 through Day 363 for Parts 1 and 2 to capture unsolicited AEs, MAAEs, SAEs, AESI, or AEs leading to withdrawal based on prompts to complete an e-diary questionnaire. A safety phone call was triggered for any relevant safety event identified in an e-diary. Alternating with e-diary completion, scripted safety calls to facilitate the collection of relevant safety information were conducted every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377.

All AEs and SAEs were treated as medically appropriate and followed until resolution, stabilization, the event was otherwise explained, or the participant was lost to follow-up.

Vaccine Effectiveness Assessments

2-dose series in vaccine-naïve (6 months – 11 years), mRNA-1273 (Part 2)

Vaccine effectiveness was based on serum antibody responses of P204 participants 6 months to <12 years of age on Day 57 compared with the serum antibody responses from young adult participants 18 years through 25 years of age from study P301, in whom clinical efficacy was demonstrated.

Blood samples were collected from a subset of participants (Immunogenicity Subset) for immunogenicity assessments at baseline on Day 1 (prior to randomization and first dose), Day 57 (28 days post-Dose 2), Day 209 (6 months post-Dose 2), and Day 394 (12 months post-Dose 2). Participants in each age group were assigned to one of five phlebotomy cohorts to provide blood specimens for protocol-specified immunogenicity assessments. Participants in three of these cohorts provided blood samples for vaccine immunogenicity three timepoints at Day 1, Day 57, and one of the following timepoints: Day 29 (28 days post-Dose 1/pre-Dose 2), Day 209, or Day 394. Blood samples from participants in the two other phlebotomy cohorts were collected for storage and potential future biomarker analysis or for exploratory serology and cell-mediated immunity (CMI).

Immunogenicity assessments measured the following:

1. Serum neutralizing antibody (nAb) levels against SARS-CoV-2 (D614G) as measured by a validated pseudovirus neutralization assay (PsVNA) conducted at Duke and reported as 50% inhibitory dose (ID50) neutralization geometric mean titers (GMTs) (LLOQ = 18.5).
2. Serum nAb against SARS-CoV-2 (D614G) as measured by a validated PsVNA (VAC62) conducted at PPD Laboratories (PPD) and reported as geometric mean concentrations (GMCs) (LLOQ=10).
3. Serum antibodies directed against SARS-CoV-2 spike (S) protein receptor binding domain (RBD) and nucleocapsid (N) protein were measured using ligand-binding MesoScale Discovery (MSD) electrochemiluminescence (ECL) multiplex assay (b) (4) conducted at PPD.
4. Baseline SARS-CoV-2 status and SARS-CoV-2 infection were evaluated using a SARS-CoV-2 RT-PCR assay validated by (b) (4). Baseline SARS-CoV-2 status was also established using an in-vitro diagnostic assay, Elecsys anti-SARS-CoV-2 ECLIA assay, to detect anti-SARS-CoV-2 N-protein IgG antibodies validated by PPD.

Single dose, vaccine-experienced (6 months – 11 years) mRNA-1273 or mRNA-1273.214 (Booster phase)

Vaccine effectiveness was based on serum antibody responses of P204 participants 6 months to <12 years of age on Day 29 after the study dose of mRNA-1273 compared with the serum antibody responses from young adult participants 18 years through 25 years of age enrolled in a clinical endpoint efficacy trial (P301).

Participants from Part 1 and Part 2 who chose to receive an additional single dose (booster dose) provided a blood sample for immunogenicity and serostatus on Day 1 (day of vaccination), and a subgroup provided one additional blood sample at one of the following timepoints relative to single (booster) dose receipt: Day 29, Day 181, or Day 366.

Immunogenicity assessments measured the serum nAb levels against SARS-CoV-2 strain D614G as measured by validated PsVNAs (VAC62 [LLOQ = 10]) conducted at PPD, Inc. and reported as GMCs.

Efficacy Assessments:
Active surveillance for COVID-19 disease and SARS-CoV-2 infection were performed (see Appendix B for case definitions). COVID-19 surveillance was conducted for all Part 2 participants who received the blinded 2-dose series and who received a single dose following the 2-dose series.

COVID-19 Symptom Surveillance:
Weekly surveys queried about the presence of the COVID-19 symptoms listed in case definitions (described above). In the event that any symptom lasted at least 48 hours (with the exception of fever and/or respiratory symptoms) without an alternative diagnosis (not including other viruses that could represent co-infection), an illness visit was scheduled within 72 hours to collect a nasal swab for SARS-CoV-2. Convalescent visits, including blood sample collection, could be scheduled approximately one month later if the investigator had uncertainty about the initial diagnosis.

Scheduled COVID-19 Laboratory Testing:
Nasal swabs were also routinely collected pre-vaccination on Days 1 and 29 and at all subsequent study visits (Day 43, if applicable, Day 57, Day 209, and Day 394). During the booster phase, nasal swabs were collected on Study Day 1 (prior to vaccination), Day 29, and Day 181.

6.1.8 Endpoints and Criteria for Study Success

Refer to section 6.1.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Vaccine-naïve, 6 months – 11 years, 25 ug or 50 ug mRNA-1273 (Part 2)
The co-primary immunogenicity endpoints in P204 Part 2 compared the immune responses (as measured by nAb GMCs and SRRs against the D614G strain) in P204 participants at Day 57 (28 days after the second vaccination) with those in young adult (18– 25 years of age) participants in Study P301 at Day 57 (28 days after the second vaccination).

Hypothesis #1
An analysis of covariance (ANCOVA) model was used with the antibody level at Day 57 as the dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18-25 years of age] in Study P301) as the fixed variable for each pediatric age group. The GMTs or GMCs of the pediatric age group at Day 57 were estimated with the geometric least square mean (GLSM) from the model.

The ratio of GMTs or GMCs was estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI was provided to assess the difference in immune response between the pediatric age group (Study P204) compared with the young adults (18-25 years of age) in Study P301 at Day 57. For each pediatric age group, noninferiority was considered demonstrated if the lower bound of the 95% CI of the ratio of GMTs or GMCs was > 0.667 based on the noninferiority margin of 1.5 with a point estimate ≥ 0.8 (minimum threshold).

Hypothesis #2

Seroresponse was a composite definition at a participant level as a value change from baseline (pre-Dose 1 of 2-dose series) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ. The number and percentage of participants with seroresponse due to vaccination was provided with 2-sided 95% CI using the Clopper-Pearson method at Day 57. The seroresponse rate difference with 95% CI using the Miettinen-Nurminen (score) confidence limits at Day 57 was provided between children receiving mRNA-1273 in Study P204 and young adults 18 through 25 years of age receiving mRNA-1273 from Study P301. For each pediatric age group, the noninferiority of seroresponse rate was considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference was > -10% with a seroresponse rate difference point estimate ≥ -5%.

Vaccine-experienced, 6 months through *11 years, 25 ug mRNA-1273 (Booster phase)*
Hypothesis #3
An ANCOVA model, similar to that used in Part 2, was used to assess the difference in the nAb level at Day 29 in children receiving mRNA-1273 in the Booster phase and nAb level at Day 57 in young adults (18-25 years of age) who received a 2-dose series of mRNA-1273 in Study P301. The noninferiority of the nAb GMT or GMC in children was considered demonstrated if the lower bound of the 95% CI of the GMT or GMC ratio was > 0.667.

Hypothesis #4
Seroresponse was a composite definition at a participant level as a value change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ. The SRR difference with 95% CI (using Miettinen-Nurminen score method) comparing the SRR at Day 29 in children in Study P204 with the SRR at Day 57 (28 days after Dose 2) in adults (18-25 years of age) in Study P301 was computed. The noninferiority of SRR in children receiving an additional dose of mRNA-1273 following a 2-dose series was considered demonstrated if the lower bound of the 95% CI of the SRR percentage difference was > -10%.

Exploratory efficacy analyses (Part 2 and Booster phase)
Exploratory analyses of incidence rates of COVID-19, asymptomatic SARS-CoV-2 infection, and SARS-CoV-2 infection, irrespective of symptoms, were performed beginning 14 days after the 2nd study dose (see Appendix B for definitions). Surveillance ended October 2022.

Subgroup analyses
Subpopulation analyses of immunogenicity endpoints were conducted for Part 2 and the Booster phase based on sex (male, female), age group (6 Months to < 2 Years, 2 Years to < 6 Years, and 6 Years to < 12 Years), SARS-CoV-2 status at baseline (pre-Dose 1 and pre-Booster dose) race, ethnicity, and obesity (based on a threshold ≥ 95th%ile based on WHO reference data), as applicable.

Clinical Reviewer Comment:
For each age group in P204 (6 through *11 years, 2* through *5 years, and 6* through *23 months), subpopulation analyses by race and ethnicity were based on the following composite "race and ethnicity" definitions:*

- *White non-Hispanic – defined as White and non-Hispanic.*
- *Communities of Color – defined as all others whose race or ethnicity is not unknown, unreported, or missing.*

Safety analyses, except summaries of solicited adverse reactions (ARs), were based on the Safety Set, which consisted of all subjects who received a study dose in the respective part.

Summaries of solicited ARs were based on the Solicited Safety Set, which consisted of all subjects in the Safety Set who contributed any solicited AR data. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported any event.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Vaccine-naïve, 6 months – 11 years, 25 µg or 50 µg mRNA-1273 (Part 2)
The populations used for study analyses in Study P204 Part 2 are defined in Table 5. Immunogenicity analyses were conducted on the Per Protocol Immunogenicity Subset (PPIS). Safety analyses were conducted on the Safety Set except for summaries of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 5. Analysis Populations, Study P204 2-dose Series

Population	Description
Randomization Set	All participants who were randomized in Part 2 of the study, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least 1 dose of a study product in Part 2 of the study.
Safety Set	All randomly assigned participants who received a dose of any study intervention in Part 2 of the study.
Solicited Safety Set	All participants in the Safety Set who contributed any solicited AR data (i.e., had at least one post-dose solicited safety assessment).
Per Protocol Set for Efficacy (PPSE)	The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who received planned doses of IP per schedule, complied with the 2nd dose injection timing, had no major protocol deviations that impact key or critical efficacy data, had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline.
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing who had baseline SARS-CoV-2 status available and at least one post-vaccination antibody assessment for the analysis endpoint.
Per Protocol (PP) Set	All participants in the FAS who received planned doses of the study products per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data. Participants who were RT-PCR positive or seropositive at baseline were excluded from the PP Set.

Population	Description
Per Protocol Immunogenicity Subset (PPIS)	All participants in the Immunogenicity Subset who met all the following criteria: • Received planned dose per schedule. • Complied with the immunogenicity testing schedule. • Had baseline and Day 57 antibody assessment for analysis endpoint. • Had no major protocol deviations that impacted key or critical data. • Were seronegative for SARS-CoV-2 at baseline. • Were negative for HIV. Primary analysis population for immunogenicity endpoints

Source: FDA-generated table based on Clinical Protocol mRNA-1273-P204 (dated, August 4, 2022), Section 8.4, Table 10
Abbreviations: RT-PCR = reverse transcription-polymerase chain reaction; IP = investigational product
*both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid

Vaccine-experienced, 6 months – 11 years, 10 ug or 25 µg mRNA-1273 (Booster phase)
The populations used for study analyses are defined in Table 6 for the single dose in part of the study evaluating a single dose in vaccine experienced children. Immunogenicity analyses were conducted on the Per Protocol Immunogenicity Subset (PPIS). Safety analyses were conducted on the Safety Set except for summaries of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 6. Analysis Populations, Study P204, Additional (Booster) Dose in Vaccine Experienced

Population	Description
Full Analysis Set (FAS)	All participants who received at least one booster/third dose
Safety Set	All randomly assigned participants who received a dose of any study intervention in Part 2 of the study.
Solicited Safety Set	All participants in the Safety Set who contributed any solicited AR data (i.e., had at least one post-dose solicited safety assessment).
Immunogenicity Subset	A subset of participants in the FAS (Booster/Third Dose Analysis) who received mRNA- 1273 Booster/Third dose and had baseline (pre-Dose 1 of mRNA-1273) SARS-CoV-2 status available, and had at least one post-booster/post-third antibody assessment for the analysis endpoint
Per-protocol (PP) Immunogenicity Subset (Booster/Third Dose Analysis)	Received 2 doses of mRNA-1273 vaccination in Part 1 open-label phase or Part 2 blinded phase per schedule, received booster dose (BD) in Booster Dose Analysis, had a negative SAS-CoV-2 status* at baseline (pre-Dose 1 of mRNA-1273, had BD-Day 29 Ab assessment for the analysis endpoint, had no major protocol deviations that impact key or critical data, and did not receive off-study COVID-19 vaccination prior to BD-Day 29 visit. If participants had a diagnosis of HIV, they were not receiving highly active antiretroviral therapy (HAART).

Population	Description
Per-protocol (PP) Immunogenicity Subset - Pre-booster SARS-CoV-2 Negative (Booster Dose Analysis)	Participants who were in the PP Immunogenicity Subset (Booster Dose Analysis), and are pre-booster SARS-CoV-2 negative* Primary analysis population for immunogenicity endpoints

Source: FDA-generated table based on Study mRNA-1273-P204 Statisitical Analysis Plan V. 5.0 (dated, July 28, 2023), Section 5
Abbreviations: RT-PCR = reverse transcription-polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
*both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid

6.1.10.1.1 Demographics

Vaccine-naïve, 6 months through *11 years, 25 µg or 50 µg mRNA-1273 (Part 2)*
The Safety Set for this study part included a total of 4,002 participants 6 years through 11 years of age, 4038 participants 2 years through 5 years of age, and 2,660 participants 6 months through 23 months of age. Demographic characteristics for the different age cohorts are shown in Table 7.

Table 7. Demographic and Baseline Characteristics, Vaccine Naïve, 6 months – 11 years of Age, 2-Dose Series, mRNA-1273, Safety Set

Characteristic	6y - 11y, vaccine-naïve mRNA-1273 (50 µg) 2 doses N=3007	6y - 11y, vaccine-naïve Placebo 2 doses N=995	2y - 5y, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=3031	2y - 5y, vaccine-naïve Placebo 2 doses N=1007	6m – 23m, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=1994	6m – 23m, vaccine-naïve Placebo 2 doses N=666
Sex, n (%)	--	--	--	--	--	--
Female	1453 (48.3)	514 (51.7)	1488 (49.1)	497 (49.4)	981 (49.2)	340 (51.1)
Male	1554 (51.7)	481 (48.3)	1543 (50.9)	510 (50.6)	1013 (50.8)	326 (48.9)
Age, years[a]	-	-	-	-	-	-
Median age	8.0y	9.0y	3.0y	3.0y	-	-
Min, Max	6y, 11y	6y, 11y	1y, 5y	1y, 5y	-	-
Age, months[a,b]	-	-	-	-	-	-
Median age	-	-	-	-	16.0m	17.0m
Min, Max	-	-	-	-	6m, 51m	6m, 23m
Race, n (%)	--	--	--	--	--	--
American Indian or Alaska Native	14 (0.5)	3 (0.3)	11 (0.4)	3 (0.3)	7 (0.4)	0
Asian	296 (9.8)	100 (10.1)	191 (6.3)	51 (5.1)	94 (4.7)	38 (5.7)
Black	310 (10.3)	93 (9.3)	142 (4.7)	38 (3.8)	62 (3.1)	18 (2.7)
Native Hawaiian or Other Pacific Islander	4 (0.1)	0	5 (0.2)	3 (0.3)	0	0
White	1958 (65.1)	668 (67.1)	2299 (75.8)	792 (78.6)	1568 (78.6)	524 (78.7)
Multiracial	330 (11.0)	98 (9.8)	323 (10.7)	100 (9.9)	215 (10.8)	76 (11.4)
Other	62 (2.1)	22 (2.2)	43 (1.4)	16 (1.6)	33 (1.7)	7 (1.1)
Unknown	10 (0.3)	1 (0.1)	4 (0.1)	0	5 (0.3)	1 (0.2)
Not reported	23 (0.8)	10 (0.1)	13 (0.4)	4 (0.4)	10 (0.5)	2 (0.3)
Ethnicity, n (%)	--	--	--	--	--	--

Characteristic	6y - 11y, vaccine-naïve mRNA-1273 (50 µg) 2 doses N=3007	6y - 11y, vaccine-naïve Placebo 2 doses N=995	2y - 5y, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=3031	2y - 5y, vaccine-naïve Placebo 2 doses N=1007	6m – 23m, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=1994	6m – 23m, vaccine-naïve Placebo 2 doses N=666
Hispanic or Latino	560 (18.6)	181 (18.2)	429 (14.2)	142 (14.1)	256 (12.8)	94 (14.1)
Not Hispanic or Latino	2419 (80.4)	804 (80.8)	2584 (85.3)	856 (85.0)	1719 (86.2)	565 (84.8)
Unknown	7 (0.2)	5 (0.5)	5 (0.2)	1 (<0.1)	17 (0.9)	1 (0.2)
Not reported	21 (0.7)	5 (0.5)	13 (0.4)	8 (0.8)	2 (0.1)	6 (0.9)
Country, n (%)	--	--	--	--	--	
USA	2977 (99.0)	985 (99.0)	2866 (94.6)	952 (94.5)	1880 (94.3)	628 (94.3)
Canada	30 (1.0)	10 (1.0)	165 (5.4)	55 (5.5)	114 (5.7)	38 (5.7)
Obesity[c], n (%)	--	--	--	--	--	
Obesity	606 (20.2)	195 (19.6)	326 (10.8)	107 (10.6)	416 (20.9)	135 (20.3)
Non-Obesity	2401 (79.8)	800 (80.4)	2703 (89.2)	899 (89.3)	1576 (79.0)	530 (79.6)
Missing	0	0	2 (<0.1)	1 (<0.1)	2 (0.1)	1 (0.2)
Baseline SARS-CoV-2 Status[d], n (%)	-	-	-	-	-	-
Negative	2710 (90.1)	884 (88.8)	2697 (89.0)	899 (89.3)	1769 (88.7)	593 (89.0)
Positive	257 (8.5)	87 (8.7)	267 (8.8)	82 (8.1)	133 (6.7)	47 (7.1)
Missing	40 (1.3)	24 (2.4)	67 (2.2)	26 (2.6)	92 (4.6)	26 (3.9)

Source: Adapted from STN#125752/276 mRNA-1273-P204 Final CSR Primary Series (6 to 11 years) Table 14.1.3.2 and Table 14.1.3.11, mRNA-1273-P204 Final CSR Primary Series (2 to 5 years) Table 14.1.3.2 and Table 14.1.3.11., mRNA-1273-P204 Final CSR Primary Series (6 to 23 months) Table 14.1.3.2 and Table 14.1.3.11.

Abbreviations: CSR= clinical study report; m= month; Max=maximum; Min=minimum; n= number of participants with demographic characteristic. N= number of participants in the Safety Set; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation; WHO=World Health Organization; y= year

Note: Data presented for blinded phase only in P204 Part 2. The Safety Set consists of all enrolled participants who received at least 1 study dose. Percentages were based on the number of participants in the Safety Set.

a. Age at study enrollment
b. Age in months is summarized for ≥6 months and <2 years group only.
c. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.
d. Baseline SARS-CoV-2 Status: Positive was defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody (bAb) specific to SARS-CoV-2 nucleocapsid on or before Day 1. Negative was defined as a negative RT-PCR test for SARS-CoV-2, and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Vaccine-experienced, 6 months – 11 years, 10 ug or 25 ug mRNA-1273 and 25 ug mRNA-1273.214 (Booster phase)

The Safety Set for this study part included a total of 2,519 participants 6 years through 11 years of age who received a single (3rd) dose of mRNA-1273 and 2,799 participants 6 months through 5 years of age who received a single (3rd) dose of mRNA-1273.214.

Clinical Reviewer Comment:

The vaccine formulation administered in this part of the study was changed from mRNA-1273 to mRNA-1273.214 to reflect the formulation authorized under EUA at the time of study conduct. Enrollment in this study part first began with the older age group (6 through 11-year-olds); participants in this older age group received mRNA-1273, while most participants in the younger age group (6 months through 5-year-olds) received mRNA-1273.214 (N=301 participants in the younger age group received mRNA-1273).

Demographic characteristics for these cohorts are shown in Table 8.

Table 8. Demographic and Baseline Characteristics, Vaccine Experienced, 6 months – 11 years, Single Dose, mRNA-1273 or mRNA-1273.214, Safety Set

Characteristic	6y - 11y, vaccine-experienced mRNA-1273 (25 µg) Single Dose N=2519	6m - 5y, vaccine-experienced mRNA-1273.214 (10 µg) Single Dose N=2766
Sex, n (%)	--	--
Female	1189 (47.2)	1361 (49.2)
Male	1330 (52.8)	1405 (50.8)
Age, years[a]	--	--
Median age	10y	3y
Min, Max [b]	7y, 13y	1y, 7y
Age, months[a,b,c]	-	-
Median age	-	39 m
Min, Max[c]	-	11m, 86m
Race, n (%)	--	--
American Indian or Alaska Native	11 (0.4)	11 (0.4)
Asian	203 (8.1)	124 (4.5)
Black	279 (11.1)	125 (4.5)
Native Hawaiian or Other Pacific Islander	4 (0.2)	2 (<0.1)
White	1657 (65.8)	2131 (77.0)
Multiracial	291 (11.6)	329 (11.9)
Other	49 (1.9)	30 (1.1)
Unknown	4 (0.2)	5 (0.2)
Not reported	21 (0.8)	9 (0.3)
Ethnicity, n (%)	--	--
Hispanic or Latino	425 (16.9)	346 (12.5)
Not Hispanic or Latino	2072 (82.3)	2405 (86.9)
Unknown	7 (0.3)	2 (<0.1)
Not reported	15 (0.6)	13 (0.5)
Country	--	--
USA	2513 (99.8)	2624 (94.9)
Canada	6 (0.2)	142 (5.1)
Obesity[d], n (%)	--	--
Obesity	514 (20.4)	421 (15.2)
Non-Obesity	2005 (79.6)	2343 (84.7)
Missing	0	2 (<0.1)
Interval between dose 2 and study dose (days), N1	2519	2766
Median (days)	235.0	317.0
Min, Max (days)	123, 434	47, 555
Baseline SARS-CoV-2 Status[e], n (%)	-	-
Negative	2288 (90.8)	1031 (37.3)
Positive	199 (7.9)	1215 (43.9)
Missing	32 (1.3)	520 (18.8)

Source: STN#125752/276 mRNA-1273-P204 Final CSR Booster (6 to 11 years) Table 14.1.3.13.2, Table 14.1.1.2.1.2 and Table 14.1.6.2, mRNA-1273-P204 Final CSR Booster (6 months to 5 years) Table 14.1.3.2, Table 14.1.3.11, Table 14.1.3.13.2, Table 14.1.1.2.1.1, Table 14.1.1.2.3.2, Table 14.1.6.2, and Table 14.1.6.4.

Abbreviations: CSR= clinical study report; m= month; Max=maximum; Min=minimum; n= number of participants with demographic characteristic, N1= number of Participants with available data; N= number of participants in the safety set; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation; WHO=World Health Organization; y= year

Note: The Safety Sets for Booster Dose Analysis for mRNA-1273 and mRNA-1273.214 included all enrolled participants who receive the booster.

[a] Age at booster dose

[b] Age groups were based on age at enrollment in Parts 1 or 2 of Study P204. Participants may have been older than the maximum for the age group at time of vaccination in the Booster Part. N = 190 (7.5%) participants in the 6 years – 11 years age group and N= 16 (0.6%) participants in the 6 months – 5 years age group were older than the maximum age for the respective group at the time of booster dose.

[c] Age in months is summarized for ≥6 months and <2 years group only.

[d] Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.

[e] Baseline SARS-CoV-2 Status: Positive was defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody (bAb) specific to SARS-CoV-2 nucleocapsid on or before Day 1. Negative was defined as a negative RT-PCR test for SARS-CoV-2, and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Clinical Reviewer Comment:
There were no imbalances in demographic characteristics that appear to impact the interpretation of study results. The higher percentage of participants in the younger age group who were SARS-CoV-2 positive at baseline is likely due to the Omicron variant surge during the pandemic that occurred prior to enrollment of this age group in the booster phase of Study P204.

6.1.10.1.2 Disposition

Vaccine-naïve, 6 months – 11 years, 25 µg or 50 µg mRNA-1273 (Part 2)
The dispositions and reasons for exclusion from analysis populations in this part of the study evaluating 2 doses of mRNA-1273 are shown in the Table 9 below. A total of 10,727 participants were randomized in the study. Of the randomized participants, 99.2% of those 6 years through 11 years, 98.8% of those 2 years through 5 years, and 98.8% of those 6 months through 23 months of age received both study doses. The Safety Set included a total of 10,698 participants (mRNA-1273 recipients: 3,007 participants 6 years through 11 years of age, 3031 participants 2 years through 5 years of age, 1,994 participants 6 months through 23 months of age). A median of 38% (range 23%-49%) of participants across groups discontinued from Part 2 of the study due to withdrawal of participant consent (9.6% - 16.1%), patient receiving EUA vaccine outside of protocol (0.5% - 22%) and other reasons (2.9% - 12.9%).

The median duration of follow-up after the second study dose was 269 days (range 8 to 696 days) in participants 6 - 11 years of age, 186 days (range 0 to 500 days) in participants 2-5 years of age, and 182 days (range 0 to 405 days) in participants 6 - 23 months of age.

The primary immunogenicity analysis population (PPIS-neg) had a total of 1,104 participants. The reasons for participant exclusion from this set were positive pre-dose SARS-CoV-2 status and no immunogenicity data on Day 57 post-dose.

Table 9. Participant Disposition Throughout the Study, Participants 6 months – 11 years of Age, Study P204, 2-Dose Series- Randomization Sets (Blinded Phase)

Disposition	6y - 11y, vaccine-naïve mRNA-1273 (50 µg) 2 doses N=3011 n (%)	6y - 11y, vaccine-naïve Placebo 2 doses N=1004 n (%)	2y - 5y, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=3040 n (%)	2y - 5y, vaccine-naïve Placebo 2 doses N=1008 n (%)	6m - 23m, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=1995an (%)	6m – 23m, vaccine-naïve Placebo 2 doses N=669 n (%)
Discontinued from study	682 (22.7)	448 (44.6)	954 (31.4)	493 (48.9)	608 (30.5)	303 (45.3)

Disposition	6y - 11y, vaccine-naïve mRNA-1273 (50 µg) 2 doses N=3011 n (%)	6y - 11y, vaccine-naïve Placebo 2 doses N=1004 n (%)	2y - 5y, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=3040 n (%)	2y - 5y, vaccine-naïve Placebo 2 doses N=1008 n (%)	6m - 23m, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=1995an (%)	6m – 23m, vaccine-naïve Placebo 2 doses N=669 n (%)
Reason for discontinuation of study	--	--	--	--	--	--
Other	86 (2.9)	31 (3.1)	388 (12.8)	66 (6.5)	258 (12.9)	48 (7.2)
Missing	2 (<0.1)	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	1 (0.1)
Withdrawal of consent	299 (9.9)	162 (16.1)	303 (10.0)	149 (14.8)	192 (9.6)	94 (14.1)
COVID-19 Non-Infection Related	4 (0.1)	0	6 (0.2)	2 (0.2)	1 (<0.1)	2 (0.3)
Other	295 (9.8)	162 (16.1)	297 (9.8)	147 (14.6)	191 (9.6)	92 (13.8)
Adverse Event	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	1 (0.1)
COVID-19 Infection	0	1 (<0.1)	0	0	0	1 (0.1)
SAR/Reactogenicity Event	0	0	0	0	0	0
Other	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Death	0	0	1 (<0.1)	0	0	0
Lost to Follow-Up	237 (7.9)	55 (5.5)	221 (7.3)	52 (5.2)	142 (7.1)	43 (6.4)
Patient Receiving EUA Vaccine Outside of Protocol	37 (1.2)	194 (19.3)	29 (1.0)	222 (22.0)	9 (0.5)	115 (17.2)
Physician Decision	18 (0.6)	3 (0.3)	7 (0.2)	1 (<0.1)	5 (0.3)	0
Pregnancy	0	0	0	0	0	0
Protocol Deviation	2 (<0.1)	2 (0.2)	2 (<0.1)	2 (0.2)	0	1 (0.1)
Study Terminated by Sponsor	0	0	303 (10.0)	149 (14.8)	0	0
Safety Set [b]	3007	995	3031	1007	1994	664
Safety follow-up through 28 days after Dose 2 [b]	2974 (98.9)	965 (97.0)	2882 (95.1)	963 (95.6)	1924 (96.5)	635 (95.3)
Solicited Safety Set [b]	3005(>99.9)	994 (99.9)	3014 (99.4)	998 (99.1)	1991 (99.8)	664 (99.7)
First Injection Solicited Safety Set [b]	3003 (99.9)	993 (99.8)	2955 (97.5)	971 (96.4)	1982 (99.4)	661 (99.2)
Second Injection Solicited Safety Set [b]	2993 (99.5)	970 (97.5)	2977 (98.2)	974 (96.7)	1975 (99.0)	646 (97.0)
Immunogenicity Set[c]	379	87	351	73	340	74
Per Protocol Immunogenicity Set (PPIS) [c]	311 (82.1)	76 (87.4)	304 (86.6)	62 (84.9)	286 (84.1)	65 (87.8)
Excluded from Per-Protocol Immunogenicity Subset[c]	68 (17.9)	11 (12.6)	47 (13.4)	11 (15.0)	54 (15.9)	9 (12.2)
Reason for exclusion from PPIS	-	-	-	-	-	-
Positive Baseline SARS-CoV-2 Status[d]	38 (10.0)	-	28 (8.0)	-	19 (5.6)	-
Did not Receive Dose 2 per Schedule	0	-	1 (0.3)	-	0	-
Received Incorrect Vaccination	0	-	0	-	0	-
Received Dose 2 Out of Window	1 (0.3)	-	2 (0.6)	-	5 (1.5)	-

Disposition	6y - 11y, vaccine-naïve mRNA-1273 (50 µg) 2 doses N=3011 n (%)	6y - 11y, vaccine-naïve Placebo 2 doses N=1004 n (%)	2y - 5y, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=3040 n (%)	2y - 5y, vaccine-naïve Placebo 2 doses N=1008 n (%)	6m - 23m, vaccine-naïve mRNA-1273 (25 µg) 2 doses N=1995an (%)	6m – 23m, vaccine-naïve Placebo 2 doses N=669 n (%)
Had no Immunogenicity Data at Day 57	17 (4.5)	-	15 (4.3)	-	29 (8.5)	-
Had Other Major Protocol Deviations	12 (3.2)	-	0	-	0	-
Participants with HIV Infection	0	-	0	-	0	-
Age is Outside of the Randomized Age Group	0	-	1 (0.3)	-	1 (0.3)	-
Received Off-study COVID-19 Vaccine at or Before Day 57	0	-	0	-	0	-

Source: mRNA-1273-P204 Final CSR Primary Series (6 to 11 years) Table 14.1.1.1.2, Table 14.1.5.2, Table 14.1.2.1.2.1, Table 14.1.2.3.2, mRNA-1273-P204 Final CSR Primary Series (2 to 5 years) Table 14.1.1.1.2, Table 14.1.5.2, Table 14.1.2.1.2.1, Table 14.1.2.3.2, mRNA-1273-P204 Final CSR Primary Series (6 to 23 months) Table 14.1.1.1.2, Table 14.1.5.2, Table 14.1.2.1.2.1, Table 14.1.2.3.2

Abbreviations: COVID-19 = coronavirus disease 2019; EUA = emergency use authorization; n= number of participants in indicated population/ SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SAR = solicited adverse reaction.

Note: Disposition is throughout the study, including blinded phase, open label/crossover phase, and booster phase if a booster dose was taken.

[a.] Percentages are based on the number of in the Randomization Set. In Randomization Sets, participants were analyzed according to the treatment group to which they were randomized.

[b.] Percentages are based on the number of participants in the Safety Set. The follow up is during the blinded phase only. In Safety Sets, Participants were included in the vaccination group corresponding to the vaccination they actually received.

[c] Numbers are based on planned treatment group and percentages are based on the number of subjects in Immunogenicity Subset. A subject who has multiple reasons for exclusion is listed under the reason appears earliest.

[d] Baseline SARS-CoV-2 Status: Positive was defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody (bAb) specific to SARS-CoV-2 nucleocapsid on or before Day 1. Negative was defined as a negative RT-PCR test for SARS-CoV-2, and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Vaccine-experienced, 6 months through *11 years, 10 µg or 25 µg mRNA-1273 (Part 2) or Vaccine-experienced, 6 months* through *11 years, 10 µg mRNA-1273.214 (Part 2)*

The dispositions and reasons for exclusion from analysis populations in this part of the study evaluating a single dose of either mRNA-1273 (6 months through 11 years) or mRNA-1273.214 (6 months through 5 years) formulations are shown in Table 10. A total of 8.4%-17.3% of participants discontinued from the study due to Withdrawal of Consent by Participant, Lost to Follow-up, and Other.

The median duration of follow-up after the study dose for participants 6 - 11 years was 369 days (range 4 to 574 days) and for participants 6 months – 5 years who received mRNA-1273.214 was 184 days (range 8 to 315). The percentages of participants with at least 6 months of safety follow-up following the study dose were 97% (6 years – 11 years), 94% (6 months – 5 years who received mRNA-1273), and 96% (6 months – 5 years who received mRNA-1273.214).

Table 10. Participant Disposition Throughout the Study, Study P204, Booster Phase, All Age Groups, Analysis Sets

Disposition	6y - 11y, vaccine-experienced mRNA-1273 (25 µg) Single Dose n(%)	6m - 5y vaccine-experienced mRNA-1273.214 (10 µg[a]) Single Dose n(%)
FAS (Part 2) [b]	N=2290	N=2766
Discontinued From Study [c]	313 (13.7)	233 (8.4)
Withdrawal of Consent by Participant	149 (5.9)	108 (3.9)
Lost to Follow-up	133 (5.3)	95 (3.4)
Other	29 (1.2)	28 (1.0)
Subject Received Another COVID-19 Vaccine Under EUA	27 (1.1)	1 (<0.1)
Physician decision	3 (0.1)	0
Death	0	1 (<0.1)
PPIS[c,d]	114 (19.3)	-
Safety Set	2290 (100)	2766 (100)
Safety follow-up through 28 days after dose	2279 (99.5)	2754 (99.6)
Solicited Safety Set	2259 (98.6)	NA[e]
FAS (Part 1 + Part 2)[f]	N=2519	N=2771
Safety Set[g]	2519 (100)	2771 (100)
Safety follow-up through 28 days after dose	2279 (99.5)	2759 (99.6)

Source: Adapted from mRNA-1273-P204 Final CSR 6 to 11 years Booster Part Tables 14.1.1.3.4.2 and 14.1.6.2 Final CSR 6 months to 5 years Booster Part Tables 14.1.1.3.5.2 and 14.1.6.4

Abbreviations: COVID-19 = coronavirus disease 2019; EUA = emergency use authorization; n= number of participants in population or with reason for discontinuation; N= total number of participants in population on which subsequent percentages are based; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SAR = solicited adverse reaction.

a. Six participants received a single 5µg dose of mRNA-1273.214 in error. These participants are included in safety analyses

b. Participants received a single dose of mRNA-1273 or mRNA-1273.214 following 2 doses of mRNA-1273 in Part 2 of P204

c. Percentages based on the FAS (Part 2)

d. Immunogenicity endpoints were evaluated in a subset of participants who received mRNA-1273. They were not pre-specified to be evaluated in participants who received mRNA-1273.214.

e. Solicited ARs were pre-specified to be collected from mRNA-1273 recipients only. As such they were not collected from participants 6 months – 5 years of age who received mRNA-1273.214.

f. Participants received a single dose of mRNA-1273 or mRNA-1273.214 following 2 doses of mRNA-1273 in Part 2 or Part 2 of P204

g. Percentages based on the FAS (Part 1 + Part 2)

Clinical Reviewer Comment:
The total number of, and reasons for, participant exclusion from the relevant analyses populations do not substantially impact the interpretation of study results.

6.1.11 Analyses of vaccine effectiveness

6.1.11.1 Vaccine-naïve, 6 months – 11 years, 2 dose series, mRNA-1273 (Part 2)

(50µg dose: 6 years – 11 years, 25µg dose: 6 months – 5 years)

Hypotheses #1 and #2

The primary immunogenicity endpoints evaluating a 2-dose series in vaccine-naïve SARS-CoV-2 seronegative participants were nAb concentrations (GM antibody levels and SRRs) against the D614G assay strain at 28 days following the last dose of mRNA-1273. Participants received the following Spikevax dosage for the 2-dose series by age study groups: 6 months - 23 months of age (25 µg), 2 years – 5 years (25 µg) and 6 years - 11 years (50 µg). The elicited nAb responses for each of these age groups were compared with those in young adults (18-25 years of age) in Study P301 (GM ratios [P204 /P301] and differences in SRR percentages [P204 – P301]. All endpoints met the pre-specified statistical success criteria (Table 11, GM ratio: LB of 95%CI >0.667 with a point estimate ≥ 0.8; SRR percentage difference LB of 95%CI >-10% with a point estimate ≥-5%).

SRR for all age groups was defined as a change from a pre-Dose 1 baseline 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.

Table 11. SARS-CoV-2 GM nAb levels and SRRs Measured by Pseudovirus nAb Assay (D614G Strain) Study P204, 2 Doses mRNA-1273 in Children 6 months to 11 years Compared with Study P301, 2 doses mRNA-1273 in Young Adults (18 years – 25 years), Day 57, PPIS Negative

nAb Responses (D614G)	**6y – 11y 2-dose Series mRNA-1273 (50ug) GMT [a] (95% CI) N=309**	**GMT Ratio P204 (6y – 11y) /P301 [95% CI][b]**	**2y – 5y 2-dose Series mRNA-1273 (25ug) GMC[a] [95% CI] N=289**	**GMC Ratio P204 (2y – 5y) /P301 [95% CI][c]**	**6m – 23m 2-dose Series mRNA-1273 (25ug) GMC[a] [95% CI] N=268**	**GMC Ratio P204/P301 [95% CI][c]**
GM level	1618.3 (1464.3, 1788.6)	1.2 (1.1, 1.4)	1394.1 (1267.0, 1533.9)	1.0 (0.9, 1.1)	1759.8 (1599.2, 1936.5)	1.3 (1.1, 1.4)
--	**Seroresponders [d] % (n/N1) [95% CI]**	**Difference in SRR% (P204- P301) [95% CI][e]**	**Seroresponders [d] % (n/N1) [95% CI]**	**Difference in SRR% (P204 - P301) [95% CI][d]**	**Seroresponders [d] % (n/N1) [95% CI]**	**Difference in SRR% (P204 - P301) [95% CI][d]**
SRR	99.0 (304/307) (97.2, 99.8)	-0.3 (-2.2, 1.6)	98.9 (281/284) (96.9, 99.8)	-0.4 (-2.5, 1.5)	100 (264/264) (98.6, 100)	0.7 (-0.8, 2.4)

Source: Adapted from STN#125752/276 Response to IR sent March 28, 2025
Abbreviations: %=percent, CI=confidence interval, GM = geometric mean, nAb = neutralizing antibody, n= number of participants meeting seroresponse definition, N=number of participants with available antibody data, N1=number of participants with available seroresponse data, PD= post-dose, SRR= seroresponse rate, m = month, y = year
Notes: P301 mRNA-1273 group includes young adults 18 years - 25 years of age. Antibody values reported as below the lower limit of quantification (LLOQ) were replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) were replaced by the ULOQ if actual values are not available. LLOQ for Duke psVNA assay for 6y – 11y = 18.5. LLOQ for PPD psVNA assay for 2y – 5y and 6m – 23m = 10.
a. The log-transformed antibody levels were analyzed using an analysis of covariance (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.
b. nAb GM level and 95%CI for P301 Young Adults (N=294) = 1322 (1193, 1465)
c. nAb GM level and 95%CI for P301 Young Adults (N=294) = 1400 (1278, 1534)
d. Seroresponse at a participant level was defined as a change from a pre-Dose 1 baseline 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. SRR% and 95%CI for P301 Young Adults (N=294) = 99.3% (97.6%, >99.9%)

Descriptive Analyses based on SARS-CoV-2 Baseline Status:
Additional analyses evaluated the nAb responses for those who were SARS-CoV-2 positive at baseline. The small number of seropositive participants limits the ability to draw firm conclusions, however the nAb GMCs following 2 doses of mRNA-1273 were higher in

participants who were SARS-CoV-2 positive at baseline (6 – 23 months [N=15]: GM level 10412 [95% CI 5579, 19431]; 2 – 5 years [N=23] GM level 7430 [4623, 11943]; and 6 years – 11 years [N=38] GM level 4258 [2875, 6307]) compared with those who were SARS-CoV-2 negative (see Table 11, above).

Subpopulation Analyses:
Subpopulation analyses of nAb responses following the 2-dose series in children 6 months -11 years by sex (male or female), race (Black or African American, White, Other), ethnicity (Hispanic or Latino, not Hispanic or Latino or missing), and obesity (obese or non-obese) demonstrate similar responses.

> ***Clinical Reviewer Comment:***
> *Descriptive analyses evaluating nAb GMCs and SRRs primary endpoints suggest higher immune responses in participants who were baseline SARS-CoV-2 exposed prior to vaccination, though statistical criteria for success were met for the primary analyses for these endpoints in seronegative participants at baseline following a 2-dose primary series of Spikevax.*

Descriptive Analyses of COVID-19 Cases
Prespecified descriptive endpoints evaluated the cases of first episode of COVID-19 starting 14 days after study vaccination with 2 doses of mRNA-1273 until the blinded date of data cutoff, which varied based on age cohort (November 30, 2021, for the 6-year – 11-year age group and June 30, 2022, for participants in the 2-year – 5-year and 6 month – 23-month groups). Descriptive analyses of relative vaccine efficacy (rVE) of mRNA-1273 for the prevention of COVID-19 disease compared with placebo are shown in Table 12.

> ***Clinical Reviewer Comment****:*
> *Although all age cohorts received the prototype vaccine, mRNA-1273 with the original Wuhan-Hu-1 SARS-CoV-2 strain, they were enrolled at different time periods during the pandemic. Each new predominant circulating strain was phylogenetically less similar to original strain. As a result, the circulating strains were mismatched with the vaccine strain, thus negatively impacting observed relative vaccine efficacy (rVE) results.*

The rVE for school age children 6y-11y had a higher rVE (76%) point estimate, but a negative LB of the 95% CI with relatively lower COVID-19 case incidence rates when compared with the two younger age cohorts, which had higher case incidence rates across study groups. As a result, the lower bounds of the 95% CI had greater precision around the rVE point estimate in the 2 years through 6 years of age and 6 months through 23 months of age cohorts.

Table 12 Incidence Rate of COVID-19 Starting 14 Days After Second mRNA-1273 Vaccination Until Blinded Phase Cut-off Date, 6m – 11y, PPSE, P204 Part 2

Age group	Predominant Circulating SARS-CoV-2 Strain	mRNA-1273 CDC COVID-19 [a] Rate/1000 person years (95% CI) [N1]	Placebo CDC COVID-19 [a] Rate/1000 person years (95% CI) [N1]	rVE CDC COVID-19 [a] % (95% CI)	mRNA-1273 P301 COVID-19 [b] Rate/1000 person years (95% CI) [N1]	Placebo P301 COVID-19 [b] Rate/1000 person years (95% CI) [N1]	rVE P301 COVID-19 [b] % (95% CI)
6 y – 11 y	Delta variant (B.1.617.2)	5.3 (1.1, 15.5) [2606]	22.1 (6.0, 56.6) [849]	76 (-41.6, 96.5)	5.3 (1.1, 15.5) [2606]	16.5 (3.4, 48.3) [849]	68 (-138.7, 95.7)
2 y – 5 y	Delta (B.1.617.2) Omicron (B.1.1.529, BA.1.1, BA.2, BA.5)	152.2 (132.2, 174.4) [2592]	427 (367, 495) [854]	46.6 (32.8, 57.4)	102.9 (86.7, 121.3) [2592]	184.8 (147.2, 229.1) [854]	44.3 (26.1, 57.8)
6 m – 23 m	Delta (B.1.617.2) Omicron (B.1.1.529, BA.1.1, BA.2, BA.5)	150.2 (125.5, 178.3) [1686]	264.2 (207.1, 332.2) [563]	43.2 (23.2, 57.6)	100.6 (80.7, 124.0) [1686]	128.8 (90.7, 177.6) [563]	21.9 (-18.0, 47.4)

Adapted from STN125752/276 mRNA-1273-P204 CSR 6y – 11y, 2 y – 5y, and 6m – 23m, Table 14.2.7.1.1.2.2 and Table 14.2.8.1.1.2.2

Abbreviations: CI = confidence interval, m=month, N1=Number of participants in the PPSE for the relevant age group, rVE= relative vaccine efficacy, y=years; PPSE= per protocol set for efficacy; RT-PCR = real time polymerase chain reaction

a. CDC Case Definition = positive RT-PCR result plus at least ONE of the following systemic symptoms: Fever (temperature ≥ 38ºC/≥100.4ºF) or chills (of any duration), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding; OR at least ONE of the following respiratory signs/symptoms: cough (of any duration), shortness of breath or difficulty breathing (of any duration).

b. P301 Case Definition = positive RT-PCR result plus at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR the participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia

Clinical Reviewer Comment:

1. *The ability to draw firm conclusions regarding rVE for some age groups (i.e., 6y* through *11y) are limited due to lower incidence of COVID-19 disease (cases).*

2. *Vaccine efficacy against CDC defined COVID-19 was approximately 40% in children 6 months through 23 months of age following 2 doses of Spikevax (Original monovalent). However, the study was conducted when Omicron BA.1 was the predominant SARS-CoV-2 variant in circulation and the study vaccine (mRNA-1273) was the original monovalent formulation that did not encode for the SARS-CoV-2 Omicron BA.1 variant, therefore the vaccine was mismatched to the circulating variant when clinical disease cases were being accrued. This suggests that vaccines matched to the predominant circulating strain are important to maintain high vaccine effectiveness against COVID-19.*

6.1.11.2 Vaccine-experienced, 6 months – 11 years, Single Dose, 10 µg or 25 µg mRNA-1273 (Booster Part)

Hypotheses #3 and #4

The primary immunogenicity endpoints evaluating a single dose in vaccine-experienced SARS-CoV-2-negative individuals were nAb concentrations (GM levels and SRRs) against the D614G assay strain at 28 days postvaccination. All participants had previously received a 2-dose series of mRNA-1273 earlier in the same study at least 3 months prior to receiving the single dose.

The elicited nAb responses following the single dose were compared with those in young adults in Study P301 (GM ratios [P204 /P301] and differences in SRR percentages [P204 – P301]. All endpoints met the pre-specified statistical success criteria (Table 13, GM ratio: LB of 95% CI >0.667; SRR percentage difference LB of 95%CI >-10%).

SRR was defined as a change from a pre-Dose 1 baseline 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.

> ***Clinical Reviewer Comment****:*
> *While participants 6 years through 11 years received mRNA-1273, most participants 6 months – 5 years of age received the bivalent mRNA-1273.214 (N=2799; N=301 received mRNA-1273). The primary immunogenicity analyses evaluated nAb responses against the D614G strain in participants 6 years* through *11 years age group; and exploratory analyses evaluated nAb responses against D614G in those participants 6 month* through *5-years of age who received mRNA-1273.*

Table 13. SARS-CoV-2 GMC and SRRs Measured by Pseudovirus nAb Assay (D614G Strain) Study P204 Booster Phase: Single Dose mRNA-1273 Children 6 months to 11 years, Day 28, Compared to P301 Young Adults, Day 57, PPIS Negative

nAb Responses (D614G)	**6 – 11 years 25µg mRNA-1273 GMC [95% CI] N=137**	**GMC Ratio P204 / P301 Young Adults[a] [95% CI [b]]**	**6 months- 5 years 10µg mRNA-1273 GMC [95% CI [b]] N=76**	**GMC Ratio P204 / P301 Young Adults[a] [95% CI]**
GM level	5575.9 (4899.2, 6346.0)	4.0 (3.4, 4.7)	5457.2 (4525.0, 6581.3)	4.0 (3.2, 4.8)
-	**Seroresponders % (n/N1) [95% CI [c]]**	**Difference in SRR% (P204 - P301 Young Adults) [95% CI]**	**Seroresponders % (n/N1) [95% CI][b]**	**Difference in SRR% (P204 - P301 Young Adults) [95% CI][b]**
SRR	100.0 (129/129) (97.2, 100.0)	0.7 (-2.2, 2.4)	100.0 (72/72) (95.0, 100.0)	0.7 (-4.4, 2.4)

Source: Adapted from STN#125752/276 Response to IR sent March 28, 2025
Abbreviations: CI=confidence interval, GMC= geometric mean concentration, nAb = neutralizing antibody, n= number of participants meeting seroresponse definition, N=number of participants with GMC data, N1=number of participants with available seroresponse data, PD= post-dose SRR= seroresponse rate
a. nAb GMC and 95%CI for P301 Young Adults (N=294) = 1400 (1278, 1534)
b. SRR% and 95%CI for P301 Young Adults (N=294) = 99.3% (97.6, >99.9)

Descriptive Analyses based on SARS-CoV-2 Baseline Status
Although firm conclusions are limited by the small numbers of participants who were SARS-CoV-2 positive at baseline in the evaluable population, the point estimate of nAb response was higher in seropositive participants 6 years – 11 years of age (8,360 [95% CI 6550 – 10671] compared with those in the primary immunogenicity analysis population.

***Clinical Reviewer Comment**:*
Due to the small sample size of participants who received mRNA-1273 in the evaluable population in the younger age group, analyses by baseline SARS-CoV-2 status were not performed for participants 6 months through *5 years of age.*

Subpopulation Analyses
Subpopulation analyses of nAb responses by sex (male or female) demonstrated similar responses to those of the primary immunogenicity analyses. Analyses of other subgroup populations based on ethnicity and race were limited by the small numbers of participants in the respective subgroups.

***Clinical Reviewer Comment**:*
The primary immunogenicity analyses evaluating neutralizing antibody responses support the effectiveness of a single dose of Spikevax administered to children 6 months through *11 years who were previously vaccinated with a COVID-19 vaccine.*

6.1.12 Analyses of vaccine safety

***Clinical Reviewer Comment**:*
Adverse reactions are presented for 2 doses in the blinded phase of Part 2 (ages 6 months – 11 years) and the single dose part of Study P204 (ages 6 years through *11 years) only. Percentages of participants reporting ARs in other study parts were similar and did not contribute additional information to vaccine reactogenicity profile. The results of analyses of AESIs, SAEs, deaths, and AEs leading to discontinuation of study vaccination or study participation are presented below for all study parts.*

6.1.12.1 Methods

See section 6.1.7

Data cut-off dates and duration of follow-up for safety follow-up in the relevant parts of study P204 are presented in Table 14.

Table 14. Data cut-off dates and duration of follow-up in study P204.

Dose Schedule, Formulation, and Age Group	**End date of blinded phase**	**Data cut-off date**	**Follow-up duration, last study dose[a] Median, days (Q1,Q3)**	**≥ 5-month follow-up[b] % (n/N1)**
2 doses, vaccine-naïve	-	-	-	-
6y - 11y, mRNA-1273	30 Nov 2021	17 May 2024	48 (42, 54)	1.8 (72/4002)
2y - 5y, mRNA-1273	30 Jun 2022	17 May 2024	186 (157, 199)	81.0 (3270/4038)
6m – 23m, mRNA-1273	30 Jun 2022	17 May 2024	185 (152, 198)	78.3 (5243/6698)
Single dose, vaccine-experienced	-	-	-	-
6y - 11y, mRNA-1273	NA	17 May 2024	368 (364, 375)	97.4 (2230/2290)

Dose Schedule, Formulation, and Age Group	End date of blinded phase	Data cut-off date	Follow-up duration, last study dose[a] Median, days (Q1,Q3)	≥ 5-month follow-up[b] % (n/N1)
6m - 5y, mRNA-1273.214	NA	17 May 2024	183 (182, 193)	96.7 (2674/2766)

Source: Adapted from STN#125752/276 Study P204 Primary Series CSR 6y-11y Table 14.1.5.2, Study P204 Primary Series CSR 2y – 5y Table 14.1.5.2, Study P204 Primary Series CSR 6m – 23m Table 14.1.5.2, P204 Booster CSR 6y – 11y Table 14.1.6.2, P204 Booster CSR 6m – 5y Table 14.1.6.2

Abbreviations: m = month; n = number of participants with at least 5 months of safety follow-up; N1 = number of participants in the respective safety set (placebo and investigational recipients; Q1 = first quartile; Q3 = third quartile; NA = not applicable; y = years

a. Duration of follow-up was defined as the time from enrollment or randomization to discontinuation from study, booster dosing date, or study completion, whichever occurred earlier.

b. % of participants with at least 5 months of safety follow-up following the final study dose

6.1.12.2 Overview of Adverse Events

Vaccine-naïve, 6 months – 11 years, mRNA-1273

A total of 3,007 participants 6 years - 11 years received 2 doses of mRNA-1273 (50µg). A total of 3,031 participants 2y – 5y received 2 doses of mRNA-1273 (25µg). A total of 1,994 participants 6m – 23m received 2 doses of mRNA-1273 (25µg). See Table 14 above for the median duration of follow-up.

Table 15 provides an overview of the safety results from study P204 in vaccine-naïve participants receiving a 2-dose series of mRNA-1273. Local and systemic ARs were more commonly reported following mRNA-1273 than following placebo. Percentages of participants with unsolicited AEs within 28 days of vaccination were similar between groups. Rates of related SAEs were similar between groups. There were no deaths.

Table 15. Overview of Participants Reporting at Least One Adverse Event Following Vaccination, Vaccine-Naïve, 2 doses, mRNA-1273 (50µg, 6y – 11y), mRNA-1273 (25µg, 6m – 5y), and Placebo (6m – 11y), Safety Set and Solicited Safety Set, P204 Part 2

Event type	6y – 11y 2 doses mRNA-1273 50 µg n/N1 (%)	6y – 11y 2 doses Placebo n/N1 (%)	2y – 5y 2 doses mRNA-1273 25 µg n/N1 (%)	2y – 5y 2 doses Placebo n/N1 (%)	6m – 23m 2 doses mRNA-1273 25 µg n/N1 (%)	6m – 23m 2 doses Placebo n/N1 (%)
Local ARs	2964/3005 (98.6)	649/994 (65.3)	2527/3013 (83.9)	578/997 (58.0)	1322/1991 (66.4)	303/664 (45.6)
Dose 1	2812/3003 (93.6)	481/993 (48.4)	1875/2954 (63.5)	407/971 (41.9)	863/1981 (43.6)	219/661 (33.1)
Dose 2	2856/2993 (95.4)	489/970 (50.4)	2186/2977 (73.4)	411/973 (42.2)	1056/1975 (53.5)	198/646 (30.7)
Grade 3 or above	167/3005 (5.6)	8/994 (0.8)	55/3013 (1.8)	4/997 (0.4)	38/1991 (1.9)	2/664 (0.3)
Systemic ARs	2605/3005 (86.7)	667/994 (67.1)	2304/3014 (76.4)	641/998 (64.2)	1777/1991 (89.3)	571/664 (86.0)
Dose 1	1740/3003 (57.9)	518/993 (52.2)	1594/2954 (54.0)	487/971 (50.2)	1499/1981 (75.7)	481/661 (72.8)
Dose 2	2339/2993 (78.1)	485/970 (50.0)	1835/2977 (61.6)	436/974 (44.8)	1460/1975 (73.9)	440/646 (68.1)
Grade 3 or above	406/3005 (13.5)	25/994 (2.5)	201/3014 (6.7)	40/998 (4.0)	101/1991 (5.1)	23/664 (3.5)
Unsolicited AEs within 28d[a]	780/3007 (25.9)	206/995 (20.7)	1083/3031 (35.7)	324/1007 (32.2)	870/1994 (43.6)	283/666 (42.5)
Severe[b]	3/3007 (<0.1)	0	3/3031 (<0.1)	2/1007 (0.2)	7/1994 (0.4)	1/666 (0.2)
Related[c]	188/3007 (6.3)	11/995 (1.1)	135/3031 (4.5)	34/1007 (3.4)	89/1994 (4.5)	17/666 (2.6)
Severe and related [b,c]	1/3007 (<0.1)	0	1/3031 (<0.1)	1/1007 (<0.1)	1/1994 (<0.1)	0
MAAEs -entire study	516/3007 (17.2)	155/995 (15.6)	1364/3031 (45.0)	411/1007 (40.8)	1047/1994 (52.5)	340/666 (51.1)

Event type	6y – 11y 2 doses mRNA-1273 50 µg n/N1 (%)	6y – 11y 2 doses Placebo n/N1 (%)	2y – 5y 2 doses mRNA-1273 25 µg n/N1 (%)	2y – 5y 2 doses Placebo n/N1 (%)	6m – 23m 2 doses mRNA-1273 25 µg n/N1 (%)	6m – 23m 2 doses Placebo n/N1 (%)
Related [c]	28/3007 (0.9)	2/995 (0.2)	29/3031 (1.0)	8/1007 (0.8)	22/1994 (1.1)	4/666 (0.6)
SAEs - entire study	8/3007 (0.3)	1/995 (0.1)	19/2031 (0.6)	3/1007 (0.3)	31/1994 (1.6)	6/666 (0.9)
Related [c]	0	0	0	0	2/1994 (0.1)	0
AESIs - entire study	7/3007 (0.2)	2/995 (0.2)	4/3031 (0.1)	1/1007 (<0.1)	8/1994 (0.4)	2/666 (0.3)
Related [c]	1/3007 (<0.1)	0	2/3031 (<0.1)	1/1007 (<0.1)	2/1994 (0.1)	0
Deaths	0	0	0	0	0	0
AEs leading to discontinuation from study vaccine	3/3007 (<0.1)	0	2/3031 (<0.1)	0	2/1994 (0.1)	0

Source: Adapted from STN#125752/276 mRNA-1273-P204 Final CSR Primary Series (6 to 23 months) Table 14.3.1.28.1.2, Table 14.3.1.7.1.2, Table 14.3.1.7.2.3, Table 14.3.1.7.1.5.1, and Table 14.3.1.7.1.6.1, CSR Primary Series (2 to 5 years) Table 14.3.1.28.1.2, Table 14.3.1.7.1.2, Table 14.3.1.7.2.3, Table 14.3.1.7.1.5.1, and Table 14.3.1.7.1.6.1, CSR Primary Series (6 to 11 years) Table 14.3.1.28.1.2, Table 14.3.1.7.1.2, Table 14.3.1.7.2.3, Table 14.3.1.7.1.5.1, and Table 14.3.1.7.1.6.1. and Response to IR sent March 28, 2025

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically-attended adverse event; n= number of participants with the respective AE, N1 = number of participants with available safety data, SAE = serious adverse event

Note: The Safety Set consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment. Percentages are based on the number of exposed participants who submitted any data for the event. An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants. Solicited ARs with toxicity grade = 0 that started after day 7 are not included in the summary.

a. Participants who reported at least one nonserious AE and did not report any serious AE are included in the summary.

b. Severe AEs include severe AEs and events with toxicity Grade 3, 4 and 5.

c. As assessed by study investigators

Vaccine-experienced, 6 years through 11 years (25 ug mRNA-1273)
Vaccine-experienced, 6 months through 5 years (10 ug mRNA-1273.214)

A total of 2,290 participants 6y -11y received a 25-µg dose of mRNA-1273 as an additional dose (7 years through 13 years at vaccination) at least 6 months after receipt of the 2-dose series of mRNA-1273 in Part 2 of Study P204. An additional 229 participants who were initially enrolled in Part 1 of the study received an additional dose of mRNA-1273 in the booster phase of the study. Data from these participants contributed to the analyses of SAEs, AESIs, and deaths. See Table 14 above for the median duration of follow-up.

> ***Clinical Reviewer Comment****:*
> *For analyses of solicited safety and unsolicited safety within 28 days, only data from the Part 2 participants are summarized because data from the small sample size of Part 1 participants do not contribute substantially to the characterization of mRNA-1273 vaccine reactogenicity or commonly observed AEs. For analyses of MAAEs, SAEs, AESIs, deaths, and AEs leading to discontinuation, the pooled data from Part 1 and Part 2 are used.*

A total of 2,766 participants in the 6m – 5y age group (11 months through 7 years at vaccination) received a 10µg dose of mRNA-1273.214 after the 2-dose series of mRNA-1273 in Part 2 of P204. See Table 14 above for the median duration of follow-up.

***Clinical Reviewer Comment**:*
There were 6 participants who received a 5-µg dose of mRNA-1273.214 in error. These 6 participants are included in the 2,766 total safety set and are not expected to impact the overall study conclusions.

Review of safety data for a single dose in vaccine-experienced participants in the 6m – 5y age group will be limited to unsolicited AEs, AESIs, SAEs, deaths, and AEs leading to discontinuation, as collection of ARs from this age group was not pre-specified. The rates and severities of solicited ARs observed in the small subset of participants in this age group were similar to those observed among participants in the same age group in Study P306 (see section 6.2.12.3.1).

Table 16 provides an overview of the safety results from study P204 in vaccine-experienced participants who received the single additional dose. Percentages of participants with unsolicited AEs within 28 days of vaccination were similar between groups. There were no SAEs or AESIs assessed as related to the study dose. There was 1 death in a participant in the 2y – 5y age group that was assessed as not related to the study dose.

Table 16. Overview of Participants Reporting at Least One Adverse Event Following Vaccination, Vaccine-Experienced, mRNA-1273 (25µg, 6y – 11y) and mRNA-1273.214 (10µg, 6m – 5y), Safety Set and Solicited Safety Set, P204 Single Dose Part

Event type	6y – 11y Single Dose mRNA-1273 (25 µg) n/N1 (%)	2y – 5y 2 doses mRNA-1273.214 (10 µg) n/N1 (%)	6m – 23m 2 doses mRNA-1273.214 (10 µg) n/N1 (%)
Local ARs	2033/2257 (90.1)	NA	NA
Grade 3 or above	41/2257 (1.8)	NA	NA
Systemic ARs	1378/2258 (61.0)	NA	NA
Grade 3 or above	104/2258 (4.6)	NA	NA
Unsolicited AEs within 28d[a]	228 (10.0)	174 (11.5)	162 (12.9)
Severe [b]	0	0	0
Related[c]	24 (1.0)	6 (0.4)	3 (0.2)
Severe and related [b,c]	0	0	0
MAAEs -entire study	753 (32.9)	546 (36.1)	537 (42.9)
Related [c]	11 (0.5)	7 (0.5)	4 (0.3)
SAEs - entire study	10 (0.4)	13 (0.9)	10 (0.8)
Related [c]	0	0	0
AESIs - entire study	11 (0.5)	1 (<0.1)	1 (<0.1)
Related [c]	0	0	0
Deaths	0	1/1514 (<0.1)	0
Related [c]	0	0	0
AEs leading to discontinuation	0	1/1514(<0.1)	0

Source: mRNA-1273-P204 Final CSR Booster Dose (6 to 11 years) Table 14.3.1.28.1.1.2, Table 14.3.1.7.4.1.2, Table 14.3.1.7.4.6.2, mRNA-1273-P204 Final CSR Booster Dose (6 months to 5 years) Table 14.3.1.7.4.1.2.2 and Table 14.3.1.7.4.6.1.2. and Response to IR sent March 28, 2025

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically-attended adverse event; n= number of participants with the respective AE, N1 = number of participants with available safety data, SAE = serious adverse event

Note: The Safety Set consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment. Percentages are based on the number of exposed participants who submitted any data for the event. An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants. Solicited ARs with toxicity grade = 0 that started after day 7 are not included in the summary.

a. Participants who reported at least one nonserious AE and did not report any serious AE are included in the summary.
b. Severe AEs include severe AEs and events with toxicity Grade 3, 4 and 5.
c. As assessed by study investigators

***Clinical Reviewer Comment**:*
The overall percentages of participants with ARs and AEs in Study P204 do not demonstrate new safety concerns for Spikevax in individuals 6 months – 11 years of age when administered as 2 doses to COVID-19 vaccine-naïve participants or as a single dose to COVID-19 vaccine-experienced participants.

6.1.12.3 Solicited Adverse Reactions

6.1.12.3.1 Two doses, vaccine-naïve, mRNA-1273

For each age group, solicited adverse reactions were more common following any dose of mRNA-1273 (93% - 99%) as compared with placebo (80% - 90%). Solicited ARs by dose of mRNA-1273 are discussed in the relevant sections below.

The most common local ARs by age group following any dose of mRNA-1273 were:

- 6y – 11y: pain (98%), axillary/groin swelling/tenderness (27%), erythema (24%)
- 2y – 5y: pain (82%), axillary/groin swelling/tenderness (14%), erythema (12%)
- 6m – 23m: pain (57%); erythema (19%); swelling (19%)

The most common systemic ARs by age group were:

- 6y – 11y: fatigue (73%), headache (62%), myalgia (35%), and chills (35%).
- 2y – 5y: Irritability/crying (72%), fatigue (62%), and sleepiness (50%)
- 6m – 23m: Irritability/crying (83%), sleepiness (52%), and loss of appetite (47%)

Most solicited ARs were of Grade 1 or 2 severity. Grade 4 ARs (fever > 40ºC) were reported by 0.2% of participants in the 6-month – 23-month group. There were no other Grade 4 ARs reported.

Clinical Reviewer Comment:
Solicited systemic ARs (other than fever) collected from participants <36 months of age were defined differently from solicited ARs collected from participants ≥ 36 months of age to be developmentally appropriate. Developmentally appropriate grading scales for local and systemic ARs were also used to assess the intensity of reported solicited ARs. See section 6.1.7 for descriptions of the solicited ARs and grading scales for each age group.

Most local and systemic reactions had an onset 1 to 2 days postvaccination, and a median duration of 2 to 3 days after onset.

Delayed solicited injection site reactions, defined as beginning between 8 to 28 days postvaccination, were reported by:

- 6y – 11y: 1.8% of mRNA-1273 recipients and 0.2% of placebo recipients.
- 2y – 5y: 4.1% of mRNA-1273 recipients and 0.2% of placebo recipients
- 6m – 23m: 1.5% of mRNA-1273 recipients and 0.2% of placebo recipients.

Most of these were delayed local reactions that were mild in severity. All were nonserious. The most common delayed local reaction among mRNA-1273 recipients was injection site erythema (1.2% of 6y – 11y; 2.5% of 2y – 5y, and 1.1% of 6m – 23m).

Vaccine-naïve, 6 years – 11 years, 2 dose series, 50 ug mRNA-1273

Table 17 and Table 18 show the solicited local and systemic ARs in the 6y – 11y age group in the blinded Part 2 of Study P204 by mRNA-1273 dose. The rates following placebo doses are shown for comparison.

The percentages of participants with solicited local ARs were similar between Dose 1 and Dose 2 of mRNA-1273 in this age group. There was a trend towards higher severity of reported local ARs following Dose 2 of mRNA-1273 with 41.3% of participants reporting Grade 2 reactions after Dose 2 as compared with 27.7% after Dose 1.

The percentages of participants reporting solicited systemic ARs were generally higher following Dose 2 of mRNA-1273 as compared with Dose 1 with a higher percentage of Grade 3 systemic ARs (overall, dose 2: 12% vs. dose 1: 2%).

There were no Grade 4 systemic or local ARs after either dose in this age group.

Table 17. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 6 Through 11 Years of Age, Solicited Safety Set

Solicited Adverse Reaction	6-11 years Blinded Phase mRNA-1273 50 µg Dose 1 N=3003 n (%)	6-11 years Blinded Phase Placebo Dose 1 N=993 n (%)	6-11 years Blinded Phase mRNA-1273 50 µg Dose 2 N=2993 n (%)	6-11 years Blinded Phase Placebo Dose 2 N=970 n (%)
Any local AR - N1	3003	993	2993	970
Any	2812 (93.6)	481 (48.4)	2856 (95.4)	489 (50.4)
Grade 1	1927 (64.2)	449 (45.2)	1499 (50.1)	445 (45.9)
Grade 2	831 (27.7)	29 (2.9)	1235 (41.3)	39 (4.0)
Grade 3	54 (1.8)	3 (0.3)	122 (4.1)	5 (0.5)
Pain at injection site - N1[a]	3003	993	2993	970
Any	2794 (93.0)	466 (46.9)	2839 (94.9)	479 (49.4)
Grade 1	2017 (67.2)	441 (44.4)	1703 (56.9)	444 (45.8)
Grade 2	749 (24.9)	25 (2.5)	1055 (35.2)	33 (3.4)
Grade 3	28 (0.9)	0	81 (2.7)	2 (0.2)
Erythema at injection site - N1[b]	3003	993	2993	970
Any	350 (11.7)	13 (1.3)	561 (18.7)	9 (0.9)
Grade 1	234 (7.8)	9 (0.9)	267 (8.9)	6 (0.6)
Grade 2	100 (3.3)	3 (0.3)	261 (8.7)	2 (0.2)
Grade 3	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Swelling at injection site - N1 [b]	3003	993	2993	970
Any	353 (11.8)	11 (1.1)	507 (16.9)	12 (1.2)
Grade 1	254 (8.5)	8 (0.8)	314 (10.5)	12 (1.2)
Grade 2	80 (2.7)	2 (0.2)	173 (5.8)	0
Grade 3	19 (0.6)	1 (0.1)	20 (0.7)	0
Axillary Swelling - N1[c]	3003	993	2993	970
Any	464 (15.5)	84 (8.5)	539 (18.0)	65 (6.7)
Grade 1	399 (13.3)	81 (8.2)	413 (13.8)	55 (5.7)
Grade 2	62 (2.1)	2 (0.2)	123 (4.1)	8 (0.8)
Grade 3	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (6-11 years) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1.

Abbreviations: AR = adverse reaction; mm = millimeter; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.

Notes: Any = Grade 1 or higher; There were no Grade 4 solicited local ARs reported; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for injection site pain is defined as: Grade 1 = Does not interfere with activity; Grade 2 = Interferes with activity; Grade 3 = Prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization.

b. Toxicity grade for injection site erythema (redness) or swelling/induration (hardness) is defined as: Grade 1 = 25-50 mm; Grade 2 = 51-100 mm; Grade 3 = >100 mm; Grade 4 = Necrosis or exfoliative dermatitis.

c. Toxicity grade for axillary (underarm) swelling or tenderness ipsilateral to the side of injection is defined as: Grade 1 = No interference activity; Grade 2 = Some interference with activity; Grade 3 = Prevents daily activity; Grade 4 = Emergency room visit or hospitalization.

Table 18. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 6 Through 11 Years of Age, Solicited Safety Set

Solicited Adverse Reaction	6-11 years Blinded Phase mRNA-1273 50 µg Dose 1 N=3003 n (%)	6-11 years Blinded Phase Placebo Dose 1 N=993 n (%)	6-11 years Blinded Phase mRNA-1273 50 µg Dose 2 N=2993 n (%)	6-11 years Blinded Phase Placebo Dose 2 N=970 n (%)
Any systemic AR – N1	3003	993	2993	970
Any	1740 (57.9)	518 (52.2)	2339 (78.1)	485 (50.0)
Grade 1	1101 (36.7)	346 (34.8)	826 (27.6)	323 (33.3)
Grade 2	585 (19.5)	160 (16.1)	1148 (38.4)	148 (15.3)
Grade 3	54 (1.8)	12 (1.2)	365 (12.2)	14 (1.4)
Fatigue – N1[a]	3002	993	2992	970
Any	1298 (43.2)	335 (33.7)	1927 (64.4)	335 (34.5)
Grade 1	852 (28.4)	215 (21.7)	800 (26.7)	226 (23.3)
Grade 2	414 (13.8)	112 (11.3)	936 (31.3)	101 (10.4)
Grade 3	32 (1.1)	8 (0.8)	191 (6.4)	8 (0.8)
Headache – N1 [a]	3002	993	2992	970
Any	938 (31.2)	307 (30.9)	1626 (54.3)	275 (28.4)
Grade 1	671 (22.4)	228 (23.0)	759 (25.4)	188 (19.4)
Grade 2	249 (8.3)	75 (7.6)	748 (25.0)	79 (8.1)
Grade 3	18 (0.6)	4 (0.4)	119 (4.0)	8 (0.8)
Myalgia (Muscle Pain) – N1 [a]	3002	993	2992	970
Any	438 (14.6)	96 (9.7)	844 (28.2)	104 (10.7)
Grade 1	315 (10.5)	73 (7.4)	429 (14.3)	74 (7.6)
Grade 2	112 (3.7)	22 (2.2)	344 (11.5)	29 (3.0)
Grade 3	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Arthralgia (Joint Pain) – N1 [a]	3002	993	2992	970
Any	260 (8.7)	75 (7.6)	484 (16.2)	84 (8.7)
Grade 1	213 (7.1)	65 (6.5)	309 (10.3)	71 (7.3)
Grade 2	44 (1.5)	9 (0.9)	150 (5.0)	13 (1.3)
Grade 3	3 (<0.1)	1 (0.1)	25 (0.8)	0
Nausea/Vomiting – N1[b]	3002	993	2992	970
Any	327 (10.9)	107 (10.8)	717 (24.0)	97 (10.0)
Grade 1	275 (9.2)	93 (9.4)	532 (17.8)	78 (8.0)
Grade 2	47 (1.6)	14 (1.4)	166 (5.5)	19 (2.0)
Grade 3	5 (0.2)	0	19 (0.6)	0
Chills – N1[c]	3002	993	2992	970
Any	309 (10.3)	67 (6.7)	906 (30.3)	73 (7.5)
Grade 1	242 (8.1)	54 (5.4)	510 (17.0)	60 (6.2)
Grade 2	64 (2.1)	13 (1.3)	377 (12.6)	13 (1.3)
Grade 3	3 (<0.1)	0	19 (0.6)	0
Fever (≥38ºC) – N1[d]	3002	993	2993	970
Any Fever	98 (3.3)	15 (1.5)	717 (24.0)	18 (1.9)
Grade 1	53 (1.8)	11 (1.1)	384 (12.8)	11 (1.1)

Solicited Adverse Reaction	6-11 years Blinded Phase mRNA-1273 50 µg Dose 1 N=3003 n (%)	6-11 years Blinded Phase Placebo Dose 1 N=993 n (%)	6-11 years Blinded Phase mRNA-1273 50 µg Dose 2 N=2993 n (%)	6-11 years Blinded Phase Placebo Dose 2 N=970 n (%)
Grade 2	28 (0.9)	2 (0.2)	219 (7.3)	5 (0.5)
Grade 3	17 (0.6)	2 (0.2)	114 (3.8)	2 (0.2)
Grade 4	0	0	0	0

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (6-11 years) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1

Abbreviations: AR = adverse reaction; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.

Percentages are based on the number of exposed participants who submitted any data for the event (N1).

Notes: Any=Grade 1 or higher; There were no Grade 4 solicited systemic ARs reported; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for fatigue, headache, myalgia, and arthralgia is defined as Grade 1 = No interference with activity; Grade 2 = Some interference with activity; Grade 3 = Significant; prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization.

b. Toxicity grade for nausea/vomiting is defined as Grade 1 = no interference with activity or 1-2 episodes/24 hours; Grade 2 = some interference with activity or >2 episodes/24 hours; Grade 3 = prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization for hypotensive shock.

c. Toxicity grade for chills is defined as Grade 1 = no interference with activity; Grade 2 = some interference with activity not requiring medical intervention; Grade 3 = prevents daily activity and requires medical intervention; Grade 4 = Requires emergency room visit or hospitalization.

d. Toxicity grade for fever is defined as: Grade 1 = 38.0 – 38.4°C; Grade 2 = 38.5 – 38.9°C; Grade 3 = 39.0 – 40.0°C; Grade 4 = >40°C.

Exploratory analyses of solicited adverse reactions by baseline SARS-CoV-2 status
After Dose 1, the frequencies of solicited local ARs were similar to those of the of the overall safety population, except for axillary swelling or tenderness, which was higher among those with a positive SARS-CoV2 status at baseline (24.5%).

In general, solicited systemic ARs after Dose 1 were more frequently reported among participants who were positive for SARS-CoV-2 status at baseline, most notably for the solicited ARs of fever (16.3%), headache (49.4%), myalgia (24.5%), and chills (19.8%).

Subpopulation analyses of solicited adverse reactions
Subpopulation analyses by sex and race and ethnicity were performed for solicited adverse reactions. Results observed among the subpopulations were similar to those of the overall safety set.

Vaccine-naïve, 2 years – 5 years, 2 doses, mRNA-1273 (25µg)
Table 19 and Table 20 show the solicited local and systemic ARs in the 2y – 5y age group in the blinded Part 2 of Study P204 by dose.

The percentage of participants with any solicited local reaction was higher following Dose 2 of mRNA-1273 (73%) as compared with Dose 1 (63%), particularly pain (Dose 2: 71%, Dose 1: 61%).

The percentage of participants with any solicited systemic AR was also higher following Dose 2 of mRNA-1273 (62%) as compared with Dose 1 (54%), particularly fatigue (dose 2: 48%, Dose 1: 40%) and fever (Dose 2: 17%, Dose 1: 9%).

Table 19. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 2 Through 5 Years of Age, Solicited Safety Set

Solicited Adverse Reaction	2-5 years Blinded Phase mRNA-1273 25 µg Dose 1 N=2955 n (%)	2-5 years Blinded Phase Placebo Dose 1 N=971 n (%)	2-5 years Blinded Phase mRNA-1273 25 µg Dose 2 N=2977 n (%)	2-5 years Blinded Phase Placebo Dose 2 N=974 n (%)
Any local AR - N1	2954	971	2977	973
Any	1875 (63.5)	407 (41.9)	2186 (73.4)	411 (42.2)
Grade 1	1643 (55.6)	388 (40.0)	1714 (57.6)	396 (40.7)
Grade 2	209 (7.1)	15 (1.5)	437 (14.7)	15 (1.5)
Grade 3	23 (0.8)	4 (0.4)	35 (1.2)	0
Pain at injection site - N1[a]	2952	971	2977	973
Any	1813 (61.4)	382 (39.3)	2127 (71.4)	402 (41.3)
Grade 1	1663 (56.3)	370 (38.1)	1760 (59.1)	393 (40.4)
Grade 2	146 (4.9)	12 (1.2)	356 (12.0)	9 (0.9)
Grade 3	4 (0.1)	0	11 (0.4)	0
Erythema at injection site - N1[b]	2953	971	2977	973
Any	166 (5.6)	14 (1.4)	265 (8.9)	17 (1.7)
Grade 1	111 (3.8)	9 (0.9)	179 (6.0	15 (1.5)
Grade 2	43 (1.5)	2 (0.2)	73 (2.5)	2 (0.2)
Grade 3	12 (0.4)	3 (0.3)	13 (0.4)	0
Swelling at injection site - N1 [b]	2953	971	2977	973
Any	137 (4.6)	17 (1.8)	247 (8.3)	13 (1.3)
Grade 1	87 (2.9)	15 (1.5)	173 (5.8)	12 (1.2)
Grade 2	40 (1.4)	0	60 (2.0)	1 (0.1)
Grade 3	10 (0.3)	2 (0.2)	14 (0.5)	0
Axillary/Groin Swelling - N1[c]	2952	971	2977	973
Any	206 (7.0)	56 (5.8)	271 (9.1)	33 (3.4)
Grade 1	196 (6.6)	55 (5.7)	250 (8.4)	30 (3.1)
Grade 2	10 (0.3)	1 (0.1)	20 (0.7)	3 (0.3)
Grade 3	0	0	1 (<0.1)	0

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (2-5 years) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1.

Abbreviations: AR = adverse reaction; mm = millimeter; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.

Notes: Any = Grade 1 or higher; There were no Grade 4 solicited local ARs reported; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for injection site pain/tenderness for participants 6-36 months/37 months – 5 years is defined as: Grade 1 = Mild discomfort to touch or some pain but no interference with normal daily activities/Does not interfere with activity; Grade 2 = Cries when limb is moved, refuses to move limb, or pain interferes with normal daily activities/Interferes with activity; Grade 3 = Significant pain at rest or pain prevents normal daily activities/Prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization.

b. Toxicity grade for injection site erythema (redness) or swelling/induration (hardness) for participants 6-36 months/37 months – 5 years is defined as: Grade 1 = 5-20 mm/25-50 mm; Grade 2 = >20-50mm/51-100 mm; Grade 3 = >50mm/>100 mm; Grade 4 = Necrosis or exfoliative dermatitis.

c. Toxicity grade for axillary (underarm) or groin swelling or tenderness ipsilateral to the side of injection for participants 6-36 months/37 months – 5 years is defined as: Grade 1 = Some swelling or tenderness but no interference with normal daily activities/No interference activity; Grade 2 = Swelling or tenderness that interferes with normal daily activities/Some interference with activity; Grade 3 = Swelling or tenderness that prevents normal daily activities/Prevents daily activity; Grade 4 = Emergency room visit or hospitalization.

Table 20. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 2 Through 5 Years of Age, Solicited Safety Set

Solicited Adverse Reaction	2-5 years Blinded Phase mRNA-1273 25 µg Dose 1 N=2955 n (%)	2-5 years Blinded Phase Placebo Dose 1 N=971 n (%)	2-5 years Blinded Phase mRNA-1273 25 µg Dose 2 N=2977 n (%)	2-5 years Blinded Phase Placebo Dose 2 N=974 n (%)
Any systemic AR – N1	2954	971	2977	974
Any	1594 (54.0)	487 (50.2)	1835 (61.6)	436 (44.8)
Grade 1	1036 (35.1)	317 (32.6)	973 (32.7)	286 (29.4)
Grade 2	488 (16.5)	143 (14.7)	725 (24.4)	135 (13.9)
Grade 3	66 (2.2)	25 (2.6)	132 (4.4)	15 (1.5)
Grade 4	4 (0.1)	2 (0.2)	5 (0.2)	0
Fatigue – N1[a]	2013	649	2005	636
Any	807 (40.1)	236 (36.4)	962 (48.0)	187 (29.4)
Grade 1	503 (25.0)	138 (21.3)	479 (23.9)	114 (17.9)
Grade 2	283 (14.1)	87 (13.4)	438 (21.8)	64 (10.1)
Grade 3	21 (1.0)	11 (1.7)	45 (2.2)	9 (1.4)
Headache – N1 [a]	2013	649	2005	636
Any	232 (11.5)	78 (12.0)	313 (15.6)	52 (8.2)
Grade 1	181 (9.0)	66 (10.2)	195 (9.7)	44 (6.9)
Grade 2	46 (2.3)	10 (1.5)	110 (5.5)	7 (1.1)
Grade 3	5 (0.2)	2 (0.3)	8 (0.4)	1 (0.2)
Myalgia (Muscle Pain) – N1 [a]	2013	649	2005	636
Any	200 (9.9)	59 (9.1)	312 (15.6)	48 (7.5)
Grade 1	138 (6.9)	45 (6.9)	193 (9.6)	31 (4.9)
Grade 2	57 (2.8)	12 (1.8)	110 (5.5)	14 (2.2)
Grade 3	5 (0.2)	2 (0.3)	9 (0.4)	3 (0.5)
Arthralgia (Joint Pain) – N1 [a]	2013	649	2005	636
Any	124 (6.2)	32 (4.9)	170 (8.5)	29 (4.6)
Grade 1	101 (5.0)	28 (4.3)	119 (5.9)	19 (3.0)
Grade 2	21 (1.0)	3 (0.5)	48 (2.4)	10 (1.6)
Grade 3	2 (<0.1)	1 (0.2)	3 (0.1)	0
Nausea/Vomiting – N1[b]	2013	649	2005	636
Any	137 (6.8)	50 (7.7)	195 (9.7)	32 (5.0)
Grade 1	113 (5.6)	38 (5.9)	151 (7.5)	27 (4.2)
Grade 2	17 (0.8)	10 (1.5)	37 (1.8)	5 (0.8)
Grade 3	7 (0.3)	2 (0.3)	7 (0.3)	0
Chills – N1[c]	2013	649	2005	636
Any	129 (6.4)	40 (6.2)	246 (12.3)	31 (4.9)
Grade 1	99 (4.9)	29 (4.5)	165 (8.2)	21 (3.3)
Grade 2	29 (1.4)	11 (1.7)	77 (3.8)	8 (1.3)
Grade 3	1 (<0.1)	0	4 (0.2)	2 (0.3)
Irritability/Crying – N1[d]	938	319	972	336
Any	511 (54.5)	163 (51.1)	532 (54.7)	153 (45.5)
Grade 1	365 (38.9)	122 (38.2)	354 (36.4)	111 (33.0)
Grade 2	134 (14.3)	36 (11.3)	168 (17.3)	39 (11.6)
Grade 3	12 (1.3)	5 (1.6)	10 (1.0)	3 (0.9)
Sleepiness – N1[e]	938	319	972	336
Any	284 (30.3)	92 (28.8)	352 (36.2)	90 (26.8)

Solicited Adverse Reaction	2-5 years Blinded Phase mRNA-1273 25 µg Dose 1 N=2955 n (%)	2-5 years Blinded Phase Placebo Dose 1 N=971 n (%)	2-5 years Blinded Phase mRNA-1273 25 µg Dose 2 N=2977 n (%)	2-5 years Blinded Phase Placebo Dose 2 N=974 n (%)
Grade 1	274 (29.2)	88 (27.6)	339 (34.9)	90 (26.8)
Grade 2	8 (0.9)	4 (1.3)	12 (1.2)	0
Grade 3	2 (0.2)	0	1 (0.1)	0
Loss of appetite – N1[f]	939	319	972	336
Any	225 (24.0)	71 (22.3)	300 (30.9)	69 (20.5)
Grade 1	190 (20.2)	60 (18.8)	249 (25.6)	61 (18.2)
Grade 2	28 (3.0)	9 (2.8)	43 (4.4)	8 (2.4)
Grade 3	7 (0.7)	2 (0.6)	8 (0.8)	0
Fever (≥38ºC) – N1[g]	2954	971	2976	972
Any Fever	262 (8.9)	59 (6.1)	503 (16.9)	65 (6.7)
Grade 1	158 (5.3)	30 (3.1)	252 (8.5)	35 (3.6)
Grade 2	73 (2.5)	19 (2.0)	173 (5.8)	28 (2.9)
Grade 3	27 (0.9)	8 (0.8)	73 (2.5)	2 (0.2)
Grade 4[h]	4 (0.1)	2 (0.2)	5 (0.2)	0

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (2-5 years) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1

Abbreviations: AR = adverse reaction; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.

Percentages are based on the number of exposed participants who submitted any data for the event (N1).

Notes: Any=Grade 1 or higher; There were no Grade 4 solicited systemic ARs reported for events other than fever; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for participants 37 months – 5 years fatigue, headache, myalgia, and arthralgia is defined as Grade 1 = No interference with activity; Grade 2 = Some interference with activity; Grade 3 = Significant; prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization.

b. Toxicity grade for participants 37 months – 5 years nausea/vomiting is defined as Grade 1 = no interference with activity or 1-2 episodes/24 hours; Grade 2 = some interference with activity or >2 episodes/24 hours; Grade 3 = prevents daily activity; Grade 4 = Requires emergency room visit or hospitalization for hypotensive shock.

c. Toxicity grade for chills for participants 37 months – 5 years is defined as Grade 1 = no interference with activity; Grade 2 = some interference with activity not requiring medical intervention; Grade 3 = prevents daily activity and requires medical intervention; Grade 4 = Requires emergency room visit or hospitalization.

d. Toxicity grade for irritability/crying for participants 6-36 months is defined as Grade 1 = Lasting <1 hour or easily consolable; Grade 2 = Lasting 1-3 hours or requiring increased attention; Grade 3 = Lasing >3 hours or inconsolable; Grade 4 = requires emergency room visit or hospitalization.

e. Toxicity grade for sleepiness for participants 6-36 months is defined as Grade 1 = Sleepier than usual or less interested in surroundings; Grade 2 = Not interested in surroundings or sleeps through meals; Grade 3 = Sleeps most of the time, hard to arouse; Grade 4 = Inability to arouse.

f. Toxicity grade for loss of appetite for participants 6-36 months is defined as Grade 1 = Eating less than normal for 1-2 feeds/meals; Grade 2 = Missed 1-2 feeds/meals completely; Grade 3 = Missed >2 feeds/meals completely or refuses most feeds/meals; Grade 4 = Requires emergency room visit or hospitalization.

g. Toxicity grade for fever for participants 6-36 months/37 months – 5 years is defined as: Grade 1 = 38.0 – 38.4°C; Grade 2 = 38.5 – 39.5°C/38.5 – 38.9°C; Grade 3 = 39.6 – 40.0°C/39.0 – 40.0°C; Grade 4 = >40°C.

h. For one mRNA-1273 recipient, Grade 4 fever was reported by the investigator but was not reported in the eDiary, and the temperature measurement was not provided.

Exploratory analyses baseline SARS-CoV-2 status, 2y-5y, vaccine naïve, 2 doses, mRNA-1273

Subgroup analyses by SARS-CoV-2 status at baseline were performed for solicited adverse reactions among mRNA-1273 recipients. After Dose 1 and Dose 2 , the frequencies of solicited ARs by baseline SARS-CoV-2 status were similar to those reported by the overall solicited safety population, except for:

- Dose 1 – the frequencies of axillary/groin swelling/tenderness, fever, and irritability/crying were slightly higher among those with a positive SARS-CoV2 status at baseline (11.2%, 13.1%, and 61.4%, respectively).

- Dose 2 - fatigue was less frequently reported by participants with a positive baseline SARS-CoV-2 status (37.3%) while sleepiness and loss of appetite were more frequently reported (46.2% and 40.9%, respectively)

Subpopulation analyses of solicited adverse reactions, 2 doses, mRNA-1273, vaccine naïve, 2 years through 5 years
Subpopulation analyses by sex and race and ethnicity were performed for solicited adverse reactions. No notable differences were observed among the subgroups.

Vaccine-naïve, 6 months – 23 months, 2 doses, mRNA-1273 (25µg)
The percentage of participants with any solicited local reaction (Table 21) was higher following Dose 2 of mRNA-1273 (54%) as compared with Dose 1 (44%), particularly pain (Dose 2: 45%, Dose 1: 37%) and swelling (Dose 2: 15%, Dose 1: 8%).

Table 21. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 6 Through 23 Months of Age, Solicited Safety Set

Solicited Adverse Reaction	6-23 months Blinded Phase mRNA-1273 25 µg Dose 1 N=1982 n (%)	6-23 months Blinded Phase Placebo Dose 1 N=661 n (%)	6-23 months Blinded Phase mRNA-1273 25 µg Dose 2 N=1975 n (%)	6-23 months Blinded Phase Placebo Dose 2 N=646 n (%)
Any local AR - N1	1981	661	1975	646
Any	863 (43.6)	219 (33.1)	1056 (53.5)	198 (30.7)
Grade 1	778 (39.3)	212 (32.1)	876 (44.4)	187 (28.9)
Grade 2	74 (3.7)	5 (0.8)	151 (7.6)	11 (1.7)
Grade 3	11 (0.6)	2 (0.3)	29 (1.5)	0
Pain at injection site - N1[a]	1980	661	1975	646
Any	722 (36.5)	196 (29.7)	893 (45.2)	169 (26.2)
Grade 1	704 (35.6)	195 (29.5)	850 (43.0)	163 (25.2)
Grade 2	18 (0.9)	1 (0.2)	42 (2.1)	6 (0.9)
Grade 3	0	0	1 (<0.1)	0
Erythema at injection site - N1[b]	1980	661	1975	646
Any	171 (8.6)	25 (3.8)	270 (13.7)	25 (3.9)
Grade 1	129 (6.5)	20 (3.0)	168 (8.5)	20 (3.1)
Grade 2	36 (1.8)	3 (0.5)	85 (4.3)	5 (0.8)
Grade 3	6 (0.3)	2 (0.3)	17 (0.9)	0
Swelling at injection site - N1 [b]	1980	661	1975	646
Any	166 (8.4)	20 (3.0)	293 (14.8)	16 (2.5)
Grade 1	124 (6.3)	19 (2.9)	206 (10.4)	14 (2.2)
Grade 2	36 (1.8)	1 (0.2)	70 (3.5)	2 (0.3)
Grade 3	6 (0.3)	0	17 (0.9)	0
Groin/Axillary Swelling - N1[c]	1979	661	1975	646
Any	116 (5.9)	31 (4.7)	173 (8.8)	31 (4.8)
Grade 1	115 (5.8)	31 (4.7)	171 (8.7)	31 (4.8)
Grade 2	1 (<0.1)	0	2 (0.1)	0
Grade 3	0	0	0	0

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (6-23 months) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1.
Abbreviations: AR = adverse reaction; mm = millimeter; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.
Notes: Any = Grade 1 or higher; There were no Grade 4 solicited local ARs reported; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for injection site pain/tenderness is defined as: Grade 1 = Mild discomfort to touch or some pain but no interference with normal daily activities; Grade 2 = Cries when limb is moved, refuses to move limb, or pain interferes with normal daily activities; Grade 3 = Significant pain at rest or pain prevents normal daily activities; Grade 4 = Requires emergency room visit or hospitalization.
b. Toxicity grade for injection site erythema (redness) or swelling/induration (hardness) is defined as: Grade 1 = 5-20 mm; Grade 2 = >20-50mm; Grade 3 = >50mm/; Grade 4 = Necrosis or exfoliative dermatitis.
c. Toxicity grade for groin or underarm swelling or tenderness ipsilateral to the side of injection is defined as: Grade 1 = Some swelling or tenderness but no interference with normal daily activities; Grade 2 = Swelling or tenderness that interferes with normal daily activities; Grade 3 = Swelling or tenderness that prevents normal daily activities; Grade 4 = Emergency room visit or hospitalization.

Rates of solicited systemic reactions (Table 22) were generally similar following each dose, except for fever which was reported at a higher rate after Dose 2 (14%) compared with Dose 1 (10%).

Table 22. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days After Each Dose, Study P204 Part 2 Blinded Phase, 6 Through 23 Months of Age, Solicited Safety Set

Solicited Adverse Reaction	6-23 months Blinded Phase mRNA-1273 25 µg Dose 1 N=1982 n (%)	6-23 months Blinded Phase Placebo Dose 1 N=661 n (%)	6-23 months Blinded Phase mRNA-1273 25 µg Dose 2 N=1975 n (%)	6-23 months Blinded Phase Placebo Dose 2 N=646 n (%)
Any systemic AR – N1	1981	661	1975	646
Any	1499 (75.7)	481 (72.8)	1460 (73.9)	440 (68.1)
Grade 1	1006 (50.8)	327 (49.5)	892 (45.2)	293 (45.4)
Grade 2	444 (22.4)	143 (21.6)	510 (25.8)	134 (20.7)
Grade 3	48 (2.4)	10 (1.5)	53 (2.7)	13 (2.0)
Irritability/Crying – N1[a]	1970	659	1968	645
Any	1325 (67.3)	412 (62.5)	1270 (64.5)	382 (59.2)
Grade 1	918 (46.6)	282 (42.8)	812 (41.3)	258 (40.0)
Grade 2	382 (19.4)	123 (18.7)	427 (21.7)	119 (18.4)
Grade 3	25 (1.3)	7 (1.1)	31 (1.6)	5 (0.8)
Sleepiness – N1[b]	1972	659	1968	645
Any	723 (36.7)	243 (36.9)	702 (35.7)	227 (35.2)
Grade 1	700 (35.5)	237 (36.0)	683 (34.7)	219 (34.0)
Grade 2	19 (1.0)	5 (0.8)	16 (0.8)	7 (1.1)
Grade 3	4 (0.2)	1 (0.2)	3 (0.2)	1 (0.2)
Loss of appetite – N1[c]	1970	659	1968	645
Any	579 (29.4)	177 (26.9)	625 (31.8)	171 (26.5)
Grade 1	503 (25.5)	157 (23.8)	533 (27.1)	154 (23.9)
Grade 2	63 (3.2)	19 (2.9)	74 (3.8)	15 (2.3)
Grade 3	13 (0.7)	1 (0.2)	18 (0.9)	2 (0.3)
Fever (≥38ºC) – N1[d]	1978	661	1972	646
Any Fever	204 (10.3)	58 (8.8)	280 (14.2)	54 (8.4)
Grade 1	103 (5.2)	31 (4.7)	142 (7.2)	23 (3.6)
Grade 2	88 (4.4)	23 (3.5)	124 (6.3)	24 (3.7)
Grade 3	12 (0.6)	3 (0.5)	9 (0.5)	7 (1.1)
Grade 4	1 (<0.1)	1 (0.2)	5 (0.3)	0

Source: Adapted from STN 125752/276, Study mRNA-1273-P204 Final Clinical Study Report, Primary Series (2-5 years) Tables 14.3.1.1.1.2.1 and 14.3.1.1.2.2.1

Abbreviations: AR = adverse reaction; N = total number of participants in the group; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event.

Percentages are based on the number of exposed participants who submitted any data for the event (N1).

Notes: Any=Grade 1 or higher; There were no Grade 4 solicited systemic ARs reported other than fever; Percentages are based on the number of exposed participants who submitted any data for the event (N1).

a. Toxicity grade for irritability/crying for participants 6-36 months is defined as Grade 1 = Lasting <1 hour or easily consolable; Grade 2 = Lasting 1-3 hours or requiring increased attention; Grade 3 = Lasing >3 hours or inconsolable; Grade 4 = requires emergency room visit or hospitalization.
b. Toxicity grade for sleepiness for participants 6-36 months is defined as Grade 1 = Sleepier than usual or less interested in surroundings; Grade 2 = Not interested in surroundings or sleeps through meals; Grade 3 = Sleeps most of the time, hard to arouse; Grade 4 = Inability to arouse
c. Toxicity grade for loss of appetite for participants 6-36 months is defined as Grade 1 = Eating less than normal for 1-2 feeds/meals; Grade 2 = Missed 1-2 feeds/meals completely; Grade 3 = Missed >2 feeds/meals completely or refuses most feeds/meals; Grade 4 = Requires emergency room visit or hospitalization.
d. Toxicity grade for fever is defined as: Grade 1 = 38.0 – 38.4°C; Grade 2 = 38.5 – 39.5°C; Grade 3 = 39.6 – 40.0°C; Grade 4 = >40°C.

Exploratory analyses by baseline SARS-CoV-2 status, vaccine naïve, 2 doses, 6m – 23m
Subgroup analyses by SARS-CoV-2 status at baseline were performed for solicited adverse reactions among mRNA-1273 recipients. Results were similar to those of the overall solicited safety population.

Subpopulation analyses of solicited adverse reactions, 6m – 23m
Subpopulation analyses by sex and race and ethnicity were performed for solicited adverse reactions. No notable differences were observed among the subgroups when compared to analyses in the overall safety population.

6.1.12.3.2 Single dose, mRNA-1273 (6 years through 11 years) and mRNA-1273.214 (6 months through 5 years), vaccine-experienced

Vaccine-experienced, 6 years- 11 years, single dose, mRNA-1273 (25ug)
Solicited Local Adverse Reactions
Table 23 includes the percentages of participants who reported any solicited local AR, by maximum severity, within 7 days after vaccination. The most frequently reported local AR was pain at injection site, reported by 89.1% of participants. Most solicited local ARs were Grade 1 in severity. Severe (Grade 3) solicited local ARs were reported by 1.8% of participants, with no Grade 4 solicited local AR reported.

The majority of solicited local ARs had onset within the first 1-2 days after vaccination. Solicited local ARs had a median duration of 2 days.

Table 23. Frequency of Solicited Local Reactions Within 7 Days After Additional Dose of mRNA-1273, Participants 6 Years Through 11 Years of Age, Study P204 Booster Phase, Solicited Safety Set

Solicited Adverse Reaction	Additional Dose of mRNA-1273 (25 µg) N1=2257 n (%)
Any local adverse reaction	--
Any	2033 (90.1)
Grade 1	1319 (58.4)
Grade 2	673 (29.8)
Grade 3	41 (1.8)
Pain at injection site[a]	--
Any	2010 (89.1)
Grade 1	1403 (62.2)
Grade 2	580 (25.7)
Grade 3	27 (1.2)
Erythema (redness) [b]	--
Any ≥25 mm	213 (9.4)
Grade 1	113 (5.0)
Grade 2	93 (4.1)

Solicited Adverse Reaction	Additional Dose of mRNA-1273 (25 µg) N1=2257 n (%)
Grade 3	7 (0.3)
Swelling (hardness) [b]	--
Any ≥25 mm	218 (9.7)
Grade 1	134 (5.9)
Grade 2	77 (3.4)
Grade 3	7 (0.3)
Axillary (or groin) swelling or tenderness [a]	--
Any	570 (25.3)
Grade 1	407 (18.0)
Grade 2	157 (7.0)
Grade 3	6 (0.3)

Source: mRNA-1273-P204 Final CSR Booster Dose (6 months to 5 years) Table 14.3.1.3.7.1.2
Abbreviations: mm = millimeter; N1=total number of participants who contributed any data for the event; n= number of participants who experienced the event.
Any= Grade 1 or higher
There were no grade 4 solicited local adverse reactions reported
[a] Pain or axillary (or groin) swelling or tenderness is defined as: Grade 1 = no interference with activity; Grade 2 = Some interference with activity; Grade 3 = Prevents daily activity; Grade 4 = Emergency room visit or hospitalization.
[b] Injection site erythema (redness) or swelling (hardness) is defined as: Grade 1 = 25-50 mm; Grade 2 = 51-100 mm; Grade 3 = > 100 mm; G4 = Necrosis or exfoliative dermatitis.

Solicited Systemic Adverse Reactions

Table 24 includes the percentages of participants who reported any solicited systemic AR, by maximum severity, within 7 days after vaccination. The most frequently reported systemic AR were fatigue and headache, reported by 45.1% and 35.4% of participants, respectively. Fever was reported by 6.7% of participants, with 1.1% reporting fever ≥39.0°C. Most solicited local ARs were Grade 1 or 2 in severity. Severe (Grade 3) solicited local ARs were reported by 4.6% of participants. One participant reported a Grade 4 systemic AR, which was an event of Grade 4 fever 4 days postvaccination in a participant with concurrent diagnosis of COVID-19.

The majority of solicited systemic ARs had onset within the first 1-2 days postvaccination. Solicited local ARs had a median duration of 2 days, with 1.8% persisting beyond 7 days. Use of antipyretic or pain medication was reported by 32.7% of participants within 7 days postvaccination.

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Additional Dose of mRNA-1273, Participants 6 Years Through 11 Years of Age, Study P204 Booster Phase, Solicited Safety Set

Solicited Adverse Reaction	mRNA-1273 (25 µg) Single Dose N1=2252-2259 n (%)
Any Systemic Reaction	--
Any	1378 (61.0)
Grade 1	732 (32.4)
Grade 2	542 (24.0)
Grade 3	103 (4.6)
Grade 4	1 (<0.1)
Fatigue[a]	--
Any	1018 (45.1)
Grade 1	569 (25.2)
Grade 2	393 (17.4)

Solicited Adverse Reaction	mRNA-1273 (25 µg) Single Dose N1=2252-2259 n (%)
Grade 3	56 (2.5)
Grade 4	0
Headache [a]	--
Any	799 (35.4)
Grade 1	487 (21.6)
Grade 2	282 (12.5)
Grade 3	30 (1.3)
Grade 4	0
Myalgia [a]	--
Any	434 (19.2)
Grade 1	278 (12.3)
Grade 2	133 (5.9)
Grade 3	23 (1.0)
Grade 4	0
Arthralgia [a]	--
Any	253 (11.2)
Grade 1	178 (7.9)
Grade 2	61 (2.7)
Grade 3	14 (0.6)
Grade 4	0
Nausea/Vomiting [b]	--
Any	272 (12.1)
Grade 1	208 (9.2)
Grade 2	53 (2.3)
Grade 3	11 (0.5)
Grade 4	0
Chills [c]	--
Any	281 (12.5)
Grade 1	185 (8.2)
Grade 2	91 (4.0)
Grade 3	5 (0.2)
Grade 4	0
Fever	--
Any Fever ≥38.0ºC	151 (6.7)
Grade 1 (38.0-38.4°C)	79 (3.5)
Grade 2 (38.5-38.9°C)	48 (2.1)
Grade 3 (39.0- 40.0°C)[a]	23 (1.0)
Grade 4 (≥40.0°C)	1 (<0.1)
Used of antipyretic or pain medication	738 (32.7)

Source: mRNA-1273-P204 Final CSR Booster Dose (6 to 11 years) Table 14.3.1.3.7.1.2

Abbreviations: N1=total number of participants who contributed any data for the event; n= number of participants who experienced the event

[a] Headache, fatigue, myalgia, arthralgia: Grade 1 = No interference with activity; Grade 2 = Some interference with activity; Grade 3 = Prevents daily activity; Grade 4 = Emergency room visit or hospitalization.

[b] Nausea/vomiting: Grade 1 = No interference with activity or 1-2 episodes/24 hours; Grade 2 = Some interference with activity or >2 episodes/24 hours; Grade 3 = Prevents daily activity; Grade 4 = Emergency room visit or hospitalization for hypotensive shock.

[c] Chills: Grade 1 = No interference with activity; Grade 2 = Some interference with activity not requiring medical intervention; Grade 3 = Prevents daily activity and requires medical intervention; Grade 4 = Emergency room visit or hospitalization.

***Clinical Reviewer Comment**:*

Assessment of the solicited safety data after a single dose in vaccine-experienced participants (booster dose) is limited by the open-label study design for this part of the

study. In general, rates of solicited ARs appeared to be similar after this single dose compared with those after the 2-dose series (see section 6.1.12.3.1).

6.1.12.4 Unsolicited AEs

Immediate unsolicited AEs (within 30 minutes of injection)
Vaccine-naïve, 6 months – 11 years, 2 doses, mRNA-1273 (Part 2)
Immediate unsolicited AEs occurring within 30 minutes of vaccination were infrequent in the blinded phase of Part 2 and occurred in 7 mRNA-1273 recipients (0.2%) and 2 placebo recipients (0.2%). Of these, 2 in the mRNA-1273 group (<0.1%) and 1 in the placebo group (0.1%) occurred after Dose 1, and 5 in the mRNA-1273 group (0.2%) and 1 in the placebo group (0.1%) occurred after Dose 2. All of the events were mild in severity and nonserious. By MedDRA PT, each event occurred in a single participant as follows: presyncope, tinnitus, flushing, abdominal pain upper, injection site bruising, injection site pruritis, and vaccination site injury in the mRNA-1273 group; and abdominal pain and diarrhea in the placebo group. None of the events were clinically concerning for anaphylaxis.

Vaccine-experienced, single dose, mRNA-1273 (6 years – 11 years) and mRNA-1273.214 (6 months – 6 years)
There were 2 immediate unsolicited AEs, both in the ≥6 months to <2 years age group. These events (injection site injury and skin laceration) were nonserious and considered mild in intensity

Unsolicited AEs within 28 days of study doses
Vaccine-naïve, 6 months – 11 years, 2 doses, mRNA-1273 (Part 2)
Overall, unsolicited AEs within 28 days of any study dose were reported by similar percentages of participants in the mRNA-1273 and placebo groups in each age group.

- Ages 6 years – 11 years: mRNA-1273 (50µg) – 26%; Placebo 21%
- Ages 2 years – 5 years: mRNA-1273 (25µg) – 36% ; Placebo 32%
- Ages 6 months – 23 months: mRNA-1273 (25µg) – 44%; Placebo 43%

Severe AEs were rare (<1% of participants in each age group).

Unsolicited AEs most commonly belonged to the following MedDRA system organ classes (SOCs) and preferred terms (PTs), by age group:

- Ages 6 years – 11 years
  - SOC *Infections and infestations* (mRNA-1273: 10%, placebo: 8%)
    - PT upper respiratory tract infection (mRNA-1273: 4%, placebo: 3%)
  - SOC *Respiratory, thoracic, & mediastinal disorders* (mRNA-1273: 6%, placebo: 7%)
    - PT oropharyngeal pain (mRNA-1273: 2.2%, placebo 2.9%)
  - SOC *General disorders & administration site* conditions (mRNA-1273: 7%, placebo 1%)
    - PT injection site erythema (mRNA-1273: 2.5%, placebo 0%)

- Ages 2 years – 5 years
  - SOC *Infections and infestations* (mRNA-1273: 21%, placebo: 20%)
    - PT upper respiratory tract infection (mRNA-1273: 9%, placebo: 10%)

  - SOC *Respiratory, thoracic, & mediastinal disorders* (mRNA-1273: 8%, placebo: 8%)
    - PT rhinorrhea (mRNA-1273: 4%, placebo 4%)
    - PT cough (mRNA-1273: 4%, placebo 4%)
  - SOC *General disorders & administration site* conditions (mRNA-1273: 5%, placebo 3%)
    - PT pyrexia (mRNA-1273: 2%, placebo 2%)

- Ages 6 months – 23 months
  - SOC *Infections and infestations* (mRNA-1273: 30%, placebo: 29%)
    - PT upper respiratory tract infection (mRNA-1273: 12%, placebo: 13%)
  - SOC *Gastrointestinal disorders* (mRNA-1273: 10%, placebo 10%)
    - PT pyrexia (mRNA-1273: 5%, placebo 2=5%)
  - SOC *Respiratory, thoracic, & mediastinal disorders* (mRNA-1273: 9%, placebo: 8%)
    - PT rhinorrhea (mRNA-1273: 5%, placebo 5%)

***Clinical Reviewer Comment**:*
No new safety concerns for Spikevax administered as a 2- dose to vaccine-naïve children 6 months – 11 years of age were identified.

Vaccine-experienced 6 years – 11 years, single dose, mRNA-1273 (25µg)
Within 28 days after receipt of an additional dose of mRNA-1273, unsolicited AEs were reported by 10.0% of participants who were initially enrolled in Part 2 of study P204. Most unsolicited AEs were under the MedDRA SOC of *Infections and infestations* (4.8%). By MedDRA PT, the most commonly reported unsolicited AEs within 28 days were upper respiratory tract infection (1.5%), urticaria (0.7%), and cough (0.5%). There was only one severe AE observed within 28 days, which was an event of abdominal pain, also classified as an SAE, that was assessed as unrelated to study vaccine. Unsolicited AEs within 28 days which were assessed as related to vaccination by the investigator were reported by 1.0% of study participants. The majority of these events were under the MedDRA SOC of *Skin and subcutaneous tissue disorders* (0.3%) and *General disorders and administration site conditions* (0.3%), and were events associated with vaccine reactogenicity.

The rates and types of unsolicited AEs were similar when including data from participants initially enrolled in Part 1 of study P204.

***Clinical Reviewer Comment**:*
No new safety concerns for Spikevax administered as a single dose to vaccine-experienced children 6 years – 11 years of age were identified.

Vaccine-experienced 6 months – 5 years, single dose, mRNA-1273.214 (10µg)
Unsolicited AEs were reported by 12.3% of participants within 28 days after receipt of an additional single dose of mRNA-1273.214. Unsolicited AEs were primarily reported under the MedDRA SOC of *Infections and infestations* (9.8%). By PT, the most commonly reported unsolicited AEs within 28 days were otitis media (1.7%), influenza (1.5%) and ear infection (1.1%). Unsolicited AEs within 28 days that were assessed as related by the investigator were reported by 0.3% of study participants, and mainly represented events associated with vaccine reactogenicity.

***Clinical Reviewer Comment**:*
No new safety concerns for Spikevax administered as a single dose to vaccine-experienced children 6 months – 5 years of age were identified.

6.1.12.5 FDA Standard MedDRA Queries of AEs within 28 days of study dose

Vaccine-naïve and vaccine-experienced participants, P204 all parts
SMQs using FDA-developed software were conducted to evaluate the Safety Set for constellations of unsolicited AEs with onset following vaccination through the end of the study. The SMQs were conducted on AE PTs that could represent various conditions, including but not limited to embolic & thrombotic events, convulsions, central nervous system (CNS) vascular disorders, hypersensitivity, peripheral neuropathy, demyelination, cardiac arrhythmias, and cardiomyopathy. There were no safety concerns identified through the SMQs evaluated.

Clinical Reviewer Comment:
There were no cases meeting the definition of myocarditis/pericarditis and no evidence of increased risk of myocarditis/pericarditis following vaccination in children 6 months through 11 years of age in study P204.

6.1.12.6 Medically Attended Adverse Events (MAAEs)

Vaccine-naïve, 6 years – 11 years, 2 doses, mRNA-1273 (50 µg)
Through the end of the blinded phase of Part 2, MAAEs were reported by 17% of mRNA-1273 recipients and 16% of placebo recipients. MAAEs were most commonly reported under the MedDRA SOC of *Infections and infestations* (9% in each group).

MAAEs occurring within 28 days of any study dose in Parts 1 and 2 and assessed as related to the study dose by investigators were reported by 0.9% of participants. These most commonly belonged to the SOCs *General disorders and administration site conditions* (0.3%) and *Skin and subcutaneous tissue disorders* (0.3%). None were severe in intensity. The following event of alopecia areata was assessed by the investigator as related to study vaccination:

- Alopecia areata: A 7-year-old female with no past medical history and no family history of immune-mediated diseases experienced progressive hair loss, diagnosed by dermatologists as alopecia areata, 27 days after receiving a first dose of mRNA-1273. She was reported with an upper respiratory tract infection 9 days later, followed by wheezing the next day. The investigator assessed the AE of alopecia areata as related to study vaccination and considered it to be not resolved. The participant withdrew from the study approximately 8 months post-Dose 2 due to withdrawal of consent.

***Clinical Reviewer Comment**:*
There is a reasonable possibility that the event of alopecia areata was related to study vaccination based on the close time to onset following study vaccination and lack of a past personal or family history of autoimmune conditions. Therefore, this event is recommended for inclusion in the USPI. The onset of upper respiratory tract infection symptoms approximately one week later does, however, provide a potential biologically plausible alternative etiology.

Vaccine-naïve, 2 years through *5 years, 2 doses, mRNA-1273 (25 µg)*
Through the end of the blinded phase of Part 2, MAAEs were reported by 17% of mRNA-1273 recipients and 16% of placebo recipients. MAAEs were most commonly reported under the MedDRA SOC of Infections and infestations (9% in each group).

MAAEs occurring within 28 days of any study dose in Part 1 and 2 and assessed as related to the study dose by investigators were reported by 0.8% of participants. These most commonly belonged to the SOCs *General disorders and administration site conditions* (0.2%) and *Infections and infestations* (0.2%). No participants reported events that were severe in intensity.

Vaccine-naïve, 6 months – 23 months, 2 doses, mRNA-1273 (25µg)
Through the end of the blinded phase of Part 2, MAAEs were reported by 53% of mRNA-1273 recipients and 51% of placebo recipients.

MAAEs occurring within 28 days of any study dose in Part 1 and 2 and assessed as related to the study dose by investigators were reported by 0.9% of participants. These most commonly belonged to the SOCs *Infections and Infestations* (0.4%) *and General disorders and administration site conditions* (0.3%). Two participants reported events that were severe in intensity (PTs *febrile convulsion* [N=1] and urticaria [N=1]).

Vaccine-experienced 6 years – 11 years, single dose, mRNA-1273 (25µg)
Through the end of the study, with a median follow-up of 12 months after receipt of the additional dose of mRNA-1273, MAAEs were reported by 33.3% of participants, including those initially enrolled in either Part 1 or Part 2 of P204. MAAEs were most commonly reported under the MedDRA SOC of *Infections and infestations* (23.8%). MAAEs assessed as related to study vaccination were reported by 0.6% of study participants. The majority of these related MAAEs were events consistent with vaccine reactogenicity (e.g., arthralgia, injection site reactions, pyrexia). There was an event of serum sickness-like reaction that was assessed by the investigator as related to study vaccination, as follows:

- Serum sickness-like reaction: A 9-year-old male experienced urticaria, arthralgia, myalgia, chills, and nausea 10 days following vaccination that was diagnosed as mild serum sickness-like reaction. Treatment included analgesics, antihistamines, and steroids. There were no other contributory factors identified and no concurrent AEs reported. The event was considered resolved 47 days after onset.

Clinical Reviewer Comment*:*
Based on the close temporal relationship to receipt of study vaccine and lack of a clear alternative etiology, there is a reasonable possibility that the event of serum sickness-like reaction may have been related to study vaccination and is recommended for inclusion in the USPI.

Vaccine-experienced 6 months – 5 years, single dose, mRNA-1273 (25µg)
Through the end of the study, based on a median duration of follow up of 184 days post-vaccination, MAAEs were reported by 39.2% of study participants. MAAEs were most commonly reported under the MedDRA SOC of *Infections and infestations* (34.1%) and represent common childhood illnesses. MAAEs assessed as related to study vaccination were reported by 0.4% of study participants (n=11). The majority of these related MAAEs were events consistent with vaccine reactogenicity (e.g., pyrexia, lymphadenopathy, rash).

6.1.12.7 Adverse Events of Special Interest (AESIs)

Participants were monitored in the study for AESIs based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (Appendix A). In addition, narrow and broad SMQs were searched to identify unsolicited AEs that had not been reported as AESIs but fit into the protocol AESI medical concept categories.

Vaccine-naïve, 6 years – 11 years, 2 doses, mRNA-1273(50 µg)
Throughout the blinded phase of Part 2, there were 9 AESIs among 7 participants in the mRNA-1273 group (0.2%) and 3 AESIs among 2 participants in the placebo group (0.2%). One AESI in the mRNA-1273 group was assessed as related to the study vaccine:

- Non-cardiac chest pain: A 7-year-old male with no past medical history was seen in the ED for mild nonserious intermittent chest pain and mild shortness of breath 2 days after his second dose of mRNA-1273. He was reported to be afebrile with a normal examination, normal echocardiogram, and normal electrocardiogram (ECG) and tested negative for COVID-19. His shortness of breath resolved the same day and his AESI of chest pain resolved within 4 days.

***Clinical Reviewer Comment**:*
Despite the observed temporal relationship with study vaccination, the event of non-cardiac chest pain was graded mild (severity) and was short in duration. Furthermore, the cardiac work-up was negative. These factors do not suggest that this event represents a safety concern. This event is not recommended for inclusion in the USPI.

Other AESIs reported were ageusia (3 participants [<0.1%] in the mRNA-1273 group and 2 [0.2%] in the placebo group) and anosmia (2 [<0.1%] and 1 [0.1%] participants, respectively). All events in the mRNA-1273 group were associated with upper respiratory tract infections or symptoms and all events in the placebo group were associated with COVID-19.

Three additional AESIs in the mRNA-1273 group, 2 events of appendicitis, and 1 event of petit mal epilepsy in a participant with a medical history of epilepsy, were also reported as SAEs. None of these events were assessed by the investigator as related to study vaccination.

Throughout the blinded and open-label crossover phases of Part 2, a total of 21 participants (0.6%) reported 26 AESIs: 18 participants (0.6%) in the mRNA-1273 group and 3 participants (0.4%) in the placebo crossover group. The most frequently reported events, by MedDRA SOC, were *Nervous system disorders* in 13 participants (0.4%) and *Infections and infestations* in 5 participants (0.1%). By MedDRA PT, the most frequently reported events were ageusia in 8 participants, anosmia in 7 participants, and appendicitis in 5 participants. Each of the remaining AESIs reported occurred in a single participant. There were no reports of myocarditis, pericarditis, or multisystem inflammatory syndrome in children (MIS-C).

The most frequently reported new AESIs occurring during the open-label crossover phase were ageusia in 5 participants, anosmia in 5 participants, and appendicitis in 3 participants. All events of ageusia and anosmia were associated with COVID-19 disease. There was also one participant in the mRNA-1273 group reported an AESI of Kawasaki disease (KD) 188 days after the study dose (also reported as an SAE). All of these AESIs were assessed by the investigator as not related to study vaccination.

***Clinical Reviewer Comment**:*
It was determined that the additional AESIs were likely not related to the study doses after careful review of the associated case narratives.

In Part 1 of the study, a total of 12 participants (1.6%) reported 12 AESIs: 5 participants (1.3%) in the 50 µg mRNA-1273 group and 7 participants (1.9%) in the 100 µg mRNA-1273 group.

Of these, there was one AESI of mild non-cardiac chest pain that occurred 72 days after Dose 2 50 µg mRNA-1273 and resolved the same day, with normal vital signs and no findings on physical examination, was assessed by the investigator as possibly related to study vaccination based on no confirmed alternative etiology.

There were no reports of myocarditis, pericarditis, or multisystem inflammatory syndrome in children (MIS-C).

Vaccine-naïve, 2 years – 5 years, 2 doses, mRNA-1273 (25 µg)
Throughout the blinded phase of Part 2, there were 11 AESIs among 9 participants in the mRNA-1273 group (0.3%) and 9 AESIs among 7 participants in the placebo group (0.7%). By MedDRA PT, each event in the vaccine group occurred in a single participant, except for erythema multiforme which was reported in 2 mRNA-1273 recipients. In the placebo group, each event occurred in a single participant, except for febrile seizure which was reported in 3 placebo recipients.

Two AESIs in the mRNA-1273 group (erythema multiforme and chest pain) were considered related to mRNA-1273 :

- Erythema multiforme: a 3-year-old male experienced mild erythema multiforme affecting his arms 3 days after Dose 2 which resolved the next day without treatment.
- Non-cardiac chest pain: A 4-year-old male experienced mild chest pain 5 days after Dose 2 which resolved spontaneously within 30 minutes. Cardiology evaluation was negative.

Clinical Reviewer Comments*:*

1. *The AESI of erythema multiforme is likely related to mRNA-1273 based on the close temporal relationship to study vaccination and absence of an alternative etiology. It is recommended for inclusion in the USPI.*

2. *For the AESI of non-cardiac chest pain, based on the close temporal relationship to study vaccination, relatedness cannot definitively be ruled out; however, the negative cardiac evaluation and rapid resolution of symptoms do not suggest this event represents a safety concern. Therefore, this AESI is not recommended for inclusion in the USPI.*

3. *There was an additional case of erythema multiforme occurring 3 days after study dose 1 in a 3-year-old participant with concurrent viral infection (influenza A) and otitis media. The event of EM resolved spontaneously. The participant received study dose 2 and did not experience another episode of EM within 28 days of study dose. The event of EM was considered not related to the study dose by the investigator, which appears reasonable. The concurrent illness provides an alternative etiology, and the negative re-challenge supports lack of vaccine causality. This event is not recommended for inclusion in the USPI.*

Throughout the blinded and open-label crossover phases of Part 2, there were no additional AESIs that were considered related to study vaccination by the study investigator. There were no cases of MIS-C reported in the mRNA-1273 group.

Clinical Reviewer Comment*:*

Following careful review of the relevant case narratives, the additional AESI are not likely related to study vaccinations.

In Part 1 of the study, there was one AESI of epilepsy was reported in 1 participant in the 50 µg group (0.6%), and there were no reported AESIs in the 25 µg group. The event of epilepsy occurred 126 days after Dose 2, resolved within 13 days, and was considered not related to study vaccination.

Vaccine-naïve, 6 months – 23 months, 2 doses, mRNA-1273 (25µg)
Throughout the blinded phase of Part 2, there were 8 AESIs among 8 participants in the mRNA-12 group (0.4%) and 2 AESIs among 2 participants in the placebo group (0.3%). By MedDRA PT, AESIs in the mRNA-1273 group included 5 events of febrile convulsion and one event each of seizure, liver injury, and erythema multiforme. In the placebo group, there was one event each of febrile convulsion and acute respiratory failure. Two AESIs of febrile convulsion and 1 of seizure that occurred in the mRNA-1273 group within 28 days of study vaccination were also considered SAEs, and related to study vaccination, and are discussed below in section 6.1.12.8. The following AESI was also considered related to study vaccination by the study investigator:

- Asymptomatic elevation in liver enzymes: A 9-month-old female experienced asymptomatic mild acute liver injury that was identified during her routine well-child check 1 day after receipt of Dose 2. She had experienced viral gastroenteritis the week before vaccination. Bloodwork was done for liver function tests (LFTs) as monitoring due to her mother having cystic fibrosis and being on medication while breastfeeding, although she had discontinued breastfeeding 3 months earlier. Repeat bloodwork 3 days later showed improvement. The event was considered resolved within 23 days and was assessed by the investigator as possibly related to study vaccination.

***Clinical Reviewer Comments**:*

1. *Despite a temporal relationship with study vaccination and the reported elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), the event of acute liver injury is more likely related to the participant's recent viral gastroenteritis. Therefore it is not recommended for inclusion in the USPI.*

2. *There was an unsolicited AE of febrile convulsion in the mRNA-1273 group that was not considered an AESI by the investigator because the event was not new in onset. The event occurred 23 days after Dose 2 in a 1-year-old male with a concurrent AE of otitis media, which provides a plausible alternative etiology this AE.*

Throughout the blinded and open-label crossover phases of Part 2, a total of 14 participants (0.6%) reported 16 AESIs: 13 participants (0.7%) in the mRNA-1273 group and 1 participant (0.2%) in the placebo crossover group. By MedDRA PT, additional AESIs that occurred beyond the blinded phase included 1 event of febrile seizure, 1 event of post-traumatic epilepsy, and 2 events of erythema multiforme. None of these events were considered related to study vaccination by the investigator.

***Clinical Reviewer Comment**:*
An additional unsolicited AE of febrile convulsion occurred 402 days after Dose 2 in an 11-month-old female mRNA-1273 recipient with a concurrent viral illness that was assessed by the investigator as not related to study vaccination. This event was considered not related to study vaccination.

There was one case of KD in the mRNA-1273 group that was considered an AESI of MIS-C. The case was also considered an SAE and was assessed as unrelated to study vaccination by the study investigator, as discussed below in section 6.1.12.8.

Vaccine-experienced 6 years – 11 years, single dose, mRNA-1273 (25µg)
Through the end of the study, AESIs were reported by 0.5% of participants (n=12). None of these AESIs occurred within 28 days of the study dose and none were considered related to the study dose.

Vaccine-experienced 6 months – 5 years, single dose, mRNA-1273 (25µg)
Through the end of the study, AESIs were reported by 2 participants (<0.1%). One was an event of seizure in a 35-month-old male participant with onset on Day 138 after vaccination, in the setting of gastroenteritis and fever the day prior to seizure onset. One was an event of Kawasaki disease in a 3-year-old female participant with onset on Day 157 postvaccination. Both AESIs were also classified as SAEs, and both were assessed by the investigator as unrelated to study vaccine. There were no cases of myocarditis or pericarditis reported in the study.

> ***Clinical Reviewer Comment****:*
> *These two AESIs were likely unrelated to study vaccine due to the prolonged interval between study vaccination and the study doses. The AESI of seizure also had a plausible alternative etiology of concurrent infectious gastroenteritis with fever.*

6.1.12.8 Serious Adverse Events (SAEs)

Vaccine-naïve, 6 years – 11 years, 2 doses, 50 µg mRNA-1273 (Part 2)
Within 28 days after vaccination in the blinded phase of Part 2, 5 participants (0.2%) in the mRNA-1273 group and 1 participant (0.1%) in the placebo group reported SAEs. The reported SAEs in the vaccine group were appendicitis, cellulitis, cellulitis orbital, petit mal epilepsy, and cholecystitis, none of which were assessed by the investigator as related to study vaccination.

Throughout the blinded phase of Part 2, SAEs were reported in 8 mRNA-1273 recipients (0.3%) and 1 placebo recipient (0.1%). The 3 additional reported SAEs in the vaccine group were appendicitis, type 1 diabetes mellitus, and pyelonephritis/ urosepsis. None of the SAEs were considered related to study vaccination by the study investigator.

Throughout the blinded and open-label crossover phases of Part 2, a total of 25 participants (0.7%) reported 32 SAEs: 22 participants (0.7%) in the mRNA-1273 group and 3 participants (0.4%) in the placebo crossover group. The most frequently reported events were under the MedDRA SOC *Infections and infestations* in 11 participants (0.3%). By MedDRA PT, the most frequently reported events were appendicitis in 5 participants and pneumonia in 2 participants. Each of the remaining SAEs reported occurred in a single participant.

One SAE in a crossover participant was assessed by the investigator as related to study vaccination.

- Abdominal pain: A 6-year-old female who received mRNA-1273 in the crossover phase with a complex medical history including gross motor delay, imperforate anus repair, and cecostomy was seen in the emergency department (ED) with abdominal pain, that began following her routine morning enema, 2 days post-Dose 2 of mRNA-1273. Abdominal x-ray showed the cecostomy catheter was displaced and there were changes were suggestive of diffuse ileus. After tolerating an oral challenge, she was discharged home from the ED. Her symptoms resolved after 2 days.

***Clinical Reviewer Comment**:*
The SAE of abdominal pain is likely not related to study vaccination because the participant's underlying medical conditions provide a more plausible explanation for the event. This event is not recommended for inclusion in the USPI.

In the mRNA-1273 group, there was one SAE of KD during the open-label crossover phase that was assessed by the investigator as an AESI of MIS-C and as not related to study vaccination (see section 6.1.12.7).

In Part 1, SAEs were reported by 8 participants (1.1%): 5 in the 50µg group (1.3%) and 2 in the 100µg group (0.8%). None were assessed as related to study vaccination by the investigator.

***Clinical Reviewer Comment**:*
It was determined that the SAEs reported in Part 1 of the study were likely not related to the study vaccinations based on careful review of the relevant clinical narratives.

Vaccine-naïve, 2 years – 5 years, 2 doses, 25 µg mRNA-1273 (Part 2)
Within 28 days after vaccination in the blinded phase of Part 2, 4 participants (0.1%) in the mRNA-1273 group and 1 participant (<0.1%) in the placebo group reported SAEs. The reported SAEs in the mRNA-1273 group were adenovirus infection, metapneumovirus infection, pneumonia viral, and seizure. The SAE of seizure, also an AESI, occurred 22 days after Dose 2 of mRNA-1273 in a 4-year-old male with no identified risk factors and resolved the same day. No evaluation or treatment was reported. In the placebo group, there was one SAE of abdominal wall abscess. None of the SAEs were assessed by the investigator as related to study vaccination.

Throughout the blinded phase of Part 2, SAEs were reported in 19 mRNA-1273 recipients (0.6%) and 3 placebo recipient (0.3%). The most frequently reported events in the vaccine group were in the MedDRA SOC *Infections and infestations* in 11 participants (0.4%). By MedDRA PT, the most frequently reported event in the vaccine group was metapneumovirus infection in 2 mRNA-1273 recipients (0.4%). All other SAEs were reported in a single participant each, including the following:

- A 2-year-old male experienced an SAE/AESI of KD 80 days after Dose 2 with concurrent rhinovirus and adenovirus. He was treated with IVIG and high dose acetylsalicylic acid. Echocardiogram was reported as normal except for a "trivial pericardial effusion." The event resolved after 49 days and was considered unrelated to study vaccination by the investigator.
- A 4-year-old female experienced an SAE of dermatomyositis 183 days after Dose 2 that was ongoing. Due to progressive symptoms, she received supportive care and treatment with steroids and IVIG. Prior to onset, she had family exposure to symptomatic COVID-19, and on the day of onset, she tested positive for SARS-CoV-2. Because of other healthcare appointments, she was discontinued from the study due to withdrawal of consent.

Clinical Reviewer Comment:
It was determined that the reported SAEs reported were likely not related to the study doses based on careful review of the clinical narratives.

Throughout the blinded and open-label crossover phases of Part 2, SAEs were reported in 32 participants (1.1%) in the mRNA-1273 group and 8 participants (1.3%) in the placebo crossover

group. The majority of reported events were under the MedDRA SOC *Infections and infestations* in 23 participants (0.6%). By MedDRA PT, all events were reported in 1 to 2 participants each. None of the SAEs were considered related to study vaccination by the investigator, including the following events in mRNA-1273 recipients:

- A 3-year-old female with a history of prematurity experienced an SAE of type 1 diabetes mellitus 268 days after Dose 2 with symptoms of enuresis, polyuria, polydipsia, and fatigue for which she was treated with insulin.
- A 3-year-old male experienced an SAE of diabetic ketoacidosis (DKA) 227 days after Dose 2 and was preceded by a SARS-CoV-2 infection 2 days prior and resolved within 2 days. The participant was diagnosed with type 1 diabetes mellitus for which he was treated with insulin.

Clinical Reviewer Comment:
The reported SAEs were likely not related to study vaccination. The reported SAEs represented medical conditions and illnesses that are common in children in this age group.

There were no reported SAEs in the 2 years -5 years age group during Part 1 of the study.

Vaccine-naïve, 6 months – 23 months, 2 doses, 25µg mRNA-1273 (Part 2)
Within 28 days after vaccination in the blinded phase of Part 2, 13 participants (0.7%) in the mRNA-1273 group and 0 participants in the placebo group reported SAEs. The SAEs in the mRNA-1273 group were most frequently reported in the MedDRA SOC *Infections and infestations*. By MedDRA PT, each SAE occurred in a single participant, except for febrile convulsion (also an AESI) which occurred in 2 participants. One SAE of febrile convulsion occurred following an SAE of pyrexia, both of which were assessed by the investigator as related to study vaccination, as follows:

- A 1-year-old female experienced pyrexia (temperature of 103.1°F) starting 6 hours after Dose 1 and a suspected febrile convulsion (unusual crying and mildly depressed mental status without observed seizure activity) the following day. Both events resolved the next day. Three days later, a fine maculopapular rash was noted, possibly consistent with roseola. The participant experienced a second AESI of febrile seizure 50 days after Dose 1 that was witnessed and lasted less than a minute. The participant subsequently received Dose 2 without incident and completed the study.

Clinical Reviewer Comment*:*
The events of pyrexia and febrile convulsion may be related to study vaccination based on the close temporal relationship to study vaccination. They are recommended for inclusion in the USPI.

Other SAEs within 28 days after vaccination in the blinded phase that were also considered AESIs, but not considered related to study vaccination, included the following:

- A 1-year-old male experienced an SAE/AESI of febrile convulsion 21 days after Dose 1 that resolved the same day. Prior to the event, he had experienced episodes of fever and rash. He was evaluated by an infectious diseases specialist and a rheumatologist and diagnosed with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA syndrome). The participant received Dose 2 without incident.
- A 1-year-old female with a history of bronchopulmonary dysplasia and hypothyroidism experienced an SAE/AESI of seizure 20 days after Dose 2. Results of a brain MRI showed no evidence of an acute intracranial process or malformation and no significant sequelae of prior intraventricular hemorrhage. EEG results showed irregular activity

consistent with seizure disorder, and she was started on antiepileptic medication. The event was considered resolved with sequelae of seizure disorder within 6 days. Subsequently, the participant was diagnosed with cerebral palsy.

***Clinical Reviewer Comment**:*
These SAEs were likely not related to study vaccination based on time to onset following receipt of the study dose and the presence of more plausible alternative etiologies.

Throughout the blinded phase of Part 2, SAEs were reported in 31 mRNA-1273 recipients (1.6%) and 6 placebo recipient (0.9%). The most frequently reported events were in the MedDRA SOC *Infections and infestations* in 0.9% of the mRNA-1273 group and 0.6% of the placebo group. By MedDRA PT, the most frequently reported events were bronchiolitis (0.2% and 0.5%, respectively), febrile convulsion (0.2% and 0, respectively), and acute respiratory failure (0 and 0.3%, respectively). SAEs of DKA and type 1 diabetes mellitus were reported in one participant and assessed by the investigator as related to study vaccination, as follows:

- A 1-year-old female with a family history of Type 1 diabetes mellitus experienced symptoms of DKA, including polydipsia, polyuria, vomiting, and tachypnea, 37 days after Dose 2 for which she was admitted to the hospital, treated, and diagnosed with type 1 diabetes mellitus. She had a preceding upper respiratory tract infection several weeks prior. The SAE of DKA was considered resolved within 7 days with sequelae of type 1 diabetes mellitus. The investigator assessed the SAE as more likely due to a genetic predisposition and potentially triggered by the recent viral upper respiratory tract infection than the study dose.

***Clinical Reviewer Comment**:*
The recent viral upper respiratory tract infection and the family history of type 1 diabetes provide a biologically plausible and more probable etiologies for the SAEs of DKA and type 1 diabetes mellitus in this participant. These events are not recommended for inclusion in the USPI.

Throughout the blinded and open-label crossover phases of Part 2, SAEs were reported in a total of 49 participants (2.0%): 45 participants (2.3%) in the mRNA-1273 group and 4 participants (0.9%) in the placebo crossover group. Events were most frequently reported under the MedDRA SOC *Infections and infestations* in 31 participants (1.3%). By MedDRA PT, the most frequently reported event was bronchiolitis in 9 participants (0.4%). No additional SAEs beyond the blinded phase were considered related to study vaccination by the investigator.

One SAE and AESI of KD, considered MIS-C by the investigator, was reported in the mRNA-1273 group during the open-label crossover phase that was not considered related to study vaccination by the investigator, as follows:

- A 1-year-old male developed clinical symptoms of KD (lymphadenopathy, rash, mucositis, and fever) 163 days after Dose 2 with concurrent human metapneumovirus infection and rhinovirus infection. He was admitted to the hospital, evaluated by specialists in infectious disease and cardiology, and received treatment including IV hydration, antipyretics, and acetylsalicylic acid. The events were considered resolved within 16 days of onset

***Clinical Reviewer Comment**:*
The SAEs reported beyond the blinded phase were likely not related to study vaccination, and overall, represented medical conditions and illnesses that are common in children in this age group.

Vaccine-experienced 6 years – 11 years, single dose, 25µg mRNA-1273
Through the end of the study, SAEs were reported by 0.4% of participants (11 participants reporting 19 events). Of these events, only one occurred within 28 days postvaccination, which was an event of abdominal pain in a 7-year-old male 16 days after the study dose that required hospitalization for diagnostic work-up. It was assessed as not related by the investigator.

Vaccine-experienced 6 months – 5 years, single dose, 25µg mRNA-1273
Serious adverse events (SAEs) were reported by 0.8% of participants (23 participants reporting 32 events). Most SAEs were reported under the MedDRA SOC of *Infections and infestations* (0.6%). The most commonly reported SAE was pneumonia, reported by 5 participants (0.2%). None of the SAEs were assessed as related by the investigator.

***Clinical Reviewer Comment**:*
Based on a careful review of case narratives of all SAEs reported in this phase of the study, it was determined that none of the SAEs were related to the study vaccine.

6.1.12.9 Deaths

Vaccine naïve and experienced participants, P204 all parts
There was one death reported in the booster phase of study P204. A 4-year-old medically complex female participant with a history of congenital diaphragmatic hernia, pulmonary hypoplasia, and chronic respiratory failure (tracheostomy/ventilator-dependent) died of cardio-respiratory arrest on Day 144 after receipt of the additional single dose of mRNA-1273.214. The participants presented to the emergency room on Day 144 in respiratory failure with bradycardia and passed away later the same day. The participants had multiple prior hospitalizations for respiratory failure, most recently on Days 74 and 128 after vaccination. This event was assessed as unrelated to the study vaccine by the investigator.

***Clinical Reviewer Comment**:*
This death was unrelated to the study vaccine due to the latency of event onset after vaccination and the participant's underlying medical conditions with recent frequent exacerbations requiring hospitalization, which provide a more plausible etiology for the participant's presentation.

6.1.12.10 AEs leading to discontinuation

Vaccine naïve participants, 2 doses, 6 years – 11 years
Up to 28 days postvaccination in the blinded phase of Part 2, 3 mRNA-1273 recipients experienced 4 AEs leading to discontinuation from study vaccination after Dose 1 and before Dose 2 as compared with 0 placebo recipients. All 3 discontinuations were related to AEs of rash (PTs: rash pruritic 10 days after vaccination, rash 11 days after vaccination, and urticaria 24 days after vaccination). None were assessed as related to study doses by study investigators.

There was a single discontinuation from study participation due to an AE in the blinded phase of Part 2. This was an 8-year-old male with a reported AE of Crohn's disease 11 days post-Dose 2.

The participant had an ongoing medical history of recurrent abdominal pain, headaches, and seizure. He underwent endoscopy following recent blood work that suggested inflammatory bowel disease (IBD). The endoscopy results showed granulomas but did not show IBD. Additional immunologic and genetic testing was performed that demonstrated no immune response to previous routine vaccinations, and further testing was conducted to evaluate for a possible diagnosis of common variable immune deficiency. The participant was treated with medications for IBD a few months after the initial reported AE. The parent chose to withdraw him from the study due to associated multiple medical appointments.

Clinical Reviewer Comment*:*
The event of Crohn's disease was likely not related to the study dose based on the participant's previous medical history and the reported evaluations and findings.

In the open-label crossover phase of Part 2, there were no unsolicited AEs leading to discontinuation from study treatment or study participation.

In Part 1 of the study, one participant in the 50-µg mRNA-1273 group experienced an event of urticaria papular 9 days after Dose 1, assessed by the investigator as related to study vaccination, that resolved within 6 days and led to withdrawal from the study.

Vaccine-naïve participants, 2 doses, 2 years – 5 years
Up to 28 days postvaccination in the blinded phase of Part 2, there were 2 mRNA-1273 recipients who experienced 3 AEs leading to discontinuation from study vaccination after Dose 1 and before Dose 2 as compared with 0 placebo recipients.

- Loss of consciousness and dyspnea: A 4-year-old male experienced mild AEs of loss of consciousness and dyspnea 1 day after receiving Dose 1 of mRNA-1273. The event of loss of consciousness resolved within less than 1 minute, and the dyspnea resolved in 1 hour. Concurrent events included fatigue and vomiting with nausea and vomiting preceding. Both events were assessed by the investigator as related to study vaccination.
- Urticaria: A 4-year-old male experienced mild urticaria on his torso and wrists on the same day as receiving Dose 1 of mRNA-1273. The event resolved after 2 days and was assessed by the investigator as related to the study vaccination.

Clinical Reviewer Comment*:*
1. *Loss of consciousness and dyspnea: The events of loss of consciousness and dyspnea were of mild severity and short duration and likely represent mild syncope. Syncope following vaccination is included in the proposed Spikevax USPI, and this event does not appear to represent a safety concern. The events are not recommended for inclusion in the USPI.*

2. *Urticaria: This event of urticaria was possibly related to study vaccination. However, the percentages of participants 2 years – 5 years of age reporting urticaria within 28 days of vaccination were similar between the mRNA-1273 recipients (0.6%) and placebo recipients (0.5%) in the blinded phase of Part 2. Urticaria following vaccination is included in the USPI (Section 6.2). This event does not represent a new safety concern.*

In the open-label crossover phase of Part 2, there were no additional unsolicited AEs leading to discontinuation from study treatment or study participation.

In Part 1 of the study, there were no reported AEs leading to discontinuation from study vaccination or study participation.

Vaccine naïve participants, 2 doses, 6 months – 23 months
In the blinded phase of Part 2, there was 1 mRNA-1273 recipient who experienced an AE leading to discontinuation from study participation.

- A 1-year-old male experienced a mild AE of urticaria after receiving Dose 1 of mRNA-1273 on the same day. The event resolved within 1 day that was assessed by the investigator as related to study vaccination.

***Clinical Reviewer Comment**:*
This event of urticaria was possibly related to study vaccination. However, the percentages of participants 6 months – 23 months of age reporting urticaria within 28 days of vaccination were similar between the mRNA-1273 recipients (0.5%) and placebo recipients (0.8%) in the blinded phase of Part 2. Urticaria following vaccination is included in the USPI (Section 6.2). This event does not represent a new safety concern.

Throughout the blinded phase of Part 2, there were no additional unsolicited AEs leading to discontinuation from the study.

Clinical Reviewer Comment:
There was a data entry error resulting in the report of an AE leading to discontinuation from study vaccination up to the blinded phase cutoff date. The event of bilateral otitis media occurred 98 days after Dose 2, resolved, and was assessed by the investigator as not related to study vaccination. The participant did not discontinue due to an AE, but rather, due to rollover to Study P306.

In the open-label crossover phase of Part 2, there were no additional unsolicited AEs leading to discontinuation from study treatment or study participation.

In Part 1 of the study, there were no reported AEs leading to discontinuation from study vaccination or study participation.

Vaccine experienced participants, single dose, 6 months – 11 years
Through the end of the study, one participant discontinued from study participation due to an AE, which was the participant in the vaccine-experienced, single dose, 2y – 5y group who died due to cardio-respiratory arrest. The event is summarized in section 6.1.12.9.

6.1.13 Study Conclusions

The results of Study P204 support the safety and effectiveness of Spikevax when administered as a single dose to COVID-19 vaccine-experienced individuals 6 months – 11 years of age and as 2 doses (28-day interval) to COVID-19 vaccine-naïve individuals 6 months – 23 months of age.

6.2 Study mRNA-1273-P306

NCT05436834: "An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of mRNA Vaccines for SARS-CoV-2 Variants in Participants Aged 6 Months to <6 Years"

Study Overview: P306 was a Phase 3 study with 4 parts:

- Part 1, 2 doses (vaccine-naïve): 2 doses of the bivalent mRNA-1273.214 (Omicron BA.1/Original strain) in participants 6 months – 5 years of age who were COVID vaccine-naïve. Safety data (MAAEs, AESIs, and SAEs) will be presented from this study part. Dates conducted: June 2022 to June 2024
- Part 2, single dose (vaccine-experienced): a single dose of bivalent mRNA-1274.214 in participants 6 months – 5 years who were Spikevax-experienced. Dates conducted: June 2022-March 2023.
- Part 3, single dose (vaccine-experienced): a single dose of monovalent mRNA-1273.815 (XBB.1.1.5) in participants 6 months – 4 years previously vaccinated with any COVID vaccine. Data from this study part were not included with this sBLA submission.
- Part 4 Single dose and 2 doses (vaccine-naïve): an ongoing study part evaluating a single dose of mRNA-1273.815 in participants 2 years – 4 years of age who were COVID vaccine-naïve and 6 months – 23 months of age who were COVID vaccine-naïve. Dates conducted: March 2022 to October 2024 (2 years - 4years of age) and March 2024 to Jan 2025 (6 months -23 months of age)

6.2.1 Objectives

Clinical Reviewer Comment:
Only key study objectives/endpoints relevant to the analyses to support the proposed USPI dosing/administration regimen with this sBLA will be reviewed, which include Parts 1, 2, and 4 of Study P306.

6.2.1.1 Immunogenicity Objectives

Vaccine-experienced, 6 months through *5 years (single dose-10 µg) mRNA-1273.214 (P306 Part 2)*
Primary Objectives/Endpoints:
To infer the effectiveness of mRNA-1273.214 (single dose, 10 µg), based on immune responses against the original SARS-CoV-2 strain (D614G) and Omicron BA.1 strain obtained 28 days after vaccination in participants aged 6 months to <6 years who previously received 2 doses of mRNA-1273 primary series

- *Hypothesis #1:* Statistical superiority of serum nAb GMC against Omicron BA.1 strain after a single dose of mRNA-1273.214 compared with that after mRNA-1273 2-dose series in Study P204 in same age group
    - **Success criterion**: Lower bound of the CI for the ratio in nAb GMCs (Day 29 in Study P306 divided by Day 57 in Study P204) >1.0.

- *Hypothesis #2*: Statistical noninferiority of the SRR against SARS-CoV-2 Omicron BA.1 strain after a single dose of mRNA-1273.214 compared with that after mRNA-1273 2-dose series in Study P204 in same age group
    - **Success criterion**: Lower bound of the 95% CI for the difference in SRRs (Day 29 in Study P306 minus Day 57 in Study P204) > -5%

      Clinical Reviewer Comment*:*
      Noninferiority using the stricter statistical criterion of a LB >-5% (as compared with the LB >-10% used for the endpoint evaluating SRR against the D614G strain) was used to account for the increased frequency of baseline seropositivity due to prior SARS-CoV-2 exposure and COVID-19 vaccination.

- *Hypothesis #3*: Statistical noninferiority of the serum nAb GMC against ancestral SARS-CoV-2 (D614G) after a single dose of mRNA-1273.214 compared with that after mRNA-1273 2-dose series in Study P204 in same age group
    - **Success criterion**: Lower bound of the CI for the ratio in nAb GMCs (Day 29 GMC in Study P306 divided by Day 57 GMC in Study P204) >0.667

- *Hypothesis #4*: Statistical noninferiority of the SRR against ancestral SARS-CoV-2 after a single dose of mRNA-1273.214 compared with that after mRNA-1273 2-dose series in Study P204 in same age group
    - **Success criterion**: Lower bound of the 95%CI for the difference in SRRs (Day 29 in Study P306 minus Day 57 in Study P204) > -10%

Exploratory Clinical Efficacy Endpoints

Descriptive clinical efficacy endpoints evaluated the incidence of SARS-CoV-2 infection, asymptomatic SARS-CoV-2 infection, and COVID-19 disease (CDC defined) beginning 14 days after vaccination (See Appendix X for protocol definitions used for these endpoints).

Vaccine-naïve, 6 months – 4 years (single dose, 25 µg) mRNA-1273.815 (P306 Part 4)
Primary Objective/Endpoints:
Objective: To infer the effectiveness mRNA-1273.815 (single dose, 25 µg) based on immune responses against the Omicron XBB.1.5 strain at 28 days post-dose (Study Day 29) in participants aged 2 through 4 years (Part 4 Cohort A) who have evidence of prior SARS-CoV-2 infection

- *Hypothesis #1:* Noninferiority of serum Ab GM value against Omicron XBB.1.5 after mRNA- 1273.815 single dose (D29) in participants aged 2 years through 4 years with evidence of prior SARS-CoV-2 infection compared with that after 2 doses of mRNA-1273.815 (at D57, i.e., 28 days after second dose) in participants aged 6 months through 23 months without evidence of prior SARS-CoV-2 infection
    Success criterion: Lower bound of the CI for the ratio in nAb GMTs (Part 4 2y - 4y/Part 4 Cohort B) >0.667

Secondary Objective/Endpoint:
Objective: To assess mRNA-1273.815 (single dose, 25 µg) immune responses against SARS-CoV-2 (Omicron XBB.1.5) obtained 28 days postdose (Day 29) in participants aged 2 years through 4 years who had evidence of prior SARS-CoV-2 infection.

- *Hypothesis #2:* Noninferiority of SRR against Omicron XBB.1.5 after mRNA-1273.815 single dose (Day 29) in participants aged 2 years through 4 years with evidence of prior SARS-CoV-2 infection compared with that after 2 doses of mRNA-1273.815 (at Day 57, i.e., 28 days after second dose) in participants aged 6 months through 23 months (Part 4 Cohort B) without evidence of prior infection
    Success criterion: Lower bound of the 95%CI for the difference in SRR percentages (Part 4 2y - 4y minus Part 4 Cohort B) > -10%

6.2.1.2. Safety Objectives

Primary Objectives: To evaluate the safety and reactogenicity of the following:

- *Vaccine-experienced, 6 months* through *5 years, 10 µg mRNA-1273.214*
    - To evaluate the safety and reactogenicity of 10µg of the mRNA-1273.214 vaccine administered as a single BD at least 4 months post-Dose 2 in

participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series

- *Vaccine-naïve, 6 months* through *4 years, 25 µg mRNA-1273.815*
    - To evaluate the safety and reactogenicity of 25µg of the mRNA-1273.815 vaccine administered as a single dose in participants aged 2y – 4y or as a 2 dose primary series (28 days apart) in participants aged 6m – 23m

Endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection.
- Unsolicited adverse events (AEs) through 28 days after each injection.
- Medically attended adverse events (MAAEs) through the entire study period.
- Serious adverse events (SAEs) through the entire study period.
- AEs leading to discontinuation from study participation post-dose through the last day of study participation
- Adverse events of special interest (AESIs), including multisystem inflammatory syndrome in children (MIS-C) and myocarditis and/or pericarditis, through the entire study period.

6.2.2 Design Overview

Study P306 is a Phase 3, open-label, four-part study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273.214 or mRNA-1273.815 vaccine in healthy infants and children 6 months – 5 years of age or 6 months – 4 years of age, respectively

Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.214:
Part 1 of this study evaluated the safety, reactogenicity, and immunogenicity of 2 doses of 25 µg bivalent (Omicron BA.1/Original strain) mRNA-1273.214 in children 6 months – 5 years of age who were COVID vaccine-naïve. Part 1 was initiated on June 21, 2022, and completed on June 13, 2024.

Clinical Reviewer Comment:
Key safety results (Unsolicited AEs within 28 days, MAAEs, AESIs, and SAEs) from this study part are discussed in this review memo.

Vaccine-experienced, 6 months – 5 years, 10 µg mRNA-1273.214
Part 2 of this study evaluated the safety, reactogenicity, and immunogenicity of a single dose of 10 µg bivalent (Omicron BA.1/Original strain) mRNA-1273.214 in children 6 months through 5 years of age who were COVID vaccine (Spikevax)-experienced. Part 2 was initiated on June 22, 2022, and completed on March 23, 2023.

Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.815
Part 3 of this study is ongoing and evaluated the safety, reactogenicity, and immunogenicity of a single dose of 25µg monovalent (XBB.1.1.5) mRNA-1273.815 in children 6 months through 4 years of age who were previously vaccinated with any COVID vaccine.

Clinical Reviewer Comment:
Data collected from Part 3 of the study were not submitted to this sBLA and are not discussed in this review memorandum.

Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.815

Part 4 of this study is ongoing and evaluated the safety, reactogenicity, and immunogenicity of either a single dose (2- through 4-year-olds) or 2 doses (6- through 23-month-olds) of the 25 µg monovalent (XBB.1.1.5) mRNA-1273.815 in children 6 months through 4 years of age who were COVID vaccine-naïve. Part 4 was initiated on March 25, 2024, with a data cutoff date of November 8, 2024.

> ***Clinical Reviewer Comment:***
> *Study Parts 2 and 4 are discussed in detail below as results from these study parts are the most relevant to the desired indication. Key safety results from Part 1 are also discussed.*

6.2.3 Population

Vaccine-experienced, 6 months – 5 years, 10 µg mRNA-1273.214:
Children 6 months through 5 years of age who were in good health (including those with stable pre-existing medical conditions) and were at or above the 2nd percentile on their growth curves (according to the WHO Child Growth Standards).

Participants had previously received 2 doses of monovalent mRNA-1273 (25 µg) given approximately 1 month apart in Study P204 (Part 2 blinded or open label part), and the second dose must have been given at least 4 months prior to enrollment. Participants were excluded from the study Part if they had previously received a COVID-19 vaccine other than the mRNA-1273 vaccine and/or had experienced an SAE in Study P204 at the time of Screening for participation in Study P306.

Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.815:
Children 6 months through 4 years of age who were in good health (including those with stable pre-existing medical conditions) and were at or above the 2nd percentile on their growth curves (per WHO child growth standards). Participants were excluded from Part 4 of the study if they had previously received any COVID-19 vaccine or any Middle East respiratory syndrome coronavirus vaccine.

6.2.4 Study Treatments or Agents Mandated by the Protocol

1. mRNA-1273.214: a bivalent vaccine containing mRNA-1273 (ancestral strain) and mRNA-1273.529 that encodes for the S-2P of the SARS-CoV-2 Omicron variant (B.1.1.529) co-formulated at a 1:1 ratio and encapsulated in LNPs, supplied as a sterile liquid for injection at an mRNA concentration of 0.1 mg/mL.
    - Part 1: 2 doses of 0.25 mL containing 25 µg total mRNA (12.5 µg ancestral, 12.5 µg Omicron BA.1)
    - Part 2: Single dose of 0.2 mL containing 10 µg total mRNA (5 µg ancestral, 5 µg Omicron BA.1)
    - Lot: 8523300102

2. mRNA-1273.815 a monovalent vaccine containing 25 µg (0.25mL) of nucleoside modified mRNA encoding for the stabilized pre-fusion spike glycoprotein of the Omicron variant lineage XBB.1.5 encapsulated in lipid nanoparticles.
    - Part 4: Lots: 7090124001 and 8527800102

6.2.5 Directions for Use

Intramuscular injection into the deltoid muscle or anterolateral thigh.

6.2.6 Sites and Centers

Evaluation of mRNA-1273.214 was in Parts 1 and 2 of the study which enrolled participants at 35 clinical sites in the U.S.

Evaluation of mRNA-1273.815 was in Part 4 of the study which enrolled participants at 34 centers in the U.S., Dominican Republic, and Panama.

6.2.7 Surveillance/Monitoring

Safety Assessments
See section 6.1.7 for safety assessments, including measures for monitoring for myocarditis/pericarditis, except as noted below. Parents/legal authorized representatives (LARs) recorded solicited ARs in the eDiary daily for 7 days following each vaccination.

The evaluation of mRNA-1273.214 (Parts 1 and 2) after the initial 7 days following vaccination, use of the the eDiary was alternated with safety telephone calls every 4 weeks as the procedure for safety follow-up.

For the evaluation of mRNA1273.815 (Part 4), the eDiary was only used to collect ARs through 7 days following vaccination. This part of the study did not include active surveillance for SARS-CoV-2 infection or COVID-19 disease except for determination of SARS-CoV-2 infection prior to study injection(s). COVID-19 and related events were recorded as AEs.

Immunogenicity Assessments-
Immunogenicity assessments measured the following:

5. Baseline SARS-CoV-2 status (Parts 1 – 4) and asymptomatic/symptomatic SARS-CoV-2 infection (Parts 1 and 2) were evaluated using a SARS-CoV-2 rtRT-PCR assay validated by (b) (4) . Baseline SARS-CoV-2 status was also established using an in-vitro diagnostic assay, Elecsys anti-SARS-CoV-2 ECLIA assay to detect anti-SARS-CoV-2 N-protein IgG antibodies validated by PPD Laboratories.
6. Serum nAb levels against SARS-CoV-2 strains (D614G, BA.1, and XBB.1.5) as measured by a validated pseudovirus neutralization assays (PsVNAs). Immunogenicity analyses were based on nAb concentrations measured using the PsVNA for each strain conducted at PPD Vaccine Laboratories
7. Serum Ab directed against SARS-CoV-2 spike (S) protein, RBD, and nucleocapsid (N) protein were measured using ligand-binding MesoScale Discovery (MSD) electrochemiluminescence (ECL) multiplex assay (b) (4) at PPD Vaccine Laboratories

In Part 2, blood samples for immunologic analyses were collected on study Days 0, 29, and 181. In Part 4-cohort 4A, blood samples for immunologic analyses were collected on study Days 0 and 29; Part 4-cohort 4B, blood samples were collected on Study Days 0, 29, and 57.

Vaccine Effectiveness Assessments
Vaccine effectiveness was assessed based on serum neutralizing antibody responses. See section 6.2.1.1.

6.2.8 Endpoints and Criteria for Study Success

Refer to section 6.2.1.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Vaccine-experienced, 6 months – 5 years (single, 10µg) mRNA-1273.214 (Part 2)
The co-primary immunogenicity endpoints in P306 Part 2 compared the immune responses (as measured by nAb GMCs and SRRs against the D614G and Omicron BA.1 strains) in P306 participants at Day 29 (28 days after vaccination) with those in participants in the same age group in Study P204 at Day 57 (28 days after the second vaccination).

Hypothesis #1 and #2
For the calculation of the nAb GMCs, an ANCOVA model used the dependent variable of the serum nAb value and a group variable (mRNA-1273.214 vs. mRNA-1273) as the fixed variable and adjusted for age group (6 months to < 2 years; 2 to < 6 years). The nAb GMCs were estimated by the geometric least squares means (GLSMs) from the model and the ratios of the GMCs of the P306 Part 2 population to those of the P204 population were calculated along with the 2-sided 95%CIs.

Hypothesis #3 and #4
Seroresponse was defined at a participant level as a nAb level change from baseline (pre-Dose 1) of ≥ 4 × LLOQ for those with a baseline nAb level below LLOQ, or at least a 4-fold rise if the baseline level was ≥ LLOQ. The difference in percentages of participants meeting the seroresponse definition was calculated between the P306 population and the P204 population and the 95%CI was calculated using the Miettinen-Nurminen score method. The statistical noninferiority criterion for nAb seroresponse against the Omicron BA.1 strain (see section 6.2.1.1) was a LB of the 95%CI > -5%; and against the Original (D614G) strain (see section 6.2.1.1) was a LB of the 95%CI > -10%.

Subgroup analyses of immunogenicity endpoints were conducted based on sex (male, female), age group (6 months to <2 years; 2 years to <6 years), SARS-CoV-2 status at baseline, race, ethnicity, and obesity (based on a threshold ≥ 95th%ile based on WHO reference data).

Safety analyses, except summaries of solicited adverse reactions (ARs), were based on the Safety Set, which consisted of all participants who received a vaccine dose. Summaries of solicited ARs were based on the Solicited Safety Set, which consisted of all subjects in the Safety Set who contributed any solicited AR data. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported any event.

A two-sided 95% CI using the Clopper-Pearson method was provided for the percentage of subjects with any solicited local AR, solicited systemic AR, or any solicited AR.

Exploratory analyses described the incidence of COVID-19 cases (CDC-defined, see Appendix B) beginning 14 days after vaccination in participants who did not have evidence of COVID-19 or SARS-CoV-2 infection prior to vaccination.

Vaccine-naïve, 6 months – 4 years, 25µg mRNA-1273.815
The primary and key secondary immunogenicity endpoints in P306 Part 4 compared the immune responses (as measured by nAb GM value and SRR against the Omicron XBB.1.5 strain) in participants in Cohort A (single dose cohort) at Day 29 (28 days after a single vaccination) to

those in participants in Cohort B (2-dose cohort) at Day 57 (28 days after the second vaccination). Evaluation of the primary and key secondary immunogenicity endpoints in Part 4 was based on the PPIS-positive set for Cohort A (participants who had evidence of prior SARS-CoV-2 infection) compared to the PPIS-negative set for Cohort B (participants without evidence of prior SARS-CoV-2 infection).

Hypothesis #1
For the calculation of the nAb GMCs, an ANCOVA model used the dependent variable of the serum nAb value and a group variable (Cohort A vs. Cohort B) as the fixed variable. The nAb GMCs were estimated by the geometric least squares means (GLSMs) from the model and the ratios of the GMCs of the Cohort A population to those of the Cohort B population were calculated along with the 2-sided 95%CIs. Statistical noninferiority was based on a lower bound (LB) of the 95%CI >0.667.

Hypothesis #2
Seroresponse was defined at a participant level as a nAb level change from baseline (pre-Dose 1) of ≥ 4 × LLOQ for those with a baseline nAb level below LLOQ, or at least a 4-fold rise if the baseline level was ≥ LLOQ. The difference in percentages of participants meeting the seroresponse definition was calculated between the Cohort A population and the Cohort B. Statistical noninferiority was based on a LB of the 95%CI > -10%.

Subgroup analyses of immunogenicity endpoints were conducted based on sex, age (6 months to <12 months; 12 months to <2 years), race, ethnicity, and obesity (defined as BMI ≥ 95th%ile based on WHO growth reference data) and Baseline antibody values (<LLOQ and ≥LLOQ).

Safety analyses, except summaries of solicited adverse reactions (ARs), were based on the Safety Set, which consisted of all subjects who at least one dose of 1273.815. Summaries of solicited ARs were based on the Solicited Safety Set, which consisted of all subjects in the Safety Set who contributed any solicited AR data. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported any event.

A two-sided 95% CI using the Clopper-Pearson method was provided for the percentage of subjects with any solicited local AR, solicited systemic AR, or any solicited AR. Subgroup analyses were provided based on sex, race, ethnicity, and obesity.

Clinical Reviewer Comment:
Statistical plans for safety analyses were the same for P306 Parts 1, 2, and 4.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The study analysis populations are defined in Table 25.

Table 25. Analysis Populations, Study P306

Population	Description
Full Analysis Set (FAS)	The Full Analysis Set (FAS) consists of all enrolled participants who receive at least 1 injection of investigational product.
Safety Set	All participants who received at least 1 dose of investigational product

Population	Description
Solicited Safety Set	All participants in the Safety Set who contributed any solicited adverse reaction (AR) data, i.e., had at least 1 postbaseline solicited safety assessment.
Per-Protocol Set (PP set)	All participants who received the planned dose of study intervention as per schedule, were SARS-CoV-2 negative prior to the study dose, and had no major protocol deviations that impacted critical data.
Per-Protocol Immunogenicity Subset (PPIS)	Participants who received the planned dose of study intervention as per schedule, complied with the immunogenicity sample collection window for specified timepoints and had Ab assessment for the analysis endpoint, and had no major protocol deviations that impacted key or critical data; if participants had a diagnosis of HIV, they were not receiving HAART; and had Baseline SARS-CoV-2 status available
Per-Protocol Immunogenicity Subset - Pre-booster SARS-CoV-2 negative (PPIS-Neg)	Participants in the PPIS who were negative for virologic or serologic evidence of SARS-CoV-2 infection on or before receipt of the study dose (negative RT-PCR from nasal swab and negative bAb specific to SARS-CoV-2 N-protein)
Per-Protocol Immunogenicity Set – Positive (PPIS-Pos)	Participants in the PPIS who are SARS-CoV-2 positive (serologic or virologic evidence of prior SARS-CoV-2 infection) before receiving the study vaccine.
Modified Intent-to-Treat Set-1 (mITT1)	The Modified Intent-to-Treat-1 (mITT1) Set consists of all participants in the FAS excluding those who received the wrong treatment who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline

Source: FDA-generated table adapted from STN#125752/276 mRNA-1273-P306 Final CSR Part 2 and Part 4 and Statistical Analysis Plan
Abbreviations: bAb = binding antibody, HAART = highly active antiretorviral therapy, HIV = human immunodeficiency virus, RT-PCR = real time polymerase chain reaction, SARS CoV 2 = severe acute respiratory syndrome coronavirus-2.

6.2.10.1.1 Demographics

Table 26 provides an overview of the demographics and baseline characteristics for participants in the Safety Sets for Study P306 Part 2 and Part 4.

Vaccine-experienced, 6 months through *5 years, 10 µg mRNA-1273.214*
The Safety Set included a total of 539 participants, from 6 months through 5 years (<6 years) of age. The majority (65.7%, 354/539) of participants were SARS-CoV-2 negative at baseline. The median time interval between completion of the 2-dose series in Study P204 and single dose vaccine administration in Study P306 was 7.9 months (range 4.0 months to 12.1 months).

Vaccine-naïve, 6 months through *4 years, 25µg mRNA-1273.815*
The Safety Set included a total of 598 participants (199 participants were 2 years – 4 years; 399 participants were 6 months through 23 months). A larger percentage of participants 2 years – 5 years were SARS-CoV-2 positive at baseline compared to those 6 months – 23 months (97% vs. 76%).

Table 26. Demographic and Baseline Characteristics, Study P306, Safety Sets

Characteristic	6m - 5y, vaccine-experienced mRNA-1273.214 (10 µg) Single Dose N=539	2y - 4y, vaccine-naïve mRNA-1273.815 (25 µg) Single Dose N=199	6m - 23m, vaccine-naïve mRNA-1273.815 (25 µg) 2 doses N=399
Sex, n (%)	--	--	--

Characteristic	6m - 5y, vaccine-experienced mRNA-1273.214 (10 µg) Single Dose N=539	2y - 4y, vaccine-naïve mRNA-1273.815 (25 µg) Single Dose N=199	6m - 23m, vaccine-naïve mRNA-1273.815 (25 µg) 2 doses N=399
Female	263 (48.8)	99 (49.7)	191 (47.9)
Male	276 (51.2)	100 (50.3)	208 (52.1)
Age, years[a]	--	--	--
Median	3.0	3.0	--
Min, Max	0.9, 5.0	2.0, 4.0	--
Age, months[b]	--	--	--
Median	--	--	13.0
Min, Max	--	--	6, 23
Race, n (%)	--	--	--
American Indian or Alaska Native	0	1 (0.3)	1 (0.5)
Asian	26 (4.8)	0	0
Black	17 (3.2)	100 (25.1)	66 (33.2)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0	0
White	437 (81.1)	41 (10.3)	48 (24.1)
Multiracial	53 (9.8)	29 (7.3)	11 (5.5)
Other	0	225 (56.4)	73 (36.7)
Unknown	1 (0.2)	1 (0.3)	0
Not reported	4 (0.7)	2 (0.5)	0
Ethnicity, n (%)			
Hispanic or Latino	59 (10.9)	338 (84.7)	138 (69.3)
Not Hispanic or Latino	476 (88.3)	57 (14.3)	58 (29.1)
Unknown	2 (0.4)	3 (0.8)	2 (1.0)
Not reported	2 (0.4)	1 (0.3)	1 (0.5)
Country, n (%)	--	--	--
United States	539 (100)	107 (53.8)	74 (18.5)
Dominican Republic	0	0	135 (33.8)
Panama	0	92 (46.2)	190 (47.6)
Obesity Status[c], n (%)	--	--	--
Obese	70 (13.0)	57 (14.3)	40 (20.1)
Not obese	469 (87.0)	342 (85.7)	159 (79.9)
Interval between Dose 2 and booster dose (months)[d]	--	--	--
Median	7.85	NA	NA
Range (min, max)	4.0, 12.1	NA	NA
Baseline SARS-CoV-2 Status[e], n (%)	--	--	--
Negative	354 (65.7)	6 (3.0)	93 (23.3)
Positive	170 (31.5)	192 (96.5)	305 (76.4)
Missing	15 (2.8)	1 (0.5)	1 (0.3)

Source: STN125752/276, P306 Final CSR Part 2 Table 14.1.3.2.2, P306 Final CSR Part 4 Table 14.1.2.4.4, and IR Response dated March 28, 2025

Abbreviations: µg=micrograms, CSR=clinical study report, n= number of participants with respective demographic/baseline characteristic, N= total safety set population, max = maximum, min = minimum, WHO = World Health Organization.

Note: The Safety Set consists of all enrolled participants who received at least 1 dose of study injection. Percentages are based on the number of participants in Safety Set.

[a] Age at study enrollment.

[b] Age in months is summarized for ≥6 months and <2 years group only.

[c] Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.

[d] Time from second dose of primary series to booster dose (months) = (booster dose day - second dose day of primary series + 1) / 30.4375.

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

The demographic characteristics of the solicited safety sets and the primary immunogenicity analysis populations were generally similar to those of the Safety Sets.

6.2.10.1.2 Participant Disposition

Table 27 provides an overview of the reasons for study discontinuation and exclusion from the primary immunogenicity populations in parts 2 and 4 in Study P306. There were no study discontinuations due to AEs.

Table 27. Disposition and Reasons for Exclusion from Primary Analysis Populations, Study P306

Disposition	6m - 5y, vaccine-experienced mRNA-1273.214 Single Dose, 10 µg n (%)[a]	2y - 4y, vaccine-naïve mRNA-1273.815 Single Dose, 25 µg n (%)	6m - 23m, vaccine-naïve mRNA-1273.815 2 doses, 25 µg n (%)
Safety Set[b]	**N=539**	**N=199**	**N=399**
Discontinued from Study	46 (8.5)	2 (1.0)	14 (3.5)
Reason for discontinuation	--	--	--
Adverse Event	0	0	0
Lost to Follow-Up	25 (4.6)	0	5 (1.3)
Withdrawal of Consent by Participant	21 (3.9)	2 (1.0)	9 (2.3)
Immunogenicity Set	**N=499**	**N=149**	**N=379**
Primary immunogenicity analysis population[c]	319 (63.9)	143 (96.0)	76 (20.1)
Reason for exclusion [d]	--	--	--
Baseline SARS-CoV-2[e]	168 (33.7)	6 (4.0)	276 (94.2)
Missing Immunogenicity Data at Day 29/Day57	12 (24.1)	0	5 (1.3)
Received Dose 2 Out of Window	NA	NA	18 (4.7)
Did not receive Dose 2 per Schedule	NA	NA	4 (1.1)

Source: STN 125752/276 P306 Final CSR Part 2 Table 14.1.2.1.2, P306 Final CSR Part 4 Table 14.1.2.4.4 response to IR dated March 28, 2025

Abbreviations: PPIS = per protocol immunogenicity set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; NA=not applicable

[a] Percentages are based on the number of participants in the relevant analysis population (i.e., Safety Set and Immunogenicity Set).

[b] The Safety Set consists of all enrolled participants who received at least 1 dose of study injection.

[c] The primary immunogenicity analysis population for P306 Part 2 consists of participants in the PPIS who were negative for virologic or serologic evidence of SARS-CoV-2 infection at baseline. The primary immunogenicity analysis populations in P306 Part 4 were participants in the PPIS who are SARS-CoV-2 positive at baseline (2 years – 4 years) or SARS-CoV-2 negative at baseline (6 months – 23 months).

[d] A participant who had multiple reasons for exclusion from the primary immunogenicity analysis population is listed under the reason that appears first.

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

Clinical Reviewer Comment:
The percentages of participants 6 months through 5 years in Study P306 included in study analyses were sufficient to support the review of safety and effectiveness data. There were no participants who were discontinued from the study due to adverse events.

6.2.11 Analyses of vaccine effectiveness

6.2.11.1 Vaccine-experienced, 6 months through 5 years, 10µg mRNA-1273.214 (Part 2)

Hypotheses #1 and #3

The co-primary immunogenicity endpoints evaluating nAb GMC against the D614G strain and Omicron BA.1 strains at 28 days following a single dose of mRNA-1273.214 were compared with the nAb GMC responses at 28 days post-Dose 2 of the 2-dose series of monovalent mRNA-1273 in participants in the same age group enrolled in Study P204 (Table 28). The ratio of GMCs (P306 single dose mRNA-1273.214/ P204 2-dose series mRNA-1273) met the pre-specified statistical noninferiority criterion for the D614G strain (LB of 95% CI of GMC ratio >0.667) and statistical superiority criterion for the Omicron BA.1 strain (LB of 95% CI of GMC ratio >1.0).

Table 28. SARS-CoV-2 GMC Measured by Pseudovirus nAb Assay (Original [D614G] and Omicron BA.1 strains) in 6 Months through 5 Years (Vaccine-experienced): Single dose Bivalent Vaccination, Study P306-Part 2, PPIS-Negative, Day 29 Compared to 2-dose Series mRNA-1273 Participants in Study P204, PPIS-Negative, Day 57

Assay Strain	6m - 5y (P306) Single Dose mRNA-1273.214 (10ug) GMC [95% CI][a] N=319	6m - 5y (P204) 2-dose Series mRNA-1273 (25ug) GMC [95% CI][a] N=590	GMC Ratio (P306/ P204) [95% CI][a,b]
Original (D614G)	4754.7 [4346.9, 5200.7]	1559.4 [1457.6, 1668.4]	3.049 [2.725, 3.411]
Omicron BA.1	805.2 [731.2, 866.8]	66.6 [62.0, 71.6]	12.085 [10.715, 13.631]

Source: STN#125752/276 mRNA-1273-P306 Final CSR Part 1 and Part 2 Table 14.2.1.4.1.2

Abbreviations: m= months of age; y= years of age; CI = confidence interval, GMC = geometric mean concentration; LS = least square; n = /number of subjects with non-missing data at the corresponding timepoint; nAb = neutralizing antibody; P PIS = per protocol immunogenicity set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: PPIS - Negative included all subjects who did not have serologic and virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).

[a] The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (children in P306 and in P204) as fixed variable, adjusted by age group (2 age groups: >=6 months and <2 years, >=2 and <6 years). Coefficients for LS Means use margins by level. In each specific age group column, age group is not a covariate. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] Statistical success criteria: D614G strain – statistical noninferiority demonstrated if LB of 95%CI >0.667; Omicron BA.1 strain – statistical superiority demonstrated if LB of 95%CI >1.0

Hypotheses #2 and #4

Analyses of the differences in SRR percentages (Table 29) against the Original strain (D614G) and Omicron BA.1 met the pre-specified statistical noninferiority criteria (LBs of the 95% CI > -10% and -5%, respectively). SRRs for these analyses were evaluated using a baseline of GMC pre-Dose 1 of the 2-dose series received in Study P204.

Table 29. **SARS-CoV-2 Seroresponse Rates (SRR) Measured by Pseudovirus nAb Assay (Original [D614G] and Omicron BA.1 strains) in 6 Months through 5 Years (Vaccine-experienced): Single dose Bivalent Vaccination, Study P306 Part 2, PPIS-Negative, Day 29 Compared with 2-dose Series mRNA-1273 Participants in Study P204, PPIS-Negative, Day 57**

Assay Strain	6 Months – 5 Years (P306) Single Dose mRNA-1273.214 (10ug) SRR[a] n/N1 (%) [95% CI][b] N=319	6 Months to 5 Years (P204) 2-dose Series mRNA-1273 (25ug) SRR[a] n/N1 (%) [95% CI][b] N=590	SRR% Difference (P306 - P204) [95% CI][c]
Original (D614G)	312/312 (100) [98.8, 100.0]	545/548 (99.5) [98.4, 99.9]	0.5 [-0.7, 1.6]
Omicron BA.1	309/312 (99) [97.2, 99.8]	477/562 (84.9) [81.6, 87.7]	14.2 [11.1, 17.5]

Source: mRNA-1273-P306 Final CSR Part 1 and Part 2 Table 14.2.2.4.1.2

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantification; N= total number of participants in the immunogenicity population, n = number of participants meeting the seroresponse definition, N1 = Number of subjects with non-missing data at baseline (pre-Dose 1 of primary series) and the corresponding timepoint; nAb = neutralizing antibody; PPIS = per protocol immunogenicity set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

Note: PPIS - Negative included all subjects who did not have serologic and virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).

[a] Seroresponse at a subject level is defined as a change from baseline (pre-Dose 1 of primary series) 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.

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

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

For the P306 PPIS-neg group, the SRR (percentage) from pre-1273.214 dose to post-1273.214 dose was 96.5% (95% CI 93.8%, 98.2%) for the Omicron BA.1 nAb responses and 93.7% (95% CI 90.4%, 96.1%) for the Original strain nAb responses.

Clinical Reviewer Comment:
Overall, the results of the primary immunogenicity analyses demonstrate that a single dose of mRNA-1273.214 (which contains 5 µg of mRNA encoding the spike protein from Omicron BA.1 and 5 µg encoding the spike protein from the Original strain) following a 2-dose series of mRNA-1273 (25 ug total of mRNA encoding spike protein from Original strain) elicited a statistically superior nAb GMC responses against Omicron BA.1 compared with the 2-dose series of mRNA-1273 and statistically noninferior responses against the Original strain. These results demonstrate that in children 6 months though 5 years, robust immune responses are elicited following a single dose of an updated Spikevax formulation when previously vaccinated at least 4 months earlier with 2 doses.

Subpopulation Analyses of Immunogenicity Endpoints
Most participants in Study P306 Part 2 were White, Non-Hispanic, and non-obese (Table 26); therefore, the numbers of participants in other subgroups were too small to draw meaningful conclusions.

Subgroup analyses by sex demonstrated generally similar nAb GMCs against the Original and BA.1 strains in male and female participants compared with the results of the overall analyses.

Subgroup analyses by baseline SARS-CoV-2 status demonstrated numerically higher nAb GMCs at Day 29 following vaccination in baseline SARS-CoV-2 positive participants (D614G: 6980 [6225, 7827]; BA.1: 2639 [2277, 3061]) compared with the primary immunogenicity analysis population.

Clinical Reviewer Comment:
Immunogenicity analyses by demographic and baseline characteristic subgroups do not suggest differences in the immune responses to Spikevax except for baseline SARS-CoV-2 positive participants, who had higher nAb responses against the Omicron BA.1 and D614G strains than those who were SARS-CoV-2 negative at baseline. These results suggest that those who are SARS-CoV-2 positive at baseline may have higher immune responses to vaccination compared with those who are SARS-CoV-2 negative.

Descriptive Analyses of SARS-CoV-2 Infections and COVID-19 Cases
Participants in the FAS who were vaccine experienced and received the single dose (6 months – 5 years of age) were monitored throughout the study for symptoms of COVID-19 disease and SARS-CoV-2 infection (see Section 6.4.7). There were no pre-specified comparator groups in the study design.

Descriptive clinical efficacy endpoints evaluated the incidence of CDC-defined COVID-19 disease, SARS-CoV-2 infection, and asymptomatic SARS-CoV-2 infection beginning 14 days after vaccination in participants who did not have evidence of COVID-19 or SARS-CoV-2 infection prior to vaccination and who received the single study dose.

6.2.11.2 Vaccine-naïve, 6 months – 4 years, 25µg mRNA-1273.815 (Part 4)

Hypothesis #1
The primary immunogenicity endpoint evaluated nAb concentrations against the Omicron XBB.1.1.5 assay strain at 28 days following a single dose of mRNA-1273.815 (25ug) in seropositive participants 2 years through 4 years of age (Cohort 4A) who were vaccine-naïve compared with the responses at 28 days post-Dose 2 of a 2-dose series of mRNA1273.815 in seronegative participants 6 months through <2 years of age (Cohort 4B) who were also vaccine-naïve (Table 30). The ratio of GMCs (Cohort 4A/Cohort 4B) met the pre-specified statistical noninferiority criterion (LB of 95%CI of GMC ratio >0.667).

Table 30. SARS-CoV-2 GMC Measured by Pseudovirus nAb Assay (Omicron XBB.1.5 strain) Study P306 Part 4: Single Dose Monovalent Vaccination, 2 Years – 4 Years (Vaccine-naïve), PPIS-Positive at Day 29 Compared to 2-dose Series Monovalent, 6 Months – 23 Months (Vaccine-naïve), Day 57, PPIS Negative at Day 57

2y – 4y Single Dose, 25 ug mRNA-1273.815 GMC (95% CI) [a] N=143	6m – 23m 2-dose Series, 25 ug mRNA-1273.815 GMC (95% CI)[a] N=76	GMC Ratio[a] (2y – 4y/ 6m – 23m) (95% CI)
2074.1 (1637.8, 2626.7)	1736.3 (1255.8, 2400.6)	1.2 (0.8, 1.78)

Source: mRNA-1273-P306 Final CSR Part 4A Table 14.2.1.1.1.4.1

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; LS = least square; m = month; n = number of subjects with non-missing data at the corresponding timepoint; nAb = neutralizing antibody; PPIS = per protocol immunogenicity set; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; y = year.
Note: The PPIS – Negative Population included all subjects who did not have serologic and virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).The PPIS – Positive Population included all subjects who had serologic or virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).
[a] The log-transformed antibody levels (Part 4A on Day 29 and Part 4B on Day 57) are analyzed using an analysis of covariance (ANCOVA) model with the group variable (Part 4A vs. Part 4B) as fixed variable. Coefficients for Least Squares Means use the observed marginal distribution of the fixed variable by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Hypothesis #2

The analyses evaluating seroresponse rates against XBB.1.1.5 failed to meet the noninferiority criterion of a LB of 95%CI of > -10% (Table 31). The SRR percentage difference point estimate (Cohort 4A-Cohort 4B) was -23% with LB of the 95% CI of -31.

Seroresponse at the participant level was defined as a change from baseline below the LLOQ (antibody concentration of 38) to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Baseline for participants in the 2 years – 4 years age group was defined as the nAb level prior to the study dose. Baseline for participants in the 6 months – 23 months age group was defined as the nAb level prior to the first study dose.

Table 31. Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against XBB.1.5 (VAC150) at 28 Days Post Single Dose of Monovalent Vaccination (Day 29), Cohort A, 2 Years through 4 Years (Vaccine-naïve), Study P306 Part 4, PPIS-Positive, Compared to 28 Days Post-Dose 2 of Monovalent Vaccination (Day 57), Cohort B, 6 Months through 23 Months (Vaccine-naïve), Study P306 Part 4, PPIS-Negative

P306 Part 4 Cohort A 2 through 4 years mRNA-1273 815 25 µg Single Dose SRR[a] n/N1 % [95% CI][b] N=143	P306 Part 4 Cohort B 6 months through 23 months mRNA-1273.815 25 µg 2 doses SRR[a] % [95% CI][b] N=76	SRR Difference (Cohort A - Cohort B) [95% CI][c]
73 (102/139) (65, 81)	96 (88.9, 99.2) (89, 99)	-23 (-31, -14)

Source: mRNA-1273-P306 Final CSR Part 4A Table 14.2.2.1.1.4.1
Abbreviations: CI = confidence interval; LLOQ = lower limit of quantification; N1 = Number of subjects with non-missing data at baseline (pre-Dose 1 of primary series, or prior to single dose) and the corresponding timepoint; nAb = neutralizing antibody; PPIS = per protocol immunogenicity set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.
Note: The PPIS – Negative Population included all subjects who did not have serologic and virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).The PPIS – Positive Population included all subjects who had serologic or virologic evidence of prior SARS-CoV-2 infection pre-dose, did not have a major protocol deviation that impacted immune response, and had immunogenicity assessment at timepoint of primary interest (28 days post-dose).
[a] Seroresponse at a participant level is defined as a change from baseline (pre-dose 1) 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. Assay LLOQ = 38.
[b] 95% CI is calculated using the Clopper-Pearson method.
[c] 95% CI is calculated using the Miettinen-Nurminen score method.

Clinical Reviewer Comment:

The statistical success was not met for the SRR immunogenicity endpoint. Participants

included in the primary immunogenicity analysis population for the 2 years through 4 years of age group had higher baseline PsVNA titers (81% ≥ LLOQ) compared with participants in the 6 months through 23 months of age group (17% ≥ LLOQ). More participants in the 6 months through 23 months of age group achieved a 4-fold rise from baseline in PsVNA nAb titers compared with the older age group. Therefore, the observed difference in SRR percentages between the two groups is likely a consequence of the seroresponse definition used to determine the primary study endpoints and does not represent a suboptimal vaccine response in 2 years through 4 years of age vaccine-naïve children.

Subpopulation Analyses of Primary Immunogenicity Endpoints
Subpopulation analyses by sex demonstrated similar nAb (GMC, SRR) responses for males and females compared with the primary analysis for all study groups. The small numbers of the study participants in other subgroups, such as race, obesity, and baseline seronegative status in Study P306 Part 4 limit the ability to draw conclusions from the analyses of the immunogenicity endpoints.

Immunogenicity Analyses in SARS-CoV-2 Positive Participants
Analyses of the nAb GMC responses for those who were seropositive at baseline demonstrated the highest GMC after Dose 2 in participants in 6 months – 23 months of age (6m – 23m age group: 4666 95% CI 4078, 5337) followed by post-Dose 1 in the 2 years – 4 years and 6 months – 23 months of age groups (2 years – 4 years: 2074 95% CI: 1598, 2693 and 6 months – 23 months: 2768 95% CI 2235, 3428).

Clinical Reviewer Comment:
The totality of immunogenicity data from Study P306 Part 4 support the effectiveness of a single dose of Spikevax in 2 years through 4 years of age children who are more likely to have been exposed to SARS-CoV-2 and a 2-dose series in children 6 months through 23 months of age who are less likely to have been exposed to SARS-CoV-2.

6.2.12 Analyses of vaccine safety

6.2.12.1 Methods
See section 6.2.7.

6.2.12.2 Overview of Adverse Events
Table 32 provides an overview of the safety results across Part 2 (mRNA-1273.214) and Part 4 (mRNA-1273.815) of Study P306 that were that were conducted during different time periods during the SARS-CoV-2 pandemic. As shown in Section 6.2.10 above, the study populations for these two study parts had distinct demographic and baseline characteristics, including baseline SARS-CoV-2 exposure status at the time of enrollment, prior to vaccination. The reported rates of severe or Grade 3 events, SAEs were low for all age groups for both formulations, and there were no deaths or AEs leading to study withdrawal reported. There was 1 SAE that was considered related to the study dose by study investigators (an SAE in a 6 month – 23-month participant who received mRNA-1273.815, see Section 6.2.12.8.2). There were no reported cases of myocarditis or pericarditis and no deaths.

Table 32. Percentages of Participants Reporting at Least One Adverse Event Following Monovalent or Bivalent Vaccination, Study P306 Part 2 and Part 4, Safety Set and Solicited Safety Set

Event type	2y - 5y mRNA-1273.214 (10 µg) Single Dose N=425 n (%)	2y - 4y mRNA-1273.815 (25 µg) Single Dose N=199 n(%)	6m- 23m mRNA-1273.214 (10 µg) Single dose N=114 n (%)	6m – 23m mRNA-1273.815 (25 µg) 2 doses N=399 n (%)
Solicited ARs within 7 days	-	-	-	-
Any local AR	222 (52.2)	59 (29.6)	47 (41.2)	102 (25.6)
Grade 3 or above	3 (0.7)	3 (1.5)	3 (2.6)	6 (1.5)
Any systemic AR	192 (45.2)	47 (23.6)	73 (64.0)	184 (46.1)
Grade 3 or above	10 (2.4)	6 (3.0)	3 (2.6)	21 (5.3)
Nonserious unsolicited AEs within 28 days[a]	78 (18.4)	39 (19.6)	34 (29.8)	197 (49.4)
Severe	0	0	0	0
Related	8 (1.9)	0	2 (1.8)	0
Severe and related	0	0	0	0
MAAEs for entire study	228 (53.6)	31 (15.6)	82 (71.9)	169 (42.4)
Related	2 (0.5)	0	1 (0.9)	0
SAEs for entire study	4 (0.9)	0	5 (4.4)	13 (3.3)
Related	0	0	0	1 (1.1)
AESIs for entire study	3 (0.7)	0		1 (0.3)
Related	0	0	0	0
Deaths	0	0		0
AEs leading to study discontinuation	0	0	0	0

Source: Adapted from STN# 125752/276, Response to IR sent March 28, 2025

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; MAAE = medically attended adverse event; N = number of participants in the safety set; n = Number of exposed participants who received the corresponding dose and reported an event within the given period, SAE = serious adverse event; AE = treatment-emergent adverse event.

Note: Percentages were based on the number of participants in the safety set

A treatment emergent AE was defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Severe unsolicited AEs included severe AEs and events with toxicity Grade 3, 4 and 5. 0 participant with toxicity Grade 4 or 5 was included. The Safety Set consisted of all enrolled participants who received at least 1 dose of study intervention. The Solicited Safety Set consisted of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment.

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

Clinical Reviewer Comment:

Differences in baseline characteristics, specifically SARS-CoV-2 exposure history and safety database size for each of the different age cohorts/formulation study groups contributed to variances observed in the rates of safety findings between mRNA-1273.214 bivalent formulation and mRNA1273.815 monovalent formulation as shown in the table above. However, the rates of observed safety events were reassuring when compared with historical data in older adolescent/adult age cohorts.

6.2.12.3 Solicited Adverse Reactions

Clinical Reviewer Comment:
Solicited adverse reactogenicity data are presented according to age group due to age-specific solicited ARs.

6.2.12.3.1 Vaccine-experienced, 6 months – 5 years, 10 µg mRNA-1273.214

Solicited ARs following a single 10µg dose of mRNA-1273.214 are shown in Table 33 (local ARs) and Table 34 (systemic ARs). Overall, solicited ARs within 7 days after vaccination were reported by 55.2% of participants. The most common solicited ARs reported by ≥10% of participants were irritability/crying (53.1%), pain (45.1%), fatigue (32.1%), loss of appetite (22.8%), sleepiness (20.6%), headache (14.2%), and myalgia (12.4%).

Most ARs were Grade 1-2, with Grade 3 systemic ARs reported by 2.4% participants and Grade 3 local ARs reported by 1.1% participants. There were no Grade 4 ARs reported. Adverse reactions had a median onset of 1 day after the study dose and median duration of 2 days.

Table 33. Frequency of Solicited Local Reactions Within 7 Days Following Bivalent Vaccination, 6 Months through 5 Years of Age (Vaccine-experienced), Study P306 Part 2, Solicited Safety Set

Solicited Local Reaction	2y – 5y mRNA-1273.214 (10 µg) Single dose N=425 n (%)	6m - 23m mRNA-1273.214 (10 µg) Single Dose N=114 n (%)
Any	222 (52.2)	47 (41.2)
Grade 1	198 (46.6)	38 (33.3)
Grade 2	21 (4.9)	6 (5.3)
Grade 3	3 (0.7)	3 (2.6)
Grade 4	0	0
Pain – N1[a]	425	114
Any	206 (48.5)	37 (32.5)
Grade 1	189 (44.5)	35 (30.7)
Grade 2	14 (3.3)	2 (1.8)
Grade 3	3 (0.7)	0
Grade 4	0	0
Erythema (Redness) – N1[b]	425	114
Any	22 (5.2)	13 (11.4)
Grade 1	18 (4.2)	7 (6.1)
Grade 2	4 (0.9)	4 (3.5)
Grade 3	0	2 (1.8)
Grade 4	0	0
Swelling (Hardness) – N1[b]	425	114
Any	21 (4.9)	10 (8.8)
Grade 1	18 (4.2)	5 (4.4)
Grade 2	3 (0.7)	2 (1.8)
Grade 3	0	3 (2.6)
Grade 4	0	0
Axillary (or Groin) Swelling or Tenderness – N1[c]	425	114
Any	28 (6.6)	6 (5.3)
Grade 1	26 (6.1)	5 (4.4)
Grade 2	2 (0.5)	1 (0.9)
Grade 3	0	0
Grade 4	0	0

Source: mRNA-1273-P306 Final CSR Part 1 and Part 2 Table 14.3.1.1.1.2.1.2.

Abbreviations: AR = adverse reaction; G = grade; mm = millimeter; N1 = number of participants who submitted any data for the event.

Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment.

[a] Pain for participant age 6 to ≤36 months/37 months to <6 years is injection site pain or tenderness/injection site pain and is defined as: G1 = Mild discomfort to touch or some pain but no interference with normal daily activities/ No interference with activity; G2 = Cries when limb is moved/refuses to move limb or pain interferes with normal daily activities/ Some interference with activity; G3 = Significant pain at rest or pain prevents normal daily activities / Prevents daily activity; G4 = Requires emergency room visit or hospitalization

[b] Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participant age 6 to ≤36 months/ 37 months to <6 years is defined as: G1 = 5 – 20 mm/25 – 50 mm; G2 = >20 – 50 mm/51 – 100 mm; G3 = >50 mm/>100 mm; G4 = Necrosis or exfoliative dermatitis.

[c] Toxicity grade for Groin or underarm swelling or tenderness for participant age 6 to ≤36 months, or for Axillary swelling or tenderness for participant age 37 months to <6 years is defined as: G1 = Some swelling or tenderness but no interference with normal daily activities/No interference with activity; G2 = Swelling or tenderness that interferes with normal daily activities/Some interference with activity; G3 = Swelling or tenderness that prevents normal daily activities/Prevents daily activity; G4 = Emergency room visit or hospitalization.

Table 34. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Bivalent Vaccination, 6 Months through 5 Years of Age (Vaccine-experienced), Study P306 Part 2, Solicited Safety Set

Solicited Adverse Reaction	2y – 5y mRNA-1273.214 (10 µg) Single Dose N=425 n (%)	6m - 23m mRNA-1273.214 (10 µg) Single Dose N=114 n (%)
Solicited Systemic ARs		
Any Systemic Reaction- N1	425	114
Any	192 (45.2)	73 (64.0)
Grade 1	114 (26.8)	51 (44.7)
Grade 2	68 (16.0)	19 (16.7)
Grade 3	10 (2.4)	3 (2.6)
Grade 4	0	0
Fever (temperature ≥38ºC) – N1[a]	425	114
Any	26 (6.1)	13 (11.4)
Grade 1	12 (2.8)	10 (8.8)
Grade 2	11 (2.6)	3 (2.6)
Grade 3	3 (0.7)	0
Grade 4	0	0
Irritability/Crying– N1[b]	115	113
Any	59 (51.3)	62 (54.9)
Grade 1	47 (40.9)	45 (39.8)
Grade 2	11 (9.6)	15 (13.3)
Grade 3	1 (0.9)	2 (1.8)
Grade 4	0	0
Sleepiness– N1[c]	115	113
Any	27 (23.5)	20 (17.7)
Grade 1	26 (22.6)	18 (15.9)
Grade 2	1 (0.9)	2 (1.8)
Grade 3	0	0
Grade 4	0	0
Loss of appetite– N1[d]	115	113
Any	21 (18.3)	31 (27.4)
Grade 1	20 (17.4)	24 (21.2)
Grade 2	1 (0.9)	6 (5.3)
Grade 3	0	1 (0.9)
Garde 4	0	0

Solicited Adverse Reaction	2y – 5y mRNA-1273.214 (10 µg) Single Dose N=425 n (%)	6m - 23m mRNA-1273.214 (10 µg) Single Dose N=114 n (%)
Fatigue – N1[e]	274	NA
Any	88 (32.1)	NA
Grade 1	44 (16.1)	NA
Grade 2	39 (14.2)	NA
Grade 3	5 (1.8)	NA
Grade 4	0	NA
Headache – N1[e]	274	NA
Any	39 (14.2)	NA
Grade 1	28 (10.2)	NA
Grade 2	8 (2.9)	NA
Grade 3	3 (1.1)	NA
Grade 4	0	NA
Myalgia – N1[e]	274	NA
Any	34 (12.4)	NA
Grade 1	21 (7.7)	NA
Grade 2	12 (4.4)	NA
Grade 3	1 (0.4)	NA
Grade 4	0	NA
Arthralgia– N1[e]	274	NA
Any	25 (9.1)	NA
Grade 1	17 (6.2)	NA
Grade 2	7 (2.6)	NA
Grade 3	1 (0.4)	NA
Grade 4	0	NA
Nausea/Vomiting– N1[f]	275	NA
Any	22 (8.0)	NA
Grade 1	15 (5.5)	NA
Grade 2	6 (2.2)	NA
Grade 3	1 (0.4)	NA
Grade 4	0	NA
Chills– N1[g]	274	NA
Any	16 (5.8)	NA
Grade 1	9 (3.3)	NA
Grade 2	7 (2.6)	NA
Grade 3	0	NA
Garde 4	0	NA

Source: mRNA-1273-P306 Final CSR Part 1 and Part 2 Table 14.3.1.1.1.2.1.2.

Abbreviations: AR = adverse reaction; G = grade; N = number of participants in safety set; n = number of participants who experienced the event; N1 = Number of exposed participants who submitted any data for the event; NA = not applicable, these ARs were not solicited from the respective age group

Notes: Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited safety set consists of all participants in the safety set who contributed any solicited AR data, i.e., had at least one post-baseline solicited safety assessment.

[a] Toxicity grade for Fever for participant aged 6 to ≤36 months/37 months to <6 years is defined as: G1 = 38˚C – 38.4˚C; G2 = 38.5˚C – 39.5˚C/38.5˚C – 38.9˚C; G3 = 39.6˚C – 40˚C/39˚C – 40˚C; G4 = >40˚C.

[b] Toxicity grade for irritability/crying for participants 6-36 months is defined as G1 = Lasting <1 hour or easily consolable; G2 = Lasting 1-3 hours or requiring increased attention; G3 = Lasing >3 hours or inconsolable; G4 = requires emergency room visit or hospitalization.

[c] Toxicity grade for sleepiness for participants 6-36 months is defined as G1 = Sleepier than usual or less interested in surroundings; G2 = Not interested in surroundings or sleeps through meals; G3 = Sleeps most of the time, hard to arouse; G4 = Inability to arouse.

[d] Toxicity grade for loss of appetite for participants 6-36 months is defined as G1 = Eating less than normal for 1-2 feeds/meals; G2 = Missed 1-2 feeds/meals completely; G3 = Missed >2 feeds/meals completely or refuses most feeds/meals; G4 = Requires emergency room visit or hospitalization.

[e] Toxicity grade for participants 37 months – 5 years fatigue, headache, myalgia, and arthralgia are defined as G1 = No interference with activity; G2 = Some interference with activity; G3 = Significant; prevents daily activity; G4 = Requires emergency room visit or hospitalization.
[f] Toxicity grade for participants 37 months – 5 years nausea/vomiting is defined as G1 = no interference with activity or 1-2 episodes/24 hours; G2 = some interference with activity or >2 episodes/24 hours; G3 = prevents daily activity; G4 = Requires emergency room visit or hospitalization for hypotensive shock.
[g] Toxicity grade for chills for participants 37 months – 5 years is defined as G1 = no interference with activity; G2 = some interference with activity not requiring medical intervention; G3 = prevents daily activity and requires medical intervention; G4 = Requires emergency room visit or hospitalization.

Subpopulation Analyses of Solicited Adverse Reactions

Subpopulation analyses of ARs by SARS-CoV-2 serostatus, sex, race, and ethnicity demonstrated no notable differences from those of the primary analyses, although some race and ethnicity subgroups had too few participants to support meaningful conclusions. No notable differences in the frequency and severity of ARs were observed between participants grouped by obesity status.

6.2.12.3.2 Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.815 (Part 4)

Solicited ARs following study doses are shown in Table 35 (local ARs) and Table 36 (systemic ARs). Overall, solicited ARs within 7 days after vaccination were reported by 41% of participants 2y – 4y and 53% of participants 6m-23m. The most common solicited ARs reported by ≥10% of participants were pain (2y-4y: 28%, 6m-23m: 20%), irritability/crying (2y - 4y: 12%, 6m-23m: 24%), loss of appetite (2y - 4y: 8.5%, 6m-23m: 19%), fever (temperature ≥38ºc, 2y - 4y: 9% and 6m-23m: 18%), and sleepiness (2y - 4y: 13%, 6m-23m: 14%).

Most ARs were of Grade 1or 2 intensities, with 4.5% of ARs in 2y - 4y and 6.5% of ARs in 6m-23m reported as Grade 3. There were no Grade 4 ARs reported. Overall, adverse reactions had a median onset of 2 days after the study dose and median duration of 2 days.

Table 35. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Solicited Safety Set

Solicited Adverse Reaction	2y – 4y mRNA-1273.815 (25 µg) Single Dose N=199 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 1 N=399 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 2 N=386 n (%)
Any local adverse reaction - N1	199	399	386
Any	59 (29.6)	69 (17.3)	55 (14.2)
Grade 1	51 (25.6)	64 (16.0)	44 (11.4)
Grade 2	5 (2.5)	4 (1.0)	6 (1.6)
Grade 3	3 (1.5)	1 (0.3)	5 (1.3)
Pain at injection site - N1[a]	199	399	386
Any	55 (27.6)	55 (13.8)	43 (11.1)
Grade 1	51 (25.6)	54 (13.5)	37 (9.6)
Grade 2	2 (1.0)	1 (0.3)	4 (1.0)
Grade 3	2 (1.0)	0	2 (0.5)
Erythema (redness) - N1[b]	199	399	386
Any	7 (3.5)	13 (3.3)	12 (3.1)
Grade 1	5 (2.5)	11 (2.8)	9 (2.3)
Grade 2	2 (1.0)	1 (0.3)	1 (0.3)
Grade 3	0	1 (0.3)	2 (0.5)
Swelling - N1[b]	199	399	386

Solicited Adverse Reaction	2y – 4y mRNA-1273.815 (25 µg) Single Dose N=199 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 1 N=399 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 2 N=386 n (%)
Any	7 (3.5)	10 (2.5)	5 (1.3)
Grade 1	6 (3.0)	8 (2.0)	3 (0.8)
Grade 2	1 (0.5)	2 (0.5)	1 (0.3)
Grade 3	0	0	1 (0.3)
Axillary (or Groin) Swelling - N1[c]	199	399	386
Any	14 (7.0)	12 (3.0)	10 (2.6)
Grade 1	9 (4.5)	11 (2.8)	8 (2.1)
Grade 2	2 (1.0)	1 (0.3)	1 (0.3)
Grade 3	3 (1.5)	0	1 (0.3)

Source: Adapted from STN#125752/276 Response to IR sent March 28, 2025 and mRNA-1273-P306 Final CSR Part 4A Table 14.3.1.1.2.1.4.

Abbreviations: AR = adverse reaction; G = grade; N = number of safety participants; n = Number of exposed participants who received the corresponding dose and reported an event; N1 = number of exposed participants who submitted any data for the event.

Note: Percentages were based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consisted of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment.

[a] Pain was tenderness/injection site pain and is defined as: G1 = Mild discomfort to touch or some pain but no interference with normal daily activities; G2 = Cries when limb is moved/refuses to move limb or pain interferes with normal daily activities G3 = Significant pain at rest or pain prevents normal daily activities; G4 = Requires emergency room visit or hospitalization

[b] Toxicity grade for injection site erythema (redness) or swelling (hardness) was defined as: G1=5-20 mm; G2≥20 - 50 mm; G3 ≥50 mm; G4 = necrosis or exfoliative dermatitis.

[c] Toxicity grade for groin or underarm swelling or tenderness was defined as: G1 = some swelling or tenderness but no interference with normal daily activities; G2 = swelling or tenderness that interfered with normal daily activities; G3 = swelling or tenderness that prevented normal daily activities; G4 = emergency room visit or hospitalization.

Table 36. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Study P306 Part 4 Cohorts A and B, Solicited Safety Set

Solicited Adverse Reaction	2y – 4y mRNA-1273.815 (25 µg) Single Dose N=199 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 1 N=399 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 2 N=386 n (%)
Any Systemic Reaction - N1	199	399	386
Any	47 (23.6)	128 (32.1)	105 (27.2)
95% CI	17.9, 30.1	27.5, 36.9	22.8, 31.9
Grade 1	29 (14.6)	86 (21.6)	67 (17.4)
Grade 2	12 (6.0)	31 (7.8)	27 (7.0)
Grade 3	6 (3.0)	11 (2.8)	11 (2.8)
Grade 4	0	0	0
Fever (temperature ≥38ºC) - N1[a]	199	399	386
Any Fever	17 (8.5)	36 (9.0)	44 (11.4)
Grade 1 (38 – 38.4˚C)	5 (2.5)	20 (5.0)	23 (6.0)
Grade 2 (38.5 – 39.5˚C)	10 (5.0)	14 (3.5)	18 (4.7)
Grade 3 (39.6 – 40˚C/)	2 (1.0)	2 (0.5)	3 (0.8)

Solicited Adverse Reaction	2y – 4y mRNA-1273.815 (25 µg) Single Dose N=199 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 1 N=399 n (%)	6m – 23m mRNA-1273.815 (25 µg) Dose 2 N=386 n (%)
Grade 4 (>40˚C)	0	0	0
Irritability/Crying - N1[b]	199	399	386
Any	24 (12.1)	69 (17.3)	50 (13.0)
Grade 1	17 (8.5)	59 (14.8)	42 (10.9)
Grade 2	5 (2.5)	9 (2.3)	7 (1.8)
Grade 3	2 (1.0)	1 (0.3)	1 (0.3)
Grade 4	0	0	0
Sleepiness - N1[c]	199	399	386
Any	25 (12.6)	41 (10.3)	27 (7.0)
Grade 1	17 (8.5)	32 (8.0)	24 (6.2)
Grade 2	6 (3.0)	7 (1.8)	2 (0.5)
Grade 3	2 (1.0)	2 (0.5)	1 (0.3)
Grade 4	0	0	0
Loss of appetite - N1[d]	199	399	386
Any	17 (8.5)	48 (12.0)	36 (9.3)
Grade 1	11 (5.5)	31 (7.8)	24 (6.2)
Grade 2	5 (2.5)	11 (2.8)	5 (1.3)
Grade 3	1 (0.5)	6 (1.5)	7 (1.8)
Grade 4	0	0	0

Source: Adapted from STN#125752/276 Study P306 Final CSR Part 4A Table 14.3.1.1.2.1.4.

Abbreviations: AR = adverse reaction; CI = confidence interval; G= grade; N = number of safety participants; n = Number of exposed participants who received the corresponding dose and reported an event; N1 = number of exposed participants who submitted any data for the event.

Note: Percentages were based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consisted of all participants in the safety set who contributed any solicited AR data, ie, had at least one post-baseline solicited safety assessment

a. Toxicity grade for fever was defined as: G1=38-38.4°C; G2=38.5 -39.5°C; G3=39.6-40°C; G4≥40°C.

b. Toxicity grade for irritability/crying was defined as follows: G1 = lasting <1 hour or easily consolable; G2 = lasting 1 to 3 hours or requiring increased attention; G3 = lasting >3 hours or inconsolable; and G4 = requires ER Visit or hospitalization.

c. Toxicity grade for sleepiness was defined as follows: G1 = sleepier than usual or less interested in surroundings; G2 = not interested in surroundings or sleeps through meals; G3 = sleeps most of the time, hard to arouse; and G4 = inability to arouse.

d. Toxicity grade for loss of appetite was defined as follows: G1 = eating less than normal for 1 to 2 feeds/meals; G2 = missed 1 to 2 feeds/meals completely; G3 = missed >2 feeds/meals completely or refuses most feeds/meals; and G4 = requires ER Visit or hospitalization.

Subpopulation Analyses by Demographic

Subpopulation analyses by sex, race, ethnicity, and obesity status were similar across subgroups, although interpretation is limited by the small number of participants in some of the subgroups.

Clinical Reviewer Comment:

Frequencies and severities of ARs were similar across age groups. Percentages of participants reporting ARs following mRNA-1273.815 were comparable with those reported after other formulations of Spikevax (see Section 6.1.12.3.1, 6.1.12.3.2, and 6.2.12.3.1) and were also similar to the frequencies and severities of solicited ARs reported in Part 1 of Study P306.

6.2.12.4 Unsolicited Adverse Events

Immediate unsolicited AEs
There were no immediate unsolicited AEs reported in Study P306 Part 2 and Part 4

Unsolicited AEs within 28 days of study dose
Unsolicited AEs within 28 days of study doses were reported by the following percentages of participants by study part:

- Part 1: 35.3% of participants (138/391)
- Part 2: 21% of participants (112/139)
- Part 4 (ages 2 years – 4 years): 20% (39/199);
- Part 4 (ages 6 months – 23 months): 52% (207/399)

For participants in Parts 1,2, and 4 of Study P306, the most frequent SOC for unsolicited AEs was *Infections and Infestations* (Part 1 - 24% of participants; Part 2 – 15% of participants; Part 4 2y - 4y – 17% of participants; and Part 4 Cohort B – 52% of participants).

The most frequently reported unsolicited AEs occurring in ≥5% of participants, by PT, were Part 1 - upper respiratory tract infection (7%) and otitis media (6%); Part 2 – upper respiratory tract infection (6%); Part 4 - nasopharyngitis (2 years – 4 years: 13%; 6 months – 23 months: 26%).

Unsolicited AEs occurring within 28 days of study dose and assessed as related to study vaccination by the investigator included:

- Part 1: diarrhea (n=2), infectious croup (n=1), and Henoch-Schönlein purpura (n=1, also reported as an AESI [see section 6.2.12.7])
- Part 2: diarrhea (n=2), dermatitis (n=2), urticaria (n=2), lymphadenopathy (n=1), cough (n=1), nasal congestion (n=1), rhinorrhea (n=1), vomiting (n=1), erythema multiforme (n=1, also reported as an AESI [see section 6.2.12.7]), injection site bruising (n=1), and noncardiac chest pain (n=1)
- Part 4: no related unsolicited AEs

Clinical Reviewer Comment:
The unsolicited AEs reported within 28 days of study dose were consistent with commonly reported medical conditions in the pediatric population and do not suggest new safety concerns for Spikevax.

6.2.12.5 FDA Standard MedDRA Queries of AEs within 28 Days of Study Dose

FDA Standard MedDRA Queries (SMQs) were conducted to evaluate for constellations of unsolicited AEs with onset following study vaccination through the data cutoff. SMQs are pre-determined sets of MedDRA PTs grouped together to represent medical concepts, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which captured AEs considered clinically relevant by the reviewer will be discussed.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, several cardiac-related SMQs were conducted, including *Cardiomyopathy*, *Cardiac Arrhythmia, Cardiac Failure, Ischemic Heart Disease, and Noninfectious Myocarditis and Pericarditis*. The search also included additional terms based on the CDC working case definition of myocarditis and pericarditis (see Appendix B).

Vaccine-naïve, 6 months through *5 years, 25 µg mRNA-1273.214 (Part 1)*
There were no events identified under the Cardiac-related SMQs, including events concerning for myocarditis or pericarditis.

Vaccine-experienced, 6 months through *5 years, 10 µg mRNA-1273.214 (Part 2)*
There were 2 events (PT palpitations and syncope) identified under the SMQs Cardiac Arrythmia and Cardiomyopathy. Both events were assessed as unrelated to the study dose. There were no events of myocarditis or pericarditis.

Vaccine-naïve, 6 months through *4 years, 25 µg mRNA-1273.815 (Part 4)*
There was one event (PT dyspnea) identified under the Cardiomyopathy SMQ. This event was assessed as not related to the study dose by the investigator. There were no events of myocarditis or pericarditis.

> ***Clinical Reviewer Comment:***
> *There were no cases meeting the definition of myocarditis/pericarditis and no evidence of increased risk of myocarditis/pericarditis following vaccination in children 6 months through 5 years of age in study P306.*

SMQs Hypersensitivity and Angioedema

Vaccine-naïve, 6 months – 5 years, 25 µg mRNA-1273.214 (Part 1)
A total of 25 events were identified under the SMQs Hypersensitivity and Angioedema. The most common PTs were seasonal allergy (n=4) and urticaria (n=3). There was 1 event assessed by the investigator as related to study dose (Henoch Schonlein Purpura, see section 6.2.12.8).

Vaccine-experienced, 6 months – 5 years, 10 µg mRNA-1273.214 (Part 2)
A total of 13 events were identified under the SMQs *Hypersensitivity* with the following PTs: dermatitis (n=3), dermatitis contact (n=2), seasonal allergy (n=3), bronchial hyperreactivity (n=2), and erythema multiforme (n=1). Of these events, 5 were assessed as related to the study dose: erythema multiforme (see section 6.2.12.8), 2 events of dermatitis, and 2 events of urticaria. There were no reported events of anaphylaxis.

Vaccine-naïve, 6 months – 4 years, 25 µg mRNA-1273.815 (Part 4)
A total of 24 events were identified under the SMQs Hypersensitivity and 3 events under the SMQ Angioedema. The most common PTs were bronchospasm (n=6) and conjunctivitis (n=3). None of these events were assessed as related to the study doses. There were no reported events of anaphylaxis.

SMQs Embolic and Thrombotic Events and Central Nervous System Vascular Disorders

Across all study parts, there were no events reported under the SMQs *Embolic and Thrombotic Events* or *Central Nervous System Vascular Disorders*.

6.2.12.6 Medically Attended Adverse Events

Through the date of data cut-off, MAAEs were reported by: Part 1 – 62% of participants (n=2 with MAAEs assessed as related by the study investigator); Part 2 - 56% of participants (n=3 with MAAEs assessed as related); Part 4 2y - 4y – 20% of participants (n=0 with MAAEs

assessed as related); and Part 4 Cohort B – 42% of participants (n=0 with MAAEs assessed as related).

The most frequently reported MAAEs (≥5% of participants), by PT, were upper respiratory tract infection (Part 1: 21%; Part 2: 22%; Part 4: 21%), otitis media (Part 1: 14%; Part 2: 13%; Part 4: 14%), pharyngitis streptococcal (Part 1: 10%; Part 2: 6%; Part 4: 8%), viral upper respiratory tract infection (Part 1: 10%; Part 2: 4%; Part 4: 6%); respiratory syncytial virus infection (Part 1: 3%; Part 2: 5%; Part 4:4%); and influenza (Part 1: 5%; Part 2: 5%; Part 4: 5%).

MAAEs, by PT, assessed as related to the study dose included diarrhea (n=1), erythema multiforme (n=1, [see section 6.2.12.7]), Henoch-Schönlein purpura (n=1, [see section 6.2.12.7]), lymphadenopathy (n=1), and urticaria (n=1).

Clinical Reviewer Comment:
Reported MAAEs were due to common childhood illnesses, particularly respiratory tract infections. Rates of reported MAAEs were higher in the youngest age group (6 months – 23 months of age) than the older age group (2 years through 4 years), reflective of general population trends for these types of illness. The number of MAAEs assessed as related to the study dose by study investigators were low and similar across age groups. There were no new safety concerns for Spikevax identified associated with the reported MAAEs.

6.2.12.7 Adverse Events of Special Interest

Participants in P306 were monitored for the AESIs listed in Appendix A. There were no reported cases of myocarditis or pericarditis in any of the study parts.

Vaccine-naïve, 6 months – 5 years, 25 µg mRNA-1273.214 (Part 1)
A total of 4 AESIs were reported (febrile convulsion in an 18-month-old with a concurrent viral illness 318 days after vaccination, febrile convulsion in a 17-month-old 165 days after vaccination, febrile convulsion in a 2-year-old with a concurrent upper respiratory tract infection 99 days after vaccination, Henoch-Schönlein purpura in an 11-month-old 3 days after the study dose). The event of Henoch-Schönlein purpura was assessed as related to the study dose by the investigator (see below).

Vaccine-experienced, 6 months – 5 years, 10 µg mRNA-1273.214 (Part 2)
A total of 4 AESIs were reported (erythema multiforme in a 4-year-old 1 day after vaccination, febrile convulsion in a 19-month-old 129 days after study vaccination, febrile convulsion in a 4-year-old 165 days after study vaccination, and seizure in a 4-year-old 110 days after vaccination). The event of erythema multiforme was assessed as related to the study dose by the investigator (see below).

Vaccine-naïve, 6 months – 4 years, 25µg mRNA-1273.815 (Part 4)
There was 1 AESI (seizure in an 11-month-old 9 days after vaccination). This AESI was assessed as not related to the study dose by investigators.

Clinical Narratives of AESIs
AESIs assessed as not related by study investigators:

- Seizure: An 11-month-old male participant experienced an SAE of pneumonia on Study Day 9 after the first study dose. The participant subsequently developed respiratory failure requiring intubation and mechanical ventilation. Four days (Study Day 13) and 8 days (Study Day 17) later, the participant experienced seizures due to hypoxia. His clinical condition subsequently improved, he was extubated, and he was ultimately discharged on Study Day 33. The investigator assessed the event as not related to the study vaccine.

AESIs assessed as related by study investigators:

- Henoch-Schönlein purpura: An 11-month-old female experienced a moderate nonserious AESI of Henoch-Schönlein purpura 3 days after receipt of the second study dose. The diagnosis was confirmed by the primary care provider and no other potential triggers were identified. The event resolved 11 days after vaccination without treatment. The investigator assessed the event as related to the study vaccine.

- Erythema multiforme: A 4-year-old female experienced a mild nonserious AESI of erythema multiforme 1 day after the study dose. The rash was characterized by multiple raised, red patches, some with central pallor and raised borders, bilaterally on arms, legs, feet and on the back. The rash was treated with oral antihistamines and resolved after 7 days. The participant had recently been treated with silver sulfadiazine for bacterial folliculitis prior to study vaccination (completed treatment 4 days before study dose). The investigator assessed the event as related to the study vaccine.

Clinical Reviewer Comment:

1. *Henoch-Schönlein Purpura: The event may have been related to the study dose and is recommended for inclusion in the USPI.*

2. *Erythema multiforme: The participant had recently experienced bacterial folliculitis and was treated silver sulfadiazine. As cited in literature reports, this may provide an alternative etiology (reported in Oaks, 2023 and Hafsi, 2025) for the onset of this adverse event. This event is not recommended for inclusion in the USPI.*

3. *AESI considered unrelated by the investigators: After careful review of the clinical narratives, these AESIs were considered not related to study vaccine based on the interval between vaccination and event and/or the presence of more likely alternative etiologies.*

6.2.12.8 Serious Adverse Events

Vaccine-naïve, 6 months – 5 years, 25µg mRNA-1273.214
Through the data cutoff, there were a total of 16 SAEs reported by 10 participants. No SAEs were reported within 28 days of the study dose. No SAEs were considered related to study doses by the study investigators.

Vaccine-experienced, 6 months – 5 years, 10µg mRNA-1273.214
Through the data cutoff, 10 SAEs were reported by 9 participants. No SAEs were reported within 28 days of the study dose. No SAEs were considered related to the study dose by the study investigators.

Vaccine-naïve, 6 months – 4 years, 25µg mRNA-1273.815

Through the data cutoff, 16 SAEs were reported by 13 participants. Of these, 12 SAEs were reported within 28 days of vaccination in 10 participants (2.5% of participants 6m – 23m of age). No SAEs were considered related to the study dose by the study investigators.

Clinical Reviewer Comment:
The case narratives were reviewed for all reported SAEs in Study P306. These SAEs were not related to the study doses and are not recommended for inclusion in the USPI.

6.2.12.9 Deaths

There were no deaths through the date of data cutoff in Study P306.

6.2.12.10 AEs leading to discontinuation

There were no AEs leading to discontinuation from the study through the date of data cutoff in Study P306.

6.2.13 Study Conclusions

The results of Study P306 support the safety and effectiveness of Spikevax when administered as a single dose to COVID-19 vaccine-experienced individuals 6 months – 5 years of age, as a single dose to COVID-19 vaccine-naïve individuals 2 years – 4 years, and as 2 doses (28 day interval) to COVID-19 vaccine-naïve individuals 6 months – 23 months of age.

7. Integrated Summary of Safety

Safety data from the two multipart studies submitted to this sBLA were reviewed under Section 6 of this memo. An integrated summary of safety would not be informative due to differences in study design and populations for each study. Section 10 (Conclusion) provides an overview of the submitted data that support the safety of Spikevax when administered to individuals 6 months through 11 years of age.

8. Integrated Summary of Effectiveness

Effectiveness data from the two multipart studies submitted to this sBLA were reviewed under Section 6 of this memo. An integrated summary of effectiveness would not be informative due to differences in study design, vaccine formulation, and population characteristics. Section 10 provides an overview of the submitted data to support the effectiveness of Spikevax when administered to individuals 6 months through 11 years of age.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were excluded from enrollment in the clinical studies submitted to this sBLA.

9.1.2 Use During Lactation

It is not known whether Spikevax is excreted in human milk. Data are not available to assess the effects of Spikevax on the breastfed infant or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

The studies submitted to this sBLA address the following PREA PMRs to assess the use of Spikevax in pediatric individuals 6 months to <12 years of age:

- PMR #1 [STN #125752/68] Study mRNA-1273-P204 to evaluate the safety of a single dose of SPIKEVAX in children 2 years through 11 years of age.

- PMR #2 [STN 125752/0] Study mRNA-1273-P204 to evaluate the safety and effectiveness of SPIKEVAX in children 6 months through <12 years of age (2-dose).

Deferral of Assessment

The Applicant has the following deferred pediatric study under PREA:

PMR #3 [STN 125752/0] Study mRNA-1273-P206 to evaluate the safety and effectiveness of SPIKEVAX in infants < 6 months of age. The following dates were agreed upon in the FDA Deferral Extension Granted Letter sent September 13, 2024, under STN 125752/219:

Final Protocol Submission: June 30, 2022 (Submitted)
Study Completion Date: December 31, 2029
Final Report Submission: June 30, 2030

Pediatric age group to be deferred: < 6 months of age

- Statutory reason for deferral: The drug or biological product is ready for approval for use in adults before pediatric studies are complete [505B(a)(4)(A)(i) of the FD&C Act].

Assessment Completed

This submission fulfills PREA PMR #1 [STN #125752/68] and PREA PMR #2 [STN 125752/0] and Spikevax will be indicated for use in individuals 6 months of age and older.

The Applicant's continued request for deferral of pediatric assessment in individuals < 6 months of age, and fulfillment of pediatric assessment in individuals 6 months through 11 years of age, were reviewed and agreed to by FDA's Pediatric Review Committee on May 13, 2025.

9.1.4 Immunocompromised Individuals

This sBLA did not contain data from clinical studies specifically addressing whether the vaccine is safe and effective for use in immunocompromised individuals.

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to Spikevax.

9.1.5 Geriatric Use

Adults, including older adults ≥65 years, were excluded from enrollment in the clinical studies submitted to this pediatric sBLA. Please refer to Section 8.5 of U.S. Prescribing Information for information regarding use of Spikevax in older adults.

10. CONCLUSIONS

The data submitted to this sBLA provide evidence to support the safety and effectiveness of Spikevax for the prevention of COVID-19 caused by SARS-CoV-2 when administered as a:

- Single dose (25 µg) in individuals 2 years through 11 years of age, irrespective of prior COVID-19 vaccination status
- Single dose (25 µg) in individuals 6 months through 23 months of age with ≥1 prior dose of a Moderna COVID-19 vaccine
- 2-dose series (25 µg each) in individuals 6 months through 23 months without prior COVID-19 vaccination

Effectiveness in Children 2 Years through 11 Years
Data provided in this sBLA support the effectiveness of a single dose (25 µg) of Spikevax in individuals 2 years through 11 years of age, irrespective of prior COVID-19 vaccination status. The following were demonstrated in the submitted clinical trial database to support the effectiveness of Spikevax in this age cohort:

- Noninferior immune responses following a single dose (25 µg) of Spikevax (monovalent XBB.1.5) in COVID-19 vaccine-naïve children 2 years through 4 years of age with evidence of prior SARS-CoV-2 infection compared with immune responses following a 2-dose series (25 µg each) of Spikevax (monovalent XBB.1.5) in COVID-19 vaccine-naïve children 6 months through 23 months of age without evidence of prior SARS-CoV-2 infection (Study P306 Part 4*). [Reviewed in Section 6.2]*).
- Noninferior immune responses following an additional single dose (25 µg) of Spikevax (Original monovalent) in previously COVID-19 vaccinated individuals 6 years through 11 years of age (Study P204 Part Booster) compared with immune responses following a 2-dose series (100 µg each) of Spikevax in COVID-19 vaccine-naïve young adults (18-25 years of age) enrolled in the pivotal field efficacy trial in adults (Study P301). [*Reviewed in Section 6.1*].
- Noninferior immune responses following an additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously COVID-19 vaccinated individuals 6 months through 5 years of age (Study P306 Part 2) compared with immune responses following a 2-dose series (25 µg each) of Spikevax in COVID-19 vaccine-naïve individuals 6 months through 5 years (Study P204 Part 2). [*Reviewed in Section 6.2*].

As described above in Study P306, a single dose of Spikevax in COVID-19 vaccine-naïve preschool age children with prior exposure to SARS-CoV-2 elicited comparable immune responses to those elicited by a 2-dose series of Spikevax in COVID-19 vaccine-naïve infant/toddlers without prior exposure. Earlier in the pandemic, when a 2-dose series was evaluated in vaccine-naïve school-age children in Study P204, 90% of whom were SARS-CoV-2 serostatus negative (*see Table 7*), robust immune responses were elicited. Based on current seroprevalence data, over 97% of school age children 5 through 11 years (see *CDC Pediatric Seroprevalence Data*) have antibodies against SARS-CoV-2 in their blood from either vaccination or infection. Based on the data submitted to this sBLA, a single dose of Spikevax in COVID-19 vaccine-naïve, seropositive school age children is anticipated to be similarly immunogenic to the responses elicited by a single dose of Spikevax in COVID-19 vaccine-naïve, seropositive preschool age children. These data support the determination that a single 25 µg dose of Spikevax is effective in children 2 years through 11 years of age, irrespective of prior COVID-19 vaccination.

Effectiveness in Children 6 Months through 23 Months
Data provided in this sBLA support the effectiveness of a 2-dose series (25 µg each) of Spikevax in individuals 6 months through 23 months of age without prior COVID-19 vaccination. The following were demonstrated in the submitted clinical trial database to support the effectiveness of Spikevax in this age cohort, if COVID-19 vaccine naïve:

- Noninferior immune responses following a 2-dose series (25 µg each) of Spikevax (Original monovalent) in COVID-19 vaccine naïve participants 6 months through 23 months of age (Study P204 Part 2) compared with immune responses following a 2-dose series (100 µg each) of Spikevax in COVID-19 vaccine-naïve young adults (18-25 years of age) without evidence of prior SARS-CoV-2 infection in the pivotal field efficacy trial in adults (Study P301) [*Reviewed in Section 6.1*].
- Descriptive data (Study P204 Part 2) suggest that Spikevax vaccine efficacy against CDC defined COVID-19 was approximately 40% in children 6 months through 23 months of age following 2 doses of Spikevax (Original monovalent). However, the study was conducted when Omicron BA.1 was the predominant SARS-CoV-2 variant in circulation and the study vaccine (mRNA-1273) was the original monovalent formulation that did not encode for the SARS-CoV-2 Omicron BA.1 variant, therefore the vaccine was mismatched to the circulating variant when clinical disease cases were being accrued. This suggests that vaccines matched to the predominant circulating strain are important to maintain high vaccine effectiveness against COVID-19 [*Reviewed in Section 6.1.11].*
- The immune responses elicited after a single dose (25 µg) of Spikevax Monovalent (Omicron XBB.1.5) in vaccine-naïve children 2 years through 4 years of age with evidence of prior SARS-CoV-2 infection were comparable to those elicited following 2-doses (25 µg each) of Spikevax Monovalent (Omicron XBB.1.5) in vaccine-naïve children 6 months through 23 months of age without evidence of prior SARS-CoV-2 infection in Study P306 Part 4 [*Reviewed in Section 6.2.11*].

Data provided in this sBLA support the effectiveness of a single (25 µg) dose of Spikevax in individuals 6 months through 23 months of age with ≥1 prior Moderna COVID-19 vaccination. The following were demonstrated in the submitted clinical trial database to support the effectiveness of Spikevax in this age cohort, if previously COVID-19 vaccinated:

- Noninferior immune responses following an additional single (10 µg) dose of a bivalent vaccine (Original and Omicron BA.1) in previously vaccinated individuals 6 months through 5 years of age (Study P306 Part 2) compared with immune responses following a 2-dose series (25 µg each) of Spikevax in COVID-19 vaccine-naïve individuals 6 months through 5 years (Study P204 Part 2). [*Reviewed in Section 6.2*]. Therefore, it is reasonable to conclude that a higher dose (25 µg) would elicit equivalent, if not greater immune responses as those elicited after a single 10 µg dose (Study P306 Part 2).

Safety in Children 2 Years through 11 Years
Data provided in this sBLA support the safety of a single dose (25 µg) of Spikevax in individuals 2 years through 11 years of age, irrespective of prior COVID-19 vaccination status. The following data were provided to support the safety of Spikevax in this age cohort:

- If COVID-19 vaccine-naïve:
    - Single dose (25 µg) of Spikevax (monovalent XBB.1.5) in children 2 years through 4 years of age with evidence of prior SARS-CoV-2 infection (P306 Part 4). [*Reviewed in Section 6.2*].

    - 2-dose series (50 µg or 25 µg each) of Spikevax (Original monovalent) in children 2 years through 11 years (Study P204 Part 2). [*Reviewed in Section 6.1*].
    - 2-dose series (25 µg each) of a bivalent vaccine (Original and Omicron BA.1) in children 2 years through 5 years of age (Study P306 Part 1). [*Reviewed in Section 6.2*].
- If previously COVID-19 vaccinated:
    - Additional single dose (25 µg or 10 µg) of Spikevax (Original monovalent) or a bivalent vaccine (Original and Omicron BA.1) in children 2 years through 11 years of age (Study P204 Part Booster). [*Reviewed in Section 6.1*].
    - Additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in children 2 years through 5 years of age (Study P306 Part 2). [*Reviewed in Section 6.2*].

Safety in Children 6 Months through 23 Months
Data provided in this sBLA support the safety of a 2-dose series (25 ug each) of Spikevax in individuals 6 months through 23 months of age with no prior history of COVID-19 vaccination. The following data were provided to support the safety in this age cohort, if COVID-19 vaccine naïve:

- 2-dose series (25 µg each) of Spikevax (Original monovalent), in children 6 months through 23 months of age with or without evidence of prior infection (Study P204 Part 2). [*Reviewed in Section 6.1*].
- 2-dose series (25 µg each) of Spikevax (monovalent XBB.1.5) in children 6 months through 23 months of age without evidence of prior SARS-CoV-2 infection (Study P306 Part 4). [*Reviewed in Section 6.2*].

Data provided in this sBLA support the safety of a single (25 µg) of Spikevax in individuals 6 months through 23 months of age with ≥1 prior Moderna COVID-19 vaccination. The following data were provided to support the safety of Spikevax in this age cohort, if previously COVID-19 vaccinated:

- Additional single dose (10 µg) of Spikevax (Original monovalent) or a bivalent vaccine (Original and Omicron BA.1) in previously COVID-19 vaccinated children in this age cohort (Study P204 Part Booster). [*Reviewed in Section 6.1*].
- Additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously COVID-19 vaccinated children in this age cohort. (Study P306 Part 2). [*Reviewed in Section 6.2*].
- 2-dose series (25 ug each) of Spikevax administered 28 days apart in children 6 months through 23 months of age (Study P204 Part 2 and Study P306 Part 4) support the use of a single 25 ug dose in children who had received one prior dose of Spikevax at least 28 days earlier. Therefore, it is reasonable to conclude that if the single dose is administered more than 28 days after prior vaccination, vaccine tolerability would be either comparable or less reactogenic than the 2nd dose when administered as a part of the 2-dose series. Data evaluating 2-dose series of the 25 ug dose support the tolerability of a single 25 ug dose in this age cohort.

In the clinical studies submitted to this sBLA, across all pediatric age groups, local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration. Across the clinical studies, there were two non-serious unsolicited events of alopecia areata and serum sickness-like reaction, two AESIs (erythema multiforme and Henoch-Schönlein purpura), and two SAEs (pyrexia and febrile convulsion) which were considered to be possibly related to Spikevax; these events will be described in Section 6 of the Spikevax US prescribing information (USPI). There were no new safety concerns identified in study data

reviewed in this application which were not already identified in the current Spikevax (Original monovalent) USPI. Based on review of available data, the clinical safety profile of the Spikevax platform was not adversely impacted by strain changes to the encoded mRNA Spike protein.

Postmarketing data with authorized or approved mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following the second vaccination, with the highest observed risk in males 12 years through 24 years of age. The risk of myocarditis is appropriately described in USPI (Section 5 Warnings and Precautions, Section 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience). There were no cases of myocarditis or pericarditis in the studies submitted to this sBLA.

The safety and effectiveness of Spikevax (Original monovalent), a bivalent vaccine (Original and Omicron BA.1), and Spikevax (XBB.1.5 monovalent) are relevant to Spikevax (2024-2025 Formula) because these vaccines are manufactured using a similar process.

Based on the totality of data and the risk-benefit considerations described in Section 11 below, the clinical reviewers conclude that the clinical trial data submitted in this application with available postmarketing data, support approval of Spikevax for the indication of active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 11 years of age with the following dosing posology to be included in the USPI:

- As a single dose in children 2 years through 11 years of age irrespective of receipt of any previously authorized Moderna COVID-19 vaccine
- As a single dose in children 6 months through 23 months who have received at least one dose of Moderna COVID-19 vaccine
- As 2 doses (1 month interval) in children 6 months – 23 months of age who are COVID-19 vaccine naïve.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 37. STN125752/276: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 is associated with significant morbidity, mortality (over 7 million deaths worldwide to date) and long-term sequelae among survivors. In the U.S., COVID-19 has been responsible for 1.2 million deaths to date with a cumulative COVID-19-associated hospitalization rate of 76.5 per 100,000 people for the 2024-2025 season, as of June 21, 2025, with the highest hospitalization rates in individuals over 65 years of age (317.4 per 100,000 people), followed by young infants and children (100 hospitalizations per 100,000 people for infants and children 6-23 months of age, and 268 hospitalizations per 100,000 people for infants less than 6 months of age). • SARS-CoV-2 continues to evolve, particularly in the spike protein's receptor-binding domain. Successive waves of variants, including Delta, Omicron BA.1, BA.5, XBB.1.5, and JN.1, have demonstrated increased transmissibility and, in some cases, greater ability to evade immunity from prior infection or vaccination. The trajectory of SARS-CoV-2 continues to remain unpredictable, including the potential emergence of variants with greater immune escape or virulence. • A large percentage of the United States population has developed immunity through some combination of vaccination and prior infection. While this has contributed to reduced rates of severe disease, it complicates assessments of vaccine effectiveness over time. The durability of immunity and the impact of waning immune protection on future disease burden are not fully known. • Updated vaccine formulations continue to show relative vaccine effectiveness (i.e., added benefit) in a population with high prevalence of immunity.	• COVID-19 continues to pose a substantial public health threat, both from acute infections and long-term complications. COVID-19 burden, including hospitalizations and deaths, are high among individuals over 65 years of age and in infants and young children. • Vaccination remains a cornerstone of the public health response, with updated formulations improving effectiveness against currently circulating variants. • Despite widespread immunity, due to ongoing viral evolution it is important to continue surveillance and to maintain flexibility in vaccine development and public health planning.
Unmet Medical Need	• COVID-19 remains a serious illness, particularly for older adults, young infants and children, and individuals with underlying health conditions. While many individuals recover within 1-2 weeks, some experience prolonged symptoms or develop post-acute sequelae known as Long-COVID, contributing to long-term morbidity. Children may also experience a serious medical condition associated with COVID-19 called Multisystem Inflammatory Syndrome in Children (MIS-C). The ability of current treatments to prevent Long-COVID and MIS-C remains unclear. • Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; these therapeutics are more effective when taken soon after disease onset and are generally more effective against mild to moderate COVID-19 cases. The age of the patient and the presence or absence of immunity from natural infection and prior COVID-19 immunization may also affect the benefit of using these treatments for COVID-19.	• Although treatments exist for those infected with SARS-CoV-2, they are generally not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (Long-COVID) and MIS-C. • Vaccines provide important protection from COVID-19. • There are no COVID-19 vaccines currently approved for infants and children less than 12 years of age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Currently, three COVID-19 vaccines (Spikevax, Comirnaty, and Nuvaxovid) have received FDA approval for prevention of COVID-19, but while Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, are authorized for use in children as young as 6 months of age under EUA, there are no COVID-19 vaccines approved for children under 12 years of age.	

Clinical Benefit	• Effectiveness of a single dose (25 µg) of Spikevax in children 2 years through 11 years of age irrespective of prior COVID-19 vaccination is based on:
	  • Immunogenicity of a single dose (25 µg) of Spikevax (XBB.1.5 monovalent formulation) in COVID-19 vaccine-naïve children 2 years through 4 years of age with evidence of prior SARS-CoV-2 as evaluated in Study P306 Part 4
	  • Immunogenicity of an additional single dose (25 µg) of Spikevax (Original monovalent) in previously vaccinated individuals 6 years through 11 years of age as evaluated in P204 Part Booster
	  • Immunogenicity of an additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously vaccinated individuals 6 months through 5 years of age as evaluated in Study P306 Part 2
	• Effectiveness of a single (25 µg) of Spikevax in individuals 6 months through 23 months of age with ≥1 prior Moderna COVID-19 vaccination is based on:
	  • Immunogenicity of an additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously vaccinated individuals 6 months through 5 years of age as evaluated in Study P306 Part 2
	• Effectiveness of a 2-dose series (25 µg each) of Spikevax in individuals 6 months through 23 months of age without prior COVID-19 vaccination is based on:
	  • Immunogenicity and descriptive efficacy of 2 doses (25 µg each) of Spikevax (Original monovalent), in COVID-19 vaccine naïve participants 6 months through 23 months of age without evidence of prior SARS-CoV-2 infection as evaluated in Study P204 Part 2 (a randomized, observer-blind, placebo-controlled trial of over 1,900 participants)
	  • Immunogenicity of 2 doses (25 µg each) of Spikevax (monovalent XBB.1.5) in vaccine-naïve children 6 months through 23 months of age without evidence of prior SARS-CoV-2 infection as evaluated in Study P306 Part 4
	• All studies listed above met their primary pre-specified success criteria
	• Uncertainties in clinical benefit include: precise estimate of relative vaccine efficacy in children less than 12 years of age, effectiveness against severe disease, durability of protection beyond 6-12 months, effectiveness in preventing asymptomatic infection or transmission, and effectiveness of future formulae (i.e., updated variant compositions) against future circulating variants.
		• The evidence for clinical benefit of Spikevax meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 6 months through 11 years of age.
		• Data from additional studies, including ongoing follow-up and real-world evidence, may address uncertainties such as the duration of protection, effectiveness against severe disease, and effectiveness in specific populations (e.g., immunocompromised individuals), and effectiveness against newly emerging variants.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most frequently reported adverse reactions were solicited local adverse reactions of injection site pain and axillary swelling or tenderness and systemic adverse reactions of irritability/crying (for participants 6 months through 36 months of age), sleepiness/fatigue, and headache (for participants 37 months through 11 years of age). These reactions were generally mild to moderate in severity, occurred within 1-3 days after vaccination, and resolved quickly. Unsolicited AEs within 28 days postvaccination were generally consistent with common childhood illnesses. Across the clinical studies, there were two non-serious unsolicited events of alopecia areata and serum sickness-like reaction, two AESIs (erythema multiforme and Henoch-Schönlein purpura) and two SAEs (pyrexia and febrile convulsion) which were considered to be possibly related to Spikevax. These events are documented in the USPI. There were no other SAEs reported in the studies submitted to this sBLA which were assessed as related to Spikevax. • No cases of vaccine-related myocarditis, pericarditis, or anaphylaxis were observed in the studies submitted to this sBLA. This is consistent with the observed epidemiology of vaccine-related myocarditis and pericarditis, which have not been shown to occur at higher frequency in children under 12 years of age. However, these events remain recognized potential risks for the vaccine class.	• In the clinical studies, across all pediatric age groups 6 months through 11 years of age, and following one or two vaccinations, local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration. Relevant related adverse events have been added to the USPI as described. There were no other new safety concerns identified in study data reviewed in this application which were not already identified in the current Spikevax (Original monovalent) USPI.
Risk Management	• Labeling for Spikevax describes the common and uncommon (but potentially serious) risks associated with the vaccine, which are unchanged based on the data reviewed in this sBLA for children 6 months through 11 years of age, as no new safety signals were identified. The Spikevax prescribing information includes warning statements for severe allergic reactions and myocarditis/pericarditis. • Postmarketing monitoring for AEs using both passive and active surveillance systems will be used to assess for emergence of any new safety concerns.	• Risk mitigation strategies for Spikevax in individuals 6 months of age and older are unchanged based on the review of this sBLA and include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of Spikevax in preventing symptomatic COVID-19 in individuals 6 months through 11 years of age is favorable compared with potential risks associated with vaccination. Study P204 was a large, multipart Phase 3 study which met its pre-specified primary endpoints, demonstrating noninferior neutralizing antibody responses against SARS-CoV-2 strains encoded for in the vaccine compared with neutralizing antibody responses following a 2-dose series in young adults generated from the pivotal efficacy study (Study P301) on which initial authorization and licensure of Spikevax was based. Study P306 was another large, multipart Phase 3 study which met its pre-specified primary endpoints, demonstrating noninferior neutralizing antibody responses against SARS-CoV-2 strains encoded for in the vaccine compared with neutralizing antibody responses following a 2-dose series in the same age group from P204, or with an internal comparator of a different age group (P306 Part 4). The safety of Spikevax in the pediatric population is adequately described in the product's prescribing information. The Applicant's routine pharmacovigilance and the additional ongoing PMR studies to assess for the risk of myocarditis and pericarditis after vaccination are adequate for monitoring of AEs postmarketing.

11.3 Discussion of Regulatory Options

The data submitted with the BLA efficacy supplement indicate the safety and effectiveness of Spikevax meet the statutory requirements to support its use in individuals 6 months through 11 years of age to prevent COVID-19 caused by SARS-CoV-2. The totality of clinical data provide evidence to support the safety and effectiveness of Spikevax with updates to the strain composition and/or valency.

11.4 Recommendations on Regulatory Actions

For the prevention of COVID-19 caused by SARS-CoV-2 in individuals 6 months through 11 years of age, the clinical reviewers recommend approval of Spikevax when administered as a single dose to individuals 2 years through 11 years of age irrespective of prior COVID-19 vaccination and to individuals 6 months through 23 months of age with at least one prior Moderna COVID-19 vaccination, and when administered as a 2-dose series (28 days apart) to individuals 6 months through 23 months of age with no prior COVID-19 vaccination. The clinical reviewers also recommend that this independent assessment of submitted clinical trial data serve as the basis to support the safety and effectiveness of future periodic strain updates to Spikevax.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

Postmarketing safety monitoring of Spikevax will include routine and enhanced pharmacovigilance with adverse event reporting under 21 CFR 600.80 as well as several ongoing PMR studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) specified in the Approval Letter for the original BLA (STN 125752/0) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical

myocarditis following Spikevax. No new safety PMR studies will be indicated since there were no new safety signals identified in the review of the data submitted to this sBLA.

As summarized in Section 9.1.3, the Applicant is required to conduct the following PREA PMR study:

1. PMR #3 [STN 125752/0] Deferred pediatric study under PREA (Study mRNA-1273-P206) to evaluate the safety and effectiveness of SPIKEVAX in infants <6 months of age.

   Final Protocol Submission: June 30, 2022 (Submitted)
   Study Completion Date: December 31, 2029
   Final Report Submission: June 30, 2030

12 APPENDICES

Appendix A. Adverse Events of Special Interest

Medical Concept	Medical Concept Descriptions/Guidance
Anosmia, Ageusia	New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	Any event of appendicitis
Rhabdomyolysis	New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome (ARDS)	New onset of ARDS/respiratory failure due to acute inflammatory lung injury DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (e.g., stroke, deep vein thrombosis [DVT], pulmonary embolism, disseminated intravascular coagulation [DIC], etc.)
Acute cardiovascular injury	New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia, confirmed by ECG (e.g., atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc. Increase in serum creatinine by ≥0.3 mg/dl (or ≥26.5 µmol/l) within 48 hours; OR Increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred within prior 7 days
Acute liver injury	New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc.: >3-fold elevation above the upper normal limit for ALT or AST; OR >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP

Medical Concept	Medical Concept Descriptions/Guidance
Dermatologic findings	Chilblain-like lesions Single organ cutaneous vasculitis; Erythema multiforme Bullous rash Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) Kawasaki's disease Hemophagocytic lymphohistiocytosis (HLH)
Thrombocytopenia	Platelet count <150 x 10^9/L (thrombocytopenia) New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. DOES NOT INCLUDE new onset of chronic arthritic conditions
New onset or worsening of neurological disease	Immune-mediated neurological disorders Guillain-Barre syndrome Acute disseminated encephalomyelitis (ADEM) Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/Encephalomyelitis Aseptic meningitis Seizures/convulsions/epilepsy Narcolepsy/hypersomnia
Anaphylaxis	Anaphylaxis associated with study drug administration
Other syndromes	Fibromyalgia Postural orthostatic tachycardia syndrome Chronic fatigue syndrome Myalgic encephalomyelitis Post viral fatigue syndrome Myasthenia gravis

Appendix B: COVID-19 Case Definitions

	CDC Definition	P301 Case Definition
Post-baseline SARS-CoV-2 PCR results	Positive	
-	AND at least one of the following	AND at least two of the following
Systemic Symptoms	• Fever (temperature ≥ 38ºC/≥100.4ºF) • Chills (of any duration) • Fatigue • Headache • Myalgia • Nasal congestion or rhinorrhea	• Fever (≥ 38ºC/≥ • 100.4ºF) • Chills • Myalgia • Headache • Sore throat

	• New loss of taste or smell • Sore throat • Abdominal pain • Diarrhea • Nausea/vomiting • Poor appetite/feeding	• New olfactory and taste disorder(s)
-	OR at least one of the following	OR at least one of the following
Respiratory Symptoms	• Cough (of any duration) • Shortness of breath or difficulty breathing (of any duration)	• Cough • Shortness of breath or difficulty breathing • Clinical or radiographical evidence of pneumonia

FDA generated table from STN#125752/276, Study P204 and P306 Statistical Analysis Plan

Appendix C: Study Case Definitions for Myocarditis and Pericarditis (CDC Criteria)

Probable acute myocarditis: Presence of ≥1 new or worsening of the following clinical symptoms: • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of: • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis AND No other identifiable cause of the symptoms and findings	Confirmed acute myocarditis: Presence of ≥1 new or worsening of the following clinical symptoms: • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of: • Histopathologic confirmation of myocarditis • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin) AND No other identifiable cause of the symptoms and findings
Acute pericarditis Presence of ≥2 new or worsening of the following clinical features:	Myopericarditis This term may be used for patients who meet criteria for both myocarditis and pericarditis.

• acute chest pain • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI	

FDA generated table adapted from STN#125752/276, Table 13 Study P306 Protocol