BLA Clinical Review Memorandum

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Applicant	Moderna TX, Inc.
Established Name	COVID-19 Vaccine, mRNA
Trade Name	SPIKEVAX
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.5 mL dose contains 50 µg modified mRNA encoding SARS-CoV-2 spike glycoprotein, encapsulated in lipid particles
Dosage Form and Route of Administration	Suspension for intramuscular injection (IM)
Dosing Regimen	Single 0.5 mL dose
Indication and Intended Population	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age 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
DVRPA	Division of Vaccines and Related Products Applications
e-diary	electronic diary
ECMO	extracorporeal membrane oxygenation
EOS	end of the study
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GM	geometric mean
GMT	geometric mean titer
IA	interim analysis
IM	intramuscular
IMV	invasive mechanical ventilation
IND	Investigational New Drug
IP	investigational product
IR	Information Request (by FDA)
LB	lower bound
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
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	non-inferiority
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
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
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

ModernaTX, Inc. (the Applicant) has submitted a supplemental Biologics License Application (sBLA) to the United States Food and Drug Administration (FDA) to support licensure of a single dose of Spikevax (2023-2024 Formula) for individuals 12 years of age and older irrespective of prior COVID-19 vaccination status. SPIKEVAX[1] is a nucleoside modified messenger RNA (mRNA) vaccine that encodes for the prefusion stabilized full-length spike (S) protein of SARS-CoV-2. The original formulation of SPIKEVAX, hereafter referred to as Spikevax (Original monovalent), encoded the S protein of the Wuhan-Hu-1 SARS-CoV-2 strain (hereafter referred to as the Original strain). Spikevax (Original monovalent) was referred to in clinical development as mRNA-1273[2] and was initially authorized under Emergency Use Authorization (EUA) on December 18, 2020 as Moderna COVID-19 Vaccine, hereafter referred to as Moderna COVID-19 Vaccine (Original monovalent), and subsequently licensed on January 31, 2022, for use as a 2-dose primary immunization series (100 µg each, 1 month apart) in individuals 18 years of age and older. The Moderna COVID-19 Vaccine (Original monovalent) was also authorized under EUA for primary series vaccination of individuals 6 months to 17 years of age and for booster vaccination of individuals 18 years of age and older; however, following emergence of the Omicron variant of SARS-CoV-2, and its sublineages (BA.4/BA.5 and other related sublineages) and observations of decreased vaccine effectiveness against Omicron sublineages compared to the Original strain, formulations of the vaccine containing Omicron components were developed to improve vaccine effectiveness. On August 31, 2022, FDA authorized the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), also referred to in clinical development as mRNA-1273.222[2], for use under EUA as a single booster dose in individuals 18 years of age and older, with concurrent revision of the authorization for the Moderna COVID-19 Vaccine (Original monovalent) to no longer include use as a booster dose in individuals 18 years of age and older in the U.S. On October 12, 2022, and December 8, 2022, FDA authorized the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 6 years through 17 years of age and individuals 6 months through 5 years of age, respectively.

On April 18, 2023, FDA authorized the use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in all individuals 6 months of age and older, with a simplified dosing schedule for use of a single dose in individuals 6 years of age and older, irrespective of prior COVID-19 vaccination status; for individuals 6 months through 5 years, a 2-dose primary series is administered to those who are COVID-19 vaccine naïve, and a single dose is administered to those who have received one or more previous doses of a Moderna COVID-19 vaccine [Original monovalent or bivalent (Original and Omicron BA.4/BA.5)] (see FDA Review Memorandum Dated April 18, 2023). The EUA actions removed authorization for Moderna COVID-19 Vaccine (Original monovalent) for use in the U.S.

On June 15, 2023, the 182nd Meeting of Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened and recommended an update to the COVID-19 vaccine composition to a monovalent XBB-lineage vaccine. Based on the totality of

[1] SPIKEVAX refers to any formulation of the approved product, Spikevax, irrespective of strain composition or valency.
[2] mRNA-1273 and variants thereof (e.g., mRNA-1273.222) refer to the investigational product prior to authorization or approval

the evidence presented at the meeting, for the 2023-2024 Formula of COVID-19 vaccines in the U.S., FDA has advised manufacturers seeking to update their COVID-19 vaccines that they should develop vaccines with a monovalent XBB.1.5 composition. With the submission of this sBLA, the Applicant has included nonclinical data to support the update in SPIKEVAX composition to a monovalent XBB.1.5 formulation, hereafter referred to as Spikevax (2023-2024 Formula).

This sBLA contains results from four clinical studies. Each of these studies had prespecified immunological endpoints with adequate success criteria to support inferring effectiveness through immunobridging.

Effectiveness Data
Effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:

- Immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve individuals 12-17 years who have evidence of prior SARS-CoV-2 infection
- Immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older

Data submitted to support the effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in COVID-19 vaccine naïve individuals 12 years of age and older come from Study P203 Part 3. In this study, immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was evaluated in COVID-19 vaccine naïve participants 12-17 years of age with evidence of prior SARS-CoV-2 infection. Predominant circulating SARS-CoV-2 variants during the study period (December 21, 2022, through June 5, 2023) included Omicron XBB1.5, BQ.1, and BQ1.1(Ma, 2023; CDC, 2023c). Therefore, enrolled participants had pre-existing natural immunity resembling the current U.S. population, as recent seroprevalence data show that ≥93% of individuals 12 years of age and older have evidence of prior SARS-CoV-2 infection (CDC, 2022a; CDC, 2022b).

The co-primary immunogenicity analyses for Study P203 (Part 3) evaluated the neutralizing antibody (nAb) geometric mean concentration (GMC) ratios against Omicron BA.4/BA.5 and Original (D614G) strains in seropositive adolescent participants post-Dose 1 compared with seronegative young adult participants post-dose 2. Specifically, the GMC after a single dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in adolescent participants with evidence of prior SARS-CoV-2 infection was compared with the GMC after a 2-dose series of Spikevax (Original monovalent) in Study P301 participants 18-25 years of age who had not had apparent prior SARS-CoV-2 infection. The immunogenicity results from Study P301 participants provided a link to established clinical efficacy of Spikevax (Original monovalent). The study met its pre-specified success criteria. These data support the effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in COVID-19 vaccine-naïve adolescents and can be extrapolated to support the effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in COVID-19 vaccine-naïve adults. This extrapolation is based on the comparable efficacy and immunogenicity results observed after a 2-dose series of

Spikevax (Original monovalent) between adolescent participants and adult participants (see Section 6.2 and original Spikevax BLA memo).

Data submitted to support the effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older come from 3 clinical studies: P203, P301, and P205 (see Sections 6.2, 6.3, 6.4, 6.5). In the adolescent (12-17 years of age) population, effectiveness of a 2-dose Spikevax (Original monovalent) series (100 µg, 1 month apart) was established in Study P203 (Part A) and serves as the foundation for the evaluation of effectiveness of Spikevax (Original monovalent) in participants who received a single 50 µg dose (Part C) at least 5 months after 2-dose series completion. The primary immunogenicity analyses of the GMC ratio and difference in percentages of seroresponse rates (SRRs) following the 50 µg single dose in adolescent participants in P203 (Part C) compared to those after the 2-dose series in young adults (18-25 years) in Study P301 (Part A), met the pre-specified success criteria.

In the adult (≥18 years) population, effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously vaccinated adults is supported by data from Study P301 (Part C), which evaluated the immunogenicity of a single (50 µg) dose of Spikevax (Original monovalent) when administered at least 6 months after completion of the 2-dose series (100 µg each, 1 month apart) of Spikevax (Original monovalent). The primary immunogenicity analyses of the GMC ratio and difference in percentages of SRRs following the single 50 µg dose in P301 (Part C) compared to those after the 2-dose series in the same set of participants met the pre-defined success criteria.

To further support the effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously vaccinated adults ≥18 years of age, additional immunogenicity data in adults are available from Study P205 (Part H). This study evaluated a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) compared with a single dose (50 µg) of Spikevax (Original monovalent) when administered to participants at least 3 months after a prior single dose (50 µg) of Spikevax (Original monovalent) at least 6 months after a 2-dose series (100 µg each) of Spikevax (Original monovalent). The primary immunogenicity analyses of the nAb geometric mean titer (GMT) ratio and difference in percentages of SRRs against both Omicron BA.4/BA.5 and the D614G strain, following Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) compared with those after Spikevax (Original monovalent), met the pre-defined success criteria. The results from Study P205 (Part H) serve as evidence that effectiveness of SPIKEVAX is preserved with strain and valency updates to the vaccine composition.

Safety Data
Safety of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:

- Safety of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve individuals 12-17 years of age who have evidence of prior SARS-CoV-2 infection
- Safety of a 2-dose series (100 µg each, 1 month apart) of Spikevax (Original monovalent) in COVID-19 vaccine naïve individuals 12 years of age and older

- Safety of a single dose (50 µg) of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older

Safety of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals ≥12 years who are COVID-19 vaccine naïve is based, in part, on safety after a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in 379 adolescent participants from Study P203 (Part 3). In this study, the median duration of follow-up for safety was 35 days. There were no unsolicited adverse events (AEs), outside of events consistent with vaccine reactogenicity, that were considered causally related to the vaccine. Safety of a single dose (50 µg) can also be inferred from the safety data of the 2-dose series (100 µg each, 1 month apart) of Spikevax (Original monovalent) in 2,486 adolescents from Study P203 (Parts A and B) and from 15,184 adults from Study P301 (Parts A and B), reviewed with the original Spikevax memo. The median duration of follow-up for safety was 312 days for the adolescent participants and 183 days for the adult participants. There were no safety concerns identified from the adolescent study which were not already described in the existing prescribing information for Spikevax (Original monovalent). A single dose (50 µg) of SPIKEVAX is expected to have a similar, if not more reassuring, safety profile compared to a 2-dose series of 100 µg each, as evaluated in these clinical studies.

Safety of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously vaccinated individuals ≥12 years of age is primarily based on safety of a single dose (50 µg) of Spikevax (Original monovalent) in 1,405 adolescent participants in Study P203 (Part C) and in 19,609 adult participants in Study P301 (Part C); and safety of a 50 µg dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in 511 adult participants in Study P205 (Part H). The median duration of safety follow-up post-vaccination were 204 days, 161 days, and 37 days, for studies P203 (Part C), P301 (Part C), and P205 (Part H), respectively. Overall, the safety profile observed after the 50 µg dose was similar to that observed after the 2-dose series of Spikevax (Original monovalent) in clinical studies.

The clinical data submitted meet FDA's statutory effectiveness standards and safety standards for data to support licensure of vaccines for prevention of COVID-19, including relevant efficacy success criteria and numbers of vaccinated study participants and follow-up time (i.e., at least 3,000 vaccinated participants in each age group with at least 6 months of total safety follow-up) for an acceptable safety database. The totality of the clinical data presented above support the proposed indication for use of SPIKEVAX as a single dose (50 µg) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status. The safety and effectiveness of Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Spikevax (2023-2024 Formula) because these vaccines are manufactured using a similar process. This independent assessment of submitted clinical trial data serves as the basis to support the safety and effectiveness of future periodic strain updates to SPIKEVAX.

Pediatric Assessment and Pediatric Research Equity Act
Pediatric studies evaluating a single dose of SPIKEVAX in children 2 years to <12 years of age, as required by the Pediatric Research Equity Act (PREA), were deferred for this application, and will be completed after approval of Spikevax (2023-2024

Formula) for use as single dose in individuals 12 years of age and older. The requirement for an assessment of a single dose of SPIKEVAX in children 0 to <2 years of age has been waived because there is evidence strongly suggesting that a single dose of SPIKEVAX would be ineffective in this age group. Safety and effectiveness data from Study P203 submitted to this sBLA (reviewed in Section 6) fulfill the pediatric study requirement for individuals 12 through 17 years of age. SPIKEVAX will be indicated for use in individuals 12 years of age and older.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

Effectiveness
Subgroup analyses of vaccine effectiveness did not suggest meaningful differences in vaccine effectiveness across age (12-17 years, 18-64 years, ≥65 years), 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 lower among older adults (≥65 years) compared with younger adults (18-64 years) and adolescents 12-17 years. Other differences between the age groups in overall rates and types of unsolicited AEs and serious adverse events (SAEs) largely reflected differences in underlying medical conditions between the age groups. No clinically meaningful differences in the occurrence of unsolicited AEs or SAEs were observed by sex, race, or ethnicity 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 August 16, 2023, SARS-CoV-2 infection has resulted in over 770 million cases of COVID-19 and an estimated 7 million deaths worldwide (WHO, 2023a). 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, 2023d), may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2022c). Symptoms associated with SARS-CoV-2 infection in children are similar to those in adults but are generally milder, with fever and cough most commonly reported (Irfan, 2021; Liguoro, 2020). However, since the January 2022 surge in cases due to Omicron BA.1, rates of COVID-19-associated hospitalizations among infants younger than 6 months old are similar to those of adults ages 65 to 74 years old (CDC, 2023e).

In the U.S., more than 6.3 million COVID-19-associated hospitalizations and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC, 2023c). Individuals 65 years of age and older accounted for approximately 14% of cases and 76% of deaths (CDC, 2021a). By contrast, individuals 18 years of age and younger represent 17% of COVID-19 cases and less than 0.3% of deaths (CDC, 2021a). 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. COVID-19 vaccines based on the Wuhan-HU-1 strain of SARS-CoV-2 (also referred to as ancestral, reference, or original strain) were launched in the U.S, starting in December 2020. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently the Omicron variant of concern. Bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines were deployed in the U.S. starting in September 2022.

The SARS-CoV-2 Omicron variant has continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by post-vaccination (with Original strain vaccines) and post-infection sera compared to the pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from post-vaccination and post-infection antibody responses. By spring 2023, BQ sublineages were rapidly replaced by XBB sublineages, both in the U.S. and globally. The XBB parent lineage resulted from a recombination of BA.2.10.1 and BA.2.75 sublineages, highlighting the relevance of recombination in generating new variants of concern. Recombination can occur during virus replication in cells infected by more than one variant.

XBB sublineages have continued to emerge that have accumulated a small number of mutations in the spike N-terminal domain and the receptor binding domain (RBD). The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world, by April. Compared to the parental XBB lineage virus, XBB.1.5 has two amino acid substitutions, G252V and S486P, in the RBD of the SARS-CoV-2 spike protein. These changes may confer additional growth advantage, likely due in part to increased affinity of the spike protein to the ACE2 receptor conferred by the S486P change (Yue, 2023). Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5. The XBB.1.9 variant has the same spike protein sequence as XBB.1.5, but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness (Jiang, 2020;

Gao, 2021). Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April 2023 the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared with the parental XBB lineage virus, XBB.1.16 has four spike substitutions, i.e., E180V, G252V, K478R, and S486P. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses rose rapidly in many other countries, including the U.S. Preliminary reports have indicated that no further immune evasion result from these substitutions in the XBB.1.16 spike protein compared with XBB.1.5 (Wang, 2023; Yamasoba, 2023). Overall, XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023; at this time (August 2023), other circulating variants worldwide include XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant variant in the U.S. in late August 2023 was EG.5. EG.5 carries an additional F456L amino acid substitution in the spike protein compared to the parent XBB.1.9.2 subvariant and XBB.1.5. Within the EG.5 lineage, the subvariant EG.5.1 has an additional spike protein substitution Q52H and represents 88% of the available sequences for EG.5 and its descendent lineages (WHO, 2023b).

SARS-CoV-2 evolution is complex and remains unpredictable. Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. 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.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1.1, or XBB.1.5 lineage, as specified.

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

2.2.1 FDA-approved Therapies for COVID-19

Oral 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:
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 extracorporeal membrane oxygenation (ECMO).

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

Oral antivirals:
Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older 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 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:
Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them (For detail of previously authorized SARS-CoV-2-targeting monoclonal antibodies, please refer to Section 2.2.5 of the FDA Review Memorandum Dated April 18, 2023).

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 (IMV), or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 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

Comirnaty and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty (Original monovalent) contains a nucleoside- modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain.

A bivalent formulation of the vaccine manufactured using a similar process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is currently authorized under EUA for administration of a single dose in individuals 5 years of age and older, three doses in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two doses if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single dose in individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer-BioNTech COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

Novavax COVID-19 Vaccine, Adjuvanted
The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 Original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older, and as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.

For additional information on dosing and schedule, please refer to the Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

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. Currently, Spikevax (Original monovalent) is authorized or approved for use in 88 countries. In the U.S.,

over 250 million doses of Moderna COVID-19 vaccines have been administered to date (CDC, 2023a).

2.5 Summary of Regulatory Activity Related to the Submission

Major sBLA-associated regulatory activities:

a. January 26, 2023: VRBPAC meeting was held to discuss harmonization of vaccine strain composition for all doses, the simplification of the COVID-19 immunization schedules, and the procedures for routine periodic strain selection.
b. April 18, 2023: The EUA of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was amended to simplify the vaccination schedule to a single dose regimen for most individuals. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of the Moderna COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.
c. June 15, 2023: The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. and the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage.
d. June 22, 2023: Under IND 19745, the Applicant was provided pre-BLA written response comments pertaining to strain change to mRNA-1273.815 LNP-B for Spikevax (2023-2024 Formula).
e. June-August 2023: Under IND 19745 and this sBLA (STN 125752.68), multiple communications were provided to the Applicant related to the 2023-2024 Formula, single-dose indication, and Pediatric Study Plan for single-dose regimen.

2.6 Other Relevant Background Information

Not applicable

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. Please see review memorandum by Dr. Brenda Baldwin, Consult Reviewer, for additional details regarding the quality of the study datasets.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The studies submitted to this sBLA were conducted in accordance with Good Clinical Practice guidelines as per 21 CFR 312. 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 3 clinical study sites. The inspections did not reveal substantive issues that would impact the data submitted in this application. Please see review memorandum by Dr. Triet Tran, BIMO reviewer, for additional details.

3.3 Financial Disclosures

Studies P301, P201, P205, and P203
Was a list of clinical investigators provided? ☑ Yes ☐ No
Total number of investigators identified: 187 (99 for P301, 8 for P201, 23 for P205, 57 for P203)
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): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Reviewer Comment: The Applicant satisfactorily addressed study investigator financial interests that could impact clinical data quality.

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 were reviewed 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 Spikevax (2023-2024 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 7.2) to monitor safety concerns that could be associated with the Spikevax (2023-2024 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 pharmacovigilance for all adverse events 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. Accumulating evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection, particularly against severe COVID-19 and hospital admissions. This evidence supports the rationale of administering a single dose of COVID-19 vaccine to individuals seropositive for SARS-CoV-2 from a prior infection, regardless of prior COVID-19 vaccination status. The feasibility of this strategy would therefore depend on the seroprevalence of SARS-CoV-2 in the population. According to the CDC, the seroprevalence of SARS-CoV-2 was estimated to be 98.8%, 97.8%, 97%, and 92.5% in persons aged 16-29 years, 30-49 years, 50-64 years, and ≥65 years, respectively (CDC, 2022a). 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, 2022b). Therefore, given the high seroprevalence of SARS-CoV-2 in individuals 12 years of age and older, FDA sought evidence from the Applicant of the safety and efficacy of a single dose (50 µg) of their COVID-19 vaccine in baseline SARS-CoV-2 seropositive individuals, irrespective of COVID-19 vaccination status. These data were submitted to this sBLA and are summarized below:

Effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:

- Immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve

individuals 12-17 years who have evidence of prior SARS-CoV-2 infection (Study P203 Part 3).
- Immunogenicity of a 50 µg booster dose of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older (Studies P203 Part C, P201 Part B, P301 Part C, and P205 Part H)

Safety of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:
- Safety of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve individuals 12-17 years who have evidence of prior SARS-CoV-2 infection (Study P203 Part 3)
- Safety of a 2-dose series (100 µg each, 1 month apart) of Spikevax (Original monovalent) in COVID-19 vaccine naïve individuals (Study P203 Part A and B).
- Safety of a single dose (50µg) of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older (Studies P203 Part C, P201 Part B, P301 Part C, and P205 Part H).

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

The following STN 125752/68 Amendments were reviewed in support of this application:

Table 1. Amendments to sBLA 125752/68

Amendment Number	Date Received	Description
1	May 8, 2023	Response to IR re: Study P301 Part C
2	May 10, 2023	CBER requested tables
5	June 21, 2023	Response to IR: re: Real world effectiveness studies
10	July 7, 2023	Response to IR re: Updated pharmacovigilance plans
11	July 11, 2023	Response to IR re: Dataset issues
12	July 17, 2023	Response to IR re: Doses administered to adolescents
15	August 2, 2023	Response to IR re: Studies P203 and P205
16	August 3, 2023	Response to IR re: Risk management plans
17	August 4, 2023	Tables and datasets for Study P203
18	August 7, 2023	Response to IR re: PREA waiver/deferral request
19	August 10, 2023	Updated draft labeling
20	August 10, 2023	Response to IR re: PREA waiver/deferral request
22	August 15, 2023	Response to IR re: Study P301 Part C, P205 Part H
23	August 17, 2023	Response to IR re: Study P301 Part C, P205 Part H, P203 Part 3
25	August 18, 2023	Response to IR re: Study P301 Part C, P203
26	August 22, 2023	Response to IR re: Study P301 Part C
27	August 23, 2023	Response to IR re: Patient-level data for real world effectiveness study
28	August 24, 2023	Response to IR re: Study P205 Part H Interim CSR
29	August 25, 2023	Response to IR re: Study P301 Part C, P203
30	August 30, 2023	Updated draft labeling
33	August 29, 2023	All information previously submitted to STN 125752/58
35	September 1, 2023	Response to IR re: Cardiac Event Adjudication committee

Amendment Number	Date Received	Description
38	September 7, 2023	Clarification of intended indication
39	September 7, 2023	Updated draft labeling
42	September 8, 2023	Updated draft labeling
44	September 8, 2023	Updated draft labeling

Source: FDA-generated table.

For the above listed amendments, the following modules were reviewed, as applicable:
Module 1 All Sections Including 1.14 Labeling
Module 2.2 Introduction
Module 2.5 Clinical Overview
Module 2.7.3 Summary of Clinical Efficacy
Module 2.7.4 Summary of Clinical Safety
Module 2.7.6 Synopses of Individual Studies
Module 5.2 Tabular Listing of All Clinical Studies
Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies

During the BLA review period, the Applicant submitted a total of 26 amendments.[3] 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.

Supportive information from EUA 27073 and clinical study protocols reviewed under IND 19745 and IND 19635 were also referenced during the review cycle.

5.3 Overview of Clinical Studies

Clinical studies submitted to support the safety and effectiveness of a single dose of SPIKEVAX including Spikevax (2023-2024 Formula) are summarized in Table 2 below. In these studies, participants received a single dose, a 2-dose series one month apart (referred to as “primary series”), and subsequent doses referred to as “booster doses”.

Table 2. Clinical Trials Submitted in Support of Effectiveness and Safety Determinations of a Single Dose of SPIKEVAX Including Spikevax (2023-2024 Formula)

Study Number	Type of Study	Study Status[a]	Participants Vaccinated (N)	Dose Regimen	Vaccine Formulation	Dose Levels Assessed
P301 Part C	Open Label; Safety, immunogenicity	Safety follow-up ongoing	19,609	1st Booster Dose	Original monovalent	50 µg
P205 Part H	Open Label; Safety, immunogenicity	Safety follow-up ongoing	511	2nd Booster Dose	Bivalent (Original + Omicron BA.4/BA.5)	50 µg

3 Only amendments relevant to the clinical review are included in the table above.

Study Number	Type of Study	Study Status[a]	Participants Vaccinated (N)	Dose Regimen	Vaccine Formulation	Dose Levels Assessed
P203 Part A and B	Randomized, observer-blind, placebo-controlled, followed by open-label phase; Safety, immunogenicity, efficacy	Completed	2,486	Primary Series	Original monovalent	2 doses, 100 µg
P203 Part C	Open Label; Safety, immunogenicity	Safety follow-up ongoing	1,405	1st Booster Dose	Original monovalent	50 µg
P203 Part 3	Open Label; Safety, immunogenicity	Ongoing	379	Single Dose	Bivalent (Original + Omicron BA.4/BA.5)	50 µg
P201 Part B	Open label; Safety, immunogenicity	Completed	171	1st Booster Dose	Original monovalent	50 µg

Source: FDA-generated table
a. As of database lock

The following clinical study reports were also submitted to the sBLA:

- Study 21-0012 (sponsored by DMID): Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (100 µg mRNA-1273 booster) study of the various EUA vaccines (Ad26.COV2.S, mRNA-1273, BNT162b2) in participants ≥18 years old (NCT04889209).
- Study P903: A Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the U.S.: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity which is an enhanced pharmacovigilance study to provide additional evaluation of AESIs (including myocarditis and pericarditis) and emerging validated safety signals.
- Study P901: A real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. with 2 doses of Moderna COVID-19 vaccine for preventing COVID-19.

Data from these studies will not be included in this clinical review memorandum or in the SPIKEVAX prescribing information as they do not contribute substantially to the proposed indication and accompanying datasets were not submitted to permit FDA independent review.

5.4 Consultations

5.4.1 Advisory Committee Meeting

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has periodically convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. At the January 26, 2023, VRBPAC meeting on COVID-19 vaccines, FDA stated that it anticipates assessing SARS-CoV-2 evolution at least annually (review of data to commence in the spring of each year) and to convene the VRBPAC in June of each year regarding strain selection for fall vaccination.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the U.S. as of early June 2023. While XBB.1.5 had declined to less than 40% of presumed circulating virus in the U.S., XBB.1.16 was on the rise and XBB.2.3 was slowly increasing in proportion (CDC COVID Data Tracker: Variant Proportions). The trajectory of virus evolution suggested that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolved. Although SARS-CoV-2 continues to evolve, the amino acid sequences of XBB.1.5, XBB.1.16, and XBB.2.3 spike protein appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new amino acid substitutions in the XBB.1.16 spike protein compared to XBB.1.5. By several measures, including escape from antibody neutralization and waning protection, the currently available bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines appear less effective against currently circulating variants (e.g., XBB-lineage viruses) than against previous strains of SARS-CoV-2. The totality of available evidence suggests that an update to the composition of COVID-19 vaccines to a monovalent XBB-lineage vaccine is warranted for 2023–2024.

The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. Sublineages considered by the VRBPAC included XBB.1.5, XBB.1.16, and XBB.2.3. Evidence influencing strain selection discussed by the Committee included virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, pre-clinical immunogenicity studies evaluating immune responses generated by candidate vaccines. The Committee also reviewed manufacturing timelines.

For the 2023-2024 Formula of COVID-19 vaccines in the U.S., the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage. Based on the evidence and other considerations presented, committee members expressed a preference for selection of XBB.1.5 for the 2023-2024 Formula. Based on the totality of the evidence, FDA advised manufacturers seeking to update their COVID-19 vaccines that for the 2023-2024 Formula of COVID-19 vaccines in the U.S. they should develop vaccines with a monovalent XBB.1.5 composition.

5.5 Literature Reviewed

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6.1 Study P203 (Part 3): Adolescent Single Dose

NCT04649151

Title: A Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 to <18 years of age.

Study Overview: Study P203 Part 3 was an open label, single-arm portion of the study evaluating the safety, reactogenicity, and effectiveness of a 2-dose series (50 µg each; administered 6 months apart) of mRNA-1273.222 (bivalent vaccine encoding equal parts the pre-fusion stabilized Spike glycoprotein of the SARS-CoV-2 Wuhan-Hu-1 strain [Original] and SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 [Omicron

BA.4/BA.5]), in healthy, COVID-19 vaccine-naïve adolescents 12 to <18 years of age. Safety and immunogenicity data from post-dose 1 of Part 3 has been submitted to the sBLA to support the safety and effectiveness of a single dose in COVID-19 vaccine-naïve individuals. The submission includes Part 3 data from start of enrollment on December 21, 2022 to the data cut-off of June 5, 2023, and included 379 vaccinated adolescents.

6.1.1 Objectives and Endpoints

Primary Objectives/Endpoints:

1. The primary safety objective is to evaluate the safety and reactogenicity of the 50 µg mRNA-1273.222 vaccine. Specifically, the rates and profile of solicited ARs and unsolicited AEs reported after 1 dose of mRNA-1273.222 are summarized.

   The safety endpoints were:
   a. Solicited local and systemic ARs through 7 days after each injection.
   b. Unsolicited AEs through 28 days after each injection.
   c. MAAEs through the entire study period.
   d. SAEs through the entire study period.
   e. AESIs through the entire study period.
   f. AEs leading to withdrawal from study participation from Dose 1 through the last day of study participation.
   g. AEs leading to discontinuation from dosing from Dose 1 through the last day of study participation.

2. The primary immunogenicity objective of the Study P203 Part 3 is to infer effectiveness of the 50 µg mRNA-1273.222 vaccine based on immune responses against SARS-CoV-2 Omicron BA.4/BA.5 and D614G strains obtained 28 days post-Dose 1 in baseline SARS-CoV-2 positive adolescent participants

   The co-primary immunogenicity endpoints were:

   a. Superiority of nAb GMC against Omicron BA.4/BA.5 after single 50 µg dose of mRNA-1273.222 in COVID-19 vaccine-naïve, baseline SARS-CoV-2 positive adolescents in Study P203 Part 3 compared to nAb GMC after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants in Study P301.
      Success criterion: The GMC ratio (adolescent post-single dose/young adult post-Dose 2) is superior if the lower bound (LB) of the 2-sided 95% confidence interval (CI) >1.0.

   b. Noninferiority nAb GMC against the D614G strain after single 50 µg dose of mRNA-1273.222 in COVID-19 vaccine-naïve, baseline SARS-CoV-2 positive adolescents in Study P203 Part 3 compared to nAb GMC after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants in Study P301.

Success criterion: The GMC ratio (adolescent post-single dose/young adult post-Dose 2) is non-inferior if the LB of the 2-sided 95% CI >0.667.

Secondary Objectives/Endpoints:
In addition to the primary immunogenicity objectives/endpoints, the following SRR endpoints were evaluated as secondary descriptive endpoints:

1. SRR against Omicron BA.4/BA.5 after single 50-µg dose of mRNA-1273.222 COVID-19 Vaccine (Bivalent) in COVID-19 vaccine-naïve, baseline SARS-CoV-2 positive adolescents in Study P203 Part 3 compared to SRR against Omicron BA.4/BA.5 after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants 18 to 25 years of age in Study P301.

2. SRR against the D614G strain after single 50 µg dose of mRNA-1273.222 COVID-19 Vaccine (Bivalent) in COVID-19 vaccine-naïve, baseline SARS-CoV-2 positive adolescents in Study P203 Part 3 compared to SRR against the D614G strain after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants 18 to 25 years of age in Study P301.

Clinical Reviewer Comment: There were additional secondary and exploratory objectives included in the original protocol that were not included in the clinical summary submitted for this sBLA review. Those objectives mainly evaluated post-Dose 2 immunogenicity and long-term persistence of the immune response post-Dose 2, which have not been completed and would not be relevant for the indication sought under this sBLA review.

6.1.2 Design Overview

Study P203 is a Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 through 17 years of age. The primary phase of the study (Parts A and B) evaluated a 2-dose primary series (100 µg, 1 month apart) of mRNA-1273 and are described in Section 6.2. In response to the global surge of SARS-CoV-2 Omicron variant and its sublineages, and to evaluate new dosing regimens in the setting of increasing SARS-CoV-2 seroprevalence, Study P203 was amended to add Part 3, an open label, single-arm portion of the study to evaluate the safety, reactogenicity, and effectiveness of a 2-dose primary series (50 ug, given 6 months apart) of mRNA-1273.222, in healthy, vaccine-naïve adolescents 12 to <18 years of age.

A total of 379 adolescent participants were enrolled in Study P203 Part 3 and received 1 dose of 50 µg mRNA-1273.222. Immune assessments are planned for after Dose 1 and after Dose 2. Participants will be followed in the study for 12 months (6 months post-Dose 2). This submission contains results of an interim analysis (IA) including safety and immunogenicity data through approximately one month following Dose 1.

Clinical Reviewer Comment: Despite the small size of Study P203 Part 3, and limited follow-up (median 35 days), these safety data are supplemented with studies of mRNA-1273 in individuals previously vaccinated with at least 2 doses of mRNA-1273 in this age cohort as well as in older age cohorts with large safety populations,

which contributes to the overall safety database for use of a single dose in individuals 12 years of age and older.

6.1.3 Population

Part 3 enrolled healthy, COVID-19 vaccine-naïve, adolescent participants 12 to <18 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273.222 is a nucleoside modified mRNA that encodes for the full-length spike proteins of SARS-CoV-2 Wuhan and Omicron BA.4/BA.5, modified to introduce 2 proline residues to stabilize the S-2P spike protein into a prefusion conformation, and encapsulated in lipid particles.

Each 0.25 mL injection contained 50 µg of mRNA-1273.222 (25 µg Original strain, 25 µg Omicron BA.4/BA.5).

Lots: 8524100101 and 8524900101

6.1.5 Directions for Use

mRNA-1273.222 was administered as an intramuscular injection into the deltoid muscle, preferentially to the nondominant arm.

6.1.6 Sites and Centers

Study P203 Part 3 was conducted in 11 centers in the U.S. and 6 centers in the Dominican Republic.

Clinical Reviewer Comment: Part 3 of Study P203 began enrollment in the U.S., but challenges enrolling enough vaccine-naïve adolescents resulted in enrollment being completed in the Dominican Republic.

6.1.7 Surveillance/Monitoring

Immunogenicity
Blood samples were collected from a random subset of participants (Immunogenicity Subset) for immunogenicity assessments at baseline (Day 1) and 28 days post-Dose 1 (Day 29). Immunogenicity assessments included the following:

- Serum nAb levels against SARS-CoV-2 (D614G and Omicron BA.4/BA.5) as measured by a validated pseudovirus neutralization assay (PsVNA). Immunogenicity analyses were based on nAb concentrations measured using the PsVNA conducted at PPD Vaccine Laboratories. nAb concentrations were measured in both the group of adolescent mRNA-1273.222 recipients in P203 Part 3 and the P301 comparator group of young adults. nAb levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses. This differed from the Duke pseudovirus neutralization assay used for other parts of P203 and Study P301 which reported results as 50% inhibitory dose (ID50) neutralization titers.

- Serum Ab directed against the nucleocapsid protein were measured using Roche Elecsys immunoassay.

Clinical Reviewer Comment: Immunogenicity assessments are also planned for Days 85, 181, 209, and 361. These assessments have not been conducted yet and are not available for review for this sBLA.

Safety
Safety assessments included the following:

- Solicited local and systemic ARs that occurred during the 7 days following Dose 1 (starting on the day of vaccination and followed by 6 subsequent days). Solicited ARs were recorded using e-diaries.
- Unsolicited AEs observed or reported during the 28 days following Dose 1 (starting the day of vaccination and followed by 27 subsequent days).
- AEs leading to discontinuation from study participation from time of Dose 1 through the entire study period.
- MAAEs leading to discontinuation from study participation from time of Dose 1 through the entire study period.
- SAEs leading to discontinuation from study participation from time of Dose 1 through the entire study period.
- AESIs leading to discontinuation from study participation from time of Dose 1 through the entire study period.
- Vital sign measurements.
- Physical examination findings.
- Details of all pregnancies in female participants from the time of Dose 1 until the end of their participation in the study.

All potential cases of myocarditis and pericarditis, as identified by the investigator or Applicant, were reviewed by an independent Cardiac Event Adjudication Committee (CEAC) to determine whether the case met the CDC criteria (Appendix D) 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 follow-up visits or calls are planned on post-Dose 1 Days 3, 8, 29, 57, 85, and every 6 weeks between Day 99 and 141. A similar schedule for safety follow-up calls is planned for after Dose 2. 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.

Clinical Reviewer Comment: Post-Dose 2 safety assessments have not been conducted yet and are not available for review for this sBLA.

6.1.8 Endpoints and Criteria for Study Success

See Sections 6.2.1 and 6.2.9.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity Analyses
To infer effectiveness of a single dose of 50 µg mRNA-1273.222, immune responses against SARS-CoV-2 Omicron BA.4/BA.5 and D614G obtained 28 days post-dose 1 in baseline SARS-CoV-2 positive adolescent participants were compared with immune responses obtained 28 days post-dose 2 of the original mRNA-1273 vaccine in young adult participants (18-25 years) in Study P301 who were SARS-CoV-2 negative at baseline.

The protocol specified success criteria for the co-primary endpoints were:

1. Co-primary Endpoint 1: neutralizing antibody (nAb) GMC against Omicron BA.4/BA.5
   The GMC ratio (adolescent Dose 1/young adult primary series) is superior if the lower bound (LB) of the 2-sided 95% CI >1.0.

2. Co-primary Endpoint 2: neutralizing antibody (nAb) GMC against the D614G strain
   The GMC ratio (adolescent Dose 1/young adult primary series) is non-inferior if the lower bound (LB) of the 2-sided 95% CI >0.667.

The primary immunogenicity objective for Part 3 is met if both superiority of nAb GMC ratio (adolescent Dose 1/young adult primary series) against Omicron BA.4/BA.5 and non-inferiority of nAb GMC ratio (adolescent Dose 1/young adult primary series) against the D614G strain and is demonstrated. The GMC ratio with 95% CI to compare post-dose 1 in vaccine-naïve, baseline SARS-CoV-2 positive adolescent participants with post-Dose 2 GMC in young adults was computed based on the analysis of covariance (ANCOVA) model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resulted least-squares (LS) means, difference of LS means, and 95% CI were back transformed to the original scale.

Secondary endpoints evaluated the SRR against Omicron BA.4/BA.5 and D614G strain after single 50-µg dose of mRNA-1273.222 in COVID-19 vaccine-naïve, baseline SARS-CoV-2 positive adolescents in Study P203 Part 3 compared to SRR against Omicron BA.4/BA.5 after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adult participants 18 to 25 years of age in Study P301. The SRR endpoints were evaluated descriptively, without hypothesis testing.

The SRR at the analysis time point was computed with 2-sided 95% Clopper-Pearson CI, and the SRR (percentage) difference with 2-sided 95% CI (using Miettinen-Nurminen score method) was calculated. The seroresponse at participant level was defined as antibody measures change from pre-Dose 1 below the LLOQ to ≥4 × LLOQ, or at least a 4-fold-rise if pre-Dose 1 was ≥LLOQ.

Analysis Timing
Per protocol, an IA of safety and immunogenicity may be performed for Part 3 after all or a subset of participants have completed follow-up through 1 month post-Dose 1. This sBLA submission includes data from this IA with a data cutoff of June 5, 2023.

An additional IA may be performed for Part 3 after all or a subset of participants have completed follow-up through 1 month post-Dose 2. The final analysis will be performed when all participants have completed all planned study procedures.

*Safety A*nalyses
Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event. Only the maximum severity was reported.

6.1.10 Study Population and Disposition

This sBLA submission includes data from the start of enrollment for Part 3 on December 21, 2022, through the data cutoff of June 5, 2023. A total of 379 adolescent participants were enrolled in Study P203 Part 3 and received a single 50 µg dose of mRNA-1273.222.

6.1.10.1 Populations Enrolled/Analyzed

The analysis population used for study analyses are defined in Table 3. Immunogenicity analyses were conducted on the Per Protocol Immunogenicity Subset-Baseline SARS-CoV-2 Positive. Safety analyses were conducted on the Safety Set except for summaries of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 3. Analysis Populations, Study P203 Part 3

Population	Description
Safety Set	All participants who received a dose of mRNA-1273.222.
Solicited Safety Set	All participants who received a dose of mRNA-1273.222 and contributed any solicited AR data (i.e., had at least one post-dose solicited safety assessment).
Immunogenicity Subset	All participants who have baseline and at least one post-vaccination antibody assessment at 28 days post-vaccination
PP Immunogenicity Subset (PPIS)	All participants in the Immunogenicity Subset who met all the following criteria: • Received planned dose per schedule • Had antibody assessment for analysis endpoint at 28 days post-vaccination • Had no major protocol deviations that impacted key or critical data
PP Immunogenicity Subset – Baseline SARS-CoV-2 Positive (PPIS-Pos)	Participants who were in the PPIS and were baseline SARS-CoV-2 positive, defined as virologic and/or serologic evidence of SARS-CoV-2 infection at baseline, i.e., RT-PCR result was positive if available at Day 1 and/or an antibody specific to SARS-CoV-2 N-protein (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) was positive on or before Day 1.

Source: FDA-generated table
Abbreviations: RT-PCR=reverse transcription-polymerase chain reaction; PPIS=PP Immunogenicity Subset

6.1.10.1.1 Demographics

The PPIS-Pos analysis population, which contributed to the co-primary immunogenicity endpoints for the study, included 245 adolescent participants who received 50 µg mRNA-1273.222 in Study P203 Part 3. The comparator group included 296 young adult (18 through 25 years of age) participants who received the 2-dose primary series (100 µg each) of mRNA-1273 in Study P301. In the adolescent population, the median age was 14 years and there was a slightly higher proportion of male participants (53.5%) compared to female participants (46.5%). Among the adolescent PPIS-Pos population, 82.0% of participants were enrolled in Dominican Republic; 94.3% were Hispanic or Latino; 51.0% of participants identified as belonging to "Other" race (which included Mestizo and Caribbean), 33.9% were Black, and 14.3% were White. In contrast, the young adult population from P301 were all enrolled in the U.S.; the majority identified as White (69.9%) and non-Hispanic or Latino (73.0%).

Table 4. Demographics and Baseline Characteristics, Participants 12 Through 17 Years of Age, Study P203 Part 3 (PPIS-Pos) and 18 Through 25 Years of Age, Study P301 (PPIS)

Characteristics	P203 Part 3 12-17 Years mRNA-1273.222 50 µg Single Dose N=245	P301 18-25 Years mRNA-1273 100 µg Primary Series N=296
Sex, n (%)	--	--
Female	114 (46.5)	153 (51.7)
Male	131 (53.5)	143 (48.3)
Age	--	--
Median (Years)	14	23
12 to <16 years, n (%)	197 (80.4)	--
16 to <18 years, n (%)	48 (19.6)	--
Country		
U.S.	44 (18.0)	296 (100)
Dominican Republic	201 (82.0)	0
Race, n (%)	--	--
American Indian or Alaska Native	0	3 (1.0)
Asian	0	30 (10.2)
Black	83 (33.9)	29 (9.8)
White	35 (14.3)	207 (69.9)
Multiracial	2 (0.8)	14 (4.7)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
Not reported	0	3 (1.0)
Other[a]	125 (51.0)	8 (2.7)
Ethnicity, n (%)	--	--
Hispanic or Latino	231 (94.3)	78 (26.4)
Not Hispanic or Latino	14 (5.7)	216 (73.0)
Not reported	0	0
Unknown	0	2 (0.7)
Obesity[b], n (%)	--	--
Obese	48 (19.6)	68 (23.0)
Non-Obese	197 (80.4)	227 (76.7)
Missing	0	1 (0.3)

Source: sBLA 125752/68, Study P203 Part 3, Table 14.1.3.17.2.
N=total number of participants in the analysis set; n=number of participants fulfilling the item
a. Other category included Mestizo and Car bbean.
b. Obesity is defined as BMI ≥ 95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m^2 for P301.

The demographic and baseline characteristics of the Safety Set for Part 3 are shown below in Table 5, and were overall similar to those shown above for the PPIS-Pos population. In the Safety Set, 85.8% of participants were enrolled in the Dominican Republic; 94.5% were Hispanic or Latino; 56.7% of participants identified as belonging to “Other” race (which included Mestizo and Caribbean), 32.2% were Black and 10.3% were White. All but one of the participants in Part 3 (99.7%) had evidence of prior SARS-CoV-2 infection at baseline.

Table 5. Demographics and Baseline Characteristics, Participants 12 Through 17 Years of Age, Study P203 Part 3, Safety Set

Characteristic	P203 Part 3 12-17 Years mRNA-1273.222 50 µg Single Dose N=379
Sex, n (%)	--
Female	179 (47.2)
Male	200 (52.8)
Age[a]	--
Median (Years)	14
12 to <16 years, n (%)	306 (80.7)
16 to <18 years, n (%)	73 (19.3)
Country	--
U.S.	54 (14.2)
Dominican Republic	325 (85.8)
Race, n (%)	--
White	39 (10.3)
Black	122 (32.2)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Multiracial	3 (0.8)
Other[a]	215 (56.7)
Ethnicity, n(%)	--
Hispanic or Latino	358 (94.5)
Not Hispanic or Latino	21 (5.5)
Obesity[b], n (%)	--
Obese	68 (17.9)
Non-Obese	311 (82.1)
Baseline SARS-CoV-2 status[c], n (%)	--
Positive	378 (99.7)
Negative	1 (0.3)

Source: sBLA 125752/68, Study P203 Part 3, Table 14.1.3.17.1.
N=total number of participants in the analysis set; n=number of participants fulfilling the item
a. Other category included Mestizo and Car bbean.
b. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P203
c. 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 at Day 1. Negative was defined as negative RT-PCR test and negative Elecsys result at Day 1.

6.1.10.1.2 Participant Disposition

Participant disposition for Study P203 Part 3 is presented below in Table 6 by analysis population. Discontinuation occurred in 2.6% of participants in Part 3. The most

common reason for discontinuation was withdrawal of consent, reported in 1.6% of participants. No participant discontinued due to an AE. Among the 379 participants in the Safety Set, 378 participants (99.7%) were included in the Solicited Safety Set. As of the data cutoff of June 5, 2023, participants had been followed for a median of 35 days (range: 4 to 167 days).

The Immunogenicity Subset included 247 participants, of which 246 (99.6%) participants were included in the Per Protocol Immunogenicity Subset (PPIS), and 245 (99.2%) were included in the PPIS – Baseline SARS-CoV-2 Positive (PPIS-Pos).

Table 6. Disposition of Adolescent Participants 12-17 Years in Study P203 Part 3, All Enrolled

Disposition	P203 Part 3 12-17 Years mRNA-1273 50 µg Single Dose n (%)
Full Analysis Set	**N=379**
Discontinued from study[a]	10 (2.6)
Reason for discontinuation of study[a]	--
Lost to follow up	1 (0.3)
Withdrawal of consent by participant	6 (1.6)
Other[b]	3 (0.8)
Safety Set	**N=379**
Solicited Safety Set[c]	378 (99.7)
Immunogenicity Subset	**N=247**
PP Immunogenicity Subset[d]	246 (99.6)
Excluded from PP Immunogenicity Subset	1 (0.4)
Reason for exclusion from the PP Immunogenicity Subset	--
Major protocol deviation	1 (0.4)
PP Immunogenicity Subset-Baseline SARS-CoV-2 Positive (PPIS-Pos)[d]	245 (99.2)

Source: sBLA 125752/68, Study P203 Part 3, Tables 14.1.1.1.8, Table 14.1.2.1.8
Abbreviations: PP=per-protocol
a. Percentages are based on the number of subjects in the Full Analysis Set
b. "Other" reasons for discontinuation from study included inability to perform study visits within specified window
c. Percentages are based on the number of subjects in the Safety Set
d. Percentages are based on the number of subjects in the Immunogenicity Subset

6.1.11 Analyses of Vaccine Effectiveness

6.1.11.1 Analyses of Primary Endpoints

Vaccine effectiveness of a single dose (50 µg) of mRNA-1273.222 in the adolescent population was inferred based on the evaluation of the nAb GMC against Omicron BA.4/BA.5 and the D614G strain elicited at 28 days after a single dose of mRNA-1273.222 (50 µg) in adolescents in P203 Part 3 as compared to after Dose 2 of the 2-dose primary series of mRNA-1273 (100 µg each) in young adults 18-25 years of age from Study P301, in whom efficacy was demonstrated. The co-primary endpoints, described in Section 6.2.8, were assessed in participants with evidence of prior SARS-CoV-2 infection (PPIS-Pos) for the adolescent group and participants without evidence of prior SARS-CoV-2 infection pre-primary series (PPIS) for the young adult group.

Results for the co-primary endpoint of GMC ratio (adolescents/young adults) against Omicron BA.4/BA.5 and D614G are displayed in Table 7, below. The GMC ratio against

Omicron BA.4/BA.5 was 49.0 (95% CI: 44.2, 54.2), which met the pre-specified superiority success criteria. The GMC ratio against D614G was 4.3 (95% CI: 3.7, 4.9), which met the pre-specified noninferiority success criteria.

Table 7. Geometric Mean Antibody Concentration (GMC) as Measured by Pseudovirus nAb Assay Against Omicron BA.4/BA.5 and D614G at 28 Days Post-Single Dose of mRNA-1273.222, Adolescent Participants 12-17 Years, Study P203 Part 3, PPIS-Pos Compared to 28 Days Post-Dose 2 of mRNA-1273, Young Adult Participants 18-25 Years, Study P301, PPIS

Strain	P203 Part 3 Adolescents 12-17 Years Baseline SARS-CoV-2 Positive mRNA-1273.222 50 µg *Single Dose* GMC [95% CI][a] N=245	P301 Young Adults 18-25 Years Baseline SARS-CoV-2 Negative mRNA-1273 100 µg *Primary Series* GMC [95% CI][a] N=296	GMC Ratio (Adolescents / Young Adults) [95% CI][a]
Omicron BA.4/BA.5	2771.0 [2570.0, 2987.6]	56.6 [52.8, 60.6]	49.0 [44.2, 54.2]
D614G	7187.1 [6480.5, 7970.8]	1692.3 [1540.6, 1858.9]	4.3 [3.7, 4.9]

Source: sBLA 125752/68, Study P203 Part 3, Table 14.2.1.1.3.8.1.1.1, Table 14.2.1.1.3.8.1.2.1
Abbreviations: CI=confidence interval; GMC=Geometric mean concentration; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification; nAb=neutralizing ant body; PPIS=Per-Protocol Immunogenicity Subset; PPIS-Pos=Per-Protocol Immunogenicity Subset-Positive
Ant body values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.
(b) (4) Neutralizing Antibody against Omicron BA.4/BA.5 (LLOQ: 103, ULOQ: 110592)
VAC62 Neutralizing Antibody against D614G (LLOQ: 10, ULOQ: 111433)
a. The log-transformed ant body levels were analyzed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resulted least square (LS) means, difference of LS means, and 95% CI were back transformed to the original scale for presentation.

Clinical Reviewer Comment: The comparative immunogenicity results from Study P203 Part 3 relative to young adults from Study P301 support the effectiveness of a single dose (50 µg) of mRNA-1273.222 against SARS-CoV-2 Omicron BA.4/BA.5 and D614G in vaccine-naïve, baseline SARS-CoV-2 seropositive adolescents 12-17 years old. Although the protocol pre-specified a 'noninferiority' statistical success criteria for the GMC ratio against the Original (D614G) strain, the results would have also satisfied the superiority criteria prespecified for the GMC ratio against Omicron BA.4/BA.5. This suggests that a single dose (50 µg) of mRNA-1273.222 (bivalent), containing 25 µg of Original strain, demonstrates a superior response relative to two 100 µg doses of mRNA-1273 (monovalent) in individuals with history of prior infection. The robust immune response following a single dose of mRNA-1273.222 likely reflects the important benefits of hybrid immunity in individuals with evidence of prior SARS-CoV-2 infection.

6.1.11.2 Subpopulation Analyses

Although no formal subpopulation analyses were included in the clinical summary submitted to this sBLA for review, the immunogenicity results after a single 50 µg dose of mRNA-1273.222 against SARS-CoV-2 Omicron BA.4/BA.5 and D614G were comparable among subgroups, including race, sex, ethnicity, BMI, and country.

6.1.11.3 Secondary Endpoints

Secondary endpoints evaluated SRR against Omicron BA.4/BA.5 and D614G at 28 days after a single dose of mRNA-1273.222 in adolescents compared to those at 28 days post-primary series of mRNA-1273 in young adults in Study P301. These analyses (Table 8) were descriptive without pre-specified hypothesis testing. The SRR against Omicron BA.4/BA.5 was high (94.7%) among adolescent bivalent vaccine recipients, whereas no participant who received the original monovalent vaccine primary series in P301 met the seroresponse definition. SRRs against D614G were similarly high among both adolescent bivalent vaccine recipients and young adult original monovalent vaccine recipients (94.6% vs 99.3%, respectively).

Table 8. Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against Omicron BA.4/BA.5 and D614G at 28 Days Post-Single Dose of mRNA-1273.222, Adolescent Participants 12-17 Years, Study P203 Part 3, PPIS-Pos Compared to 28 Days Post-Dose 2 of mRNA-1273, Young Adult Participants 18-25 Years, Study P301, PPIS

Strain	P203 Part 3 Adolescents 12-17 Years Baseline SARS-CoV-2 Positive mRNA-1273.222 50 µg *Single Dose* SRR[a] % (n/N1) [95% CI][b]	P301 Young Adults 18-25 Years Baseline SARS-CoV-2 Negative mRNA-1273 100 µg *Primary Series* SRR[a] % (n/N1) [95% CI][b]	Difference in SRR% (Adolescents minus Young Adults) [95% CI][c]
Omicron BA.4/BA.5	94.7 (232/245) [91.1, 97.1)]	0 (0/294) [0.0, 1.2]	94.7% [91.1, 96.9]
D614G	94.6 (228/241) [91.0, 97.1]	99.3 (293/294) [97.6, 99.9]	-4.7% [-8.4, -2.1]

Source: sBLA 125752/68, Study P203 Part 3, Table 14.2.1.2.3.8.1.1.1, Tables 14.2.1.2.3.8.1.2.1,
Abbreviations: CI=confidence interval; N1=Number of subjects with non-missing data at baseline and the corresponding timepoint; n=Number of subjects with non-missing data the corresponding timepoint nAb=neutralizing antibody; SRR=seroresponse rate; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification; PPIS=Per-Protocol Immunogenicity Subset; PPIS-Pos=Per-Protocol Immunogenicity Subset-Positive
(b) (4) Neutralizing Antibody against Omicron BA.4/BA.5 (LLOQ: 103, ULOQ: 110592)
VAC62 Neutralizing Antibody against D614G (LLOQ: 10, ULOQ: 111433)
a. Seroresponse from pre-Dose 1 baseline at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on N1
b. 95% CI is calculated using the Clopper-Pearson method
c. 95% CI is calculated during the Miettinen-Nurminen (score) confidence limits

Clinical Reviewer Comment: Although the SRRs are descriptive, with no pre-specified hypothesis testing, the results suggest that non-inferiority criteria could have been met. There appears to be no seroresponse seen against Omicron BA.4/BA.5 in baseline SARS-CoV-2 negative young adults who were vaccinated with the 100 µg 2-dose series of mRNA-1273. The baseline nAb titers against Omicron BA.4/BA.5 for all P301 participants was below the lower limit of quantification (LLOQ) and was imputed a value of 51.5 (half of the LLOQ) as prespecified in the Statistical Analysis Plan. The change in nAb titers against Omicron BA.4/BA.5 at 28 days post-Dose 2 of the 2-dose series was only 5.1 (51.5 to 56.6), which is not a 4-fold rise in nAb titers. It is possible that this reflects a significant lack of cross-reactivity between the original mRNA-1273 vaccine and the Omicron BA.4/BA.5 variant.

6.1.12 Safety Analyses

P203 Part 3 was an open-label study and did not include a contemporaneous comparator group for safety. Safety analyses for Part 3 included data from 379 participants who received mRNA-1273.222. As of the data cutoff of June 5, 2023, the median duration of safety follow-up was 35 days (range: 4-167 days) and 261 (68.9%) of participants had at least 28 days of follow-up post-vaccination.

6.1.12.1 Methods

See Section 6.1.7 above.

6.1.12.2 Overview of Adverse Events

Table 9 below summarizes AEs among mRNA-1273.222 recipients in Part 3. The proportion of participants who reported at least one solicited local and systemic ARs within 7 days post-vaccination were 44.7% and 39.7%, respectively.

Among mRNA-1273.222 recipients, 12.9% (n=49) reported unsolicited AEs occurring within 28 days following vaccine administration. Through the data cutoff of June 5, 2023, MAAEs were reported in 12.4% (n=47) in vaccine recipients. There were no AESIs reported following vaccination and no AEs leading to study discontinuation. There were three SAEs reported, all of which were considered unrelated to the study vaccine by the investigator and are described in further detail in Section 6.1.12.8.

Table 9. Number and Percentage of Participants Reporting at Least One Safety Event, Participants 12-17 Years, Safety Set and Solicited Safety Set, Study P203 Part 3

Event Type	P203 Part 3 12-17 Years mRNA-1273.222 50 µg Single Dose n (%)
Solicited adverse reactions within 7 days[a]	N1=378
Solicited local adverse reaction	169 (44.7)
Grade 3 solicited local adverse reaction	10 (2.6)
Solicited systemic adverse reaction	150 (39.7)
Grade 3 or higher solicited systemic adverse reaction	17 (4.5)
Unsolicited adverse events[b]	N=379
Unsolicited adverse event up to 28 days after booster injection	49 (12.9)
Non-serious unsolicited adverse event	47 (12.4)
Related non-serious unsolicited AE	14 (3.7)
Severe non-serious unsolicited AE	1 (0.3)
Related severe non-serious unsolicited AE	1 (0.3)
Medically attended adverse events[c]	47 (12.4)
Related MAAE[c]	7 (1.8)
SAEs[c]	3 (0.8)
AESIs[c]	0
Deaths[c]	0
AEs leading to study discontinuation[c]	0

Source: sBLA 125752/68, Study P203 Part 3, Tables 14.3.1.1.1.8.2.1, 14.3.1.7.8.1.1.1, 14.3.1.7.8.3.2.1
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants who received mRNA-1273.222 in Part 3; N1 = Number of exposed participants who submitted any data for the event
a. Percentages are based on the number of participants in the Solicited Safety set
b. Percentages are based on the number of safety participants in Part 3.
c. All numbers reflect AEs reported through the data cut-off of June 5, 2023.

6.1.12.3 Solicited Adverse Reactions

The frequency and severity of solicited local and systemic adverse reactions within 7 days following vaccination with mRNA-1273.222 are shown below in Table 10 and Table 11. Assessment of mRNA-1273.222 reactogenicity is limited by the open-label study design for this part of P203. To provide a frame of reference to assess the rates of solicited adverse reactions following a single dose of mRNA-1273.222, the rates of solicited adverse reactions following Dose 1 and Dose 2 (1 month dosing interval) of the primary series (double-blinded Study P203 Part A, reviewed in Section 6.2) are included in these tables.

By order of frequency (>10% of participants), adverse reactions in participants 12 through 17 years of age within 7 days following administration of mRNA-1273.222 were pain at the injection site (42.6%), headache (27.6%), myalgia (15.6%), fatigue (12.2%), and axillary swelling or tenderness (11.4%).

Solicited Local Reactions

Table 10 below presents frequencies and severities of reported solicited local adverse reactions (ARs) within 7 days following mRNA-1273.222. Overall, the reported rates of solicited local ARs following mRNA-1273.222 appeared to be less than that reported following Dose 1 or Dose 2 of the primary series (44.7% vs. 94.2% and 93.4%, respectively). Injection site pain was the most frequently reported solicited local AR following mRNA-1273.222. Most of the solicited local ARs following booster dose were Grade 1 or Grade 2, with Grade 3 solicited local ARs reported by 2.6% of mRNA-1273.222 recipients, which was lower compared to that reported after Dose 1 or Dose 2 of the primary series (6.9% and 8.9%, respectively). No Grade 4 solicited local ARs were reported within 7 days following mRNA-1273.222.

Most (>95%) of solicited local ARs reported within 7 days following mRNA-1273.222 occurred within 1 to 2 days post-vaccination, with a median onset of 2-days post-vaccination and resolved after a median of 2 days (range 1 to 36 days). Solicited local ARs persisting beyond 7 days post-vaccination were reported by 1.6% of participants.

Table 10. Frequency of Solicited Local Adverse Reactions in Adolescent Participants 12-17 Years Within 7 Days of Primary Series Dose 1 & Dose 2 (Study P203, Part A) and 7 Days of Single Dose mRNA-1273.222 (Study P203 Part 3), Solicited Safety Set

Event	P203, Part A 12-17 Years Primary Series Dose 1 mRNA-1273 100 µg N=2482 n (%)	P203, Part A 12-17 Years Primary Series Dose 2a mRNA-1273 100 µg N=2478 n (%)	P203 Part 3 12-17 Years mRNA-1273.222 50 µg N=1351 n (%)
Local adverse reaction	N1=2482	N1= 2478	N1=378
Any	2339 (94.2)	2314 (93.4)	169 (44.7)
Grade 3	171 (6.9)	220 (8.9)	10 (2.6)
Pain	N1=2482	N1= 2478	N1=378
Any	2310 (93.1)	2290 (92.4)	161 (42.6)
Grade 3b	133 (5.4)	126 (5.1)	4 (1.1)
Erythema (redness)	N1=2482	N1= 2478	N1= 378
Any ≥25 mm	329 (13.3)	484 (19.5)	11 (2.9)
Grade 3c	22 (0.9)	72 (2.9)	6 (1.6)

Event	P203, Part A 12-17 Years Primary Series Dose 1 mRNA-1273 100 µg N=2482 n (%)	P203, Part A 12-17 Years Primary Series Dose 2a mRNA-1273 100 µg N=2478 n (%)	P203 Part 3 12-17 Years mRNA-1273.222 50 µg N=1351 n (%)
Swelling (hardness)	N1=2482	N1= 2478	N1=378
Any ≥25 mm	401 (16.2)	508 (20.5)	10 (2.6)
Grade 3c	27 (1.1)	56 (2.3)	3 (0.8)
Axillary swelling or tenderness	N1=2481	N1= 2477	N1=378
Any	576 (23.2)	519 (21.0)	43 (11.4)
Grade 3b	11 (0.4)	7 (0.3)	1 (0.3)

Source: sBLA 125752/68, Study P203 Part 3, Tables 14.3.1.1.1.8.2.1 for Part 3; Table 14.3.1.1.1.1 and Table 14.3.1.1.1.2 for Part A.
N=The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post dose-2, or 1 post-mRNA-1273.222 solicited safety assessment through 6 days post-vaccination).
N1 = Number of exposed participants who submitted any data for the event
No grade 4 solicited local adverse reactions were reported.
Any=Grade 1 or higher.
a. 28-day interval between primary series dose 1 and primary series dose 2
b. Pain and axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity
c. Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm

Solicited Systemic Reactions

Table 11 below presents frequencies and severities of reported solicited systemic reactions within 7 days following mRNA-1273.222. Overall, the percentage of participants reporting solicited systemic ARs within 7 days following mRNA-1273.222 was lower relative to those reported following Dose 1 or Dose 2 of the primary series (39.7% vs. 68.5% and 86.1%, respectively). Similarly, the percentage of participants reporting Grade 3 or higher solicited systemic ARs within 7 days following mRNA-1273.222 was lower when compared to that reported within 7 days following Dose 1 or Dose 2 of the primary series (4.2% vs. 4.4% and 13.8%, respectively). Headache, myalgia, and fatigue were the most frequently reported systemic ARs, reported in 27.6%, 15.6%, and 12.2% of mRNA-1273.222 recipients, respectively. Overall, fever was reported by 8.2% of mRNA-1273.222 recipients compared with 2.3% and 12.0% of mRNA-1273 recipients after Dose 1 and Dose 2 of the primary series, respectively. Fever ≥39°C post-vaccination was reported by 3.2% of mRNA-1273.222 recipients, including 1 participant with Grade 4 fever (fever of 40.5°C on Day 5; participant reported concurrent AE of lower respiratory tract infection).

Solicited systemic ARs had a median onset of 2 days after receipt of mRNA-1273.222 and resolved after a median of 2 days (range 1 to 38 days). Solicited systemic ARs persisting beyond 7 days post-vaccination were reported by 3.7% of participants.

Table 11. Frequency of Solicited Systemic Adverse Reactions in Adolescent Participants 12-17 Years Within 7 Days of Primary Series Dose 1 & Dose 2 (Study P203, Part A) and 7 Days of mRNA-1273.222 (Study P203 Part 3), Solicited Safety Set

Event	P203, Part A 12-17 Years Primary Series Dose 1 mRNA-1273 100 µg n (%) N=2482	P203, Part A 12-17 Years Primary Series Dose 2[a] mRNA-1273 100 µg n (%) N=2478	P203 Part 3 12-17 Years Single Dose mRNA-1273.222 50 µg n (%) N=378
Any systemic adverse reaction	N1=2482	N1= 2478	N1=378
Any	1701 (68.5)	2134 (86.1)	150 (39.7)
Grade 3	108 (4.4)	341 (13.8)	16 (4.2)
Grade 4	0	3 (0.1)	1 (0.3)
Fever	N1=2480	N1= 2477	N1=378
Any: ≥38.0°C	57 (2.3)	298 (12.0)	31 (8.2)
Grade 3: 39°C to 40.0°C	9 (0.4)	48 (1.9)	10 (2.6)
Grade 4: >40.0°C	0	1 (<0.1)	1 (0.3)[f]
Headache[b]	N1=2480	N1= 2478	N1=377
Any	1106 (44.6)	1739 (70.2)	104 (27.6)
Grade 3	56 (2.3)	112 (4.5)	5 (1.3)
Grade 4	0	1 (<0.1)	0
Fatigue[c]	N1=2481	N1= 2478	N1=377
Any	1188 (47.9)	1679 (67.8)	46 (12.2)
Grade 3	33 (1.3)	188 (7.6)	0
Grade 4	0	0	0
Myalgia[c]	N1=2480	N1= 2477	N1=377
Any	670 (27.0)	1155 (46.6)	59 (15.6)
Grade 3	24 (1.0)	129 (5.2)	1 (0.3)
Grade 4	0	0	0
Arthralgia[c]	N1=2480	N1= 2477	N1=377
Any	371 (15.0)	716 (28.9)	37 (9.8)
Grade 3	15 (0.6)	57 (2.3)	1 (0.3)
Grade 4	0	0	0
Nausea/vomiting[d]	N1=2480	N1= 2477	N1=377
Any	281 (11.3)	591 (23.9)	18 (4.8)
Grade 3	2 (<0.1)	2 (<0.1)	0
Grade 4	0	1 (<0.1)	0
Chills[e]	N1=2480	N1= 2477	N1=377
Any	456 (18.4)	1066 (43.0)	20 (5.3)
Grade 3	4 (0.2)	11 (0.4)	1 (0.3)
Grade 4	0	0	0
Use of antipyretic or pain medication	N1=2482	N1=2478	N1=378
Any	748 (30.1)	1242 (50.1)	76 (20.1)

Source: sBLA 125752/68, Study P203 Part 3, Table 14.3.1.1.1.8.2.1; Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.1.5.3.1, and Table 14.1.5.3.2 for Part A.
N=The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post dose-2, or 1 post-mRNA-1273.222 solicited safety assessment through 6 days post-vaccination).
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).
The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post dose-2, or 1 post-mRNA-1273.222 solicited safety assessment through 6 days post-vaccination).
Any=grade 1 or higher.
Medications were collected on the eDiary.
a. 28-day interval between primary series dose 1 and primary series dose 2
b. Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
c. Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
d. Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
e. Chills: Grade 3 prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.
f. Analyses of solicited safety submitted to the sBLA included 2 events of grade 4 fever. One participant reported a temperature of 40.5C on Day 6, which was later confirmed by the site to be recorded in error.

Reviewer Comment: The relatively small sample size and lack of control group limits the interpretability of the rates of solicited adverse reactions in Part 3 of Study P203. Generally, the rates of solicited adverse reactions after the single 50 µg dose, in a study population that was almost all baseline SARS-CoV-2 positive, were less than those observed after Dose 1 or Dose 2 of the 100 µg 2-dose series. Rates of any fever were 8.2% following the single 50 µg dose, which was higher than the 2.3% observed after Dose 1 of the primary series, but less than the 12.0% observed following Dose 2 of the 2-dose series.

6.1.12.4 Unsolicited Adverse Events Through 28 Days Post-Vaccination

Unsolicited AEs within 28 days of vaccination were reported by 12.9% of participants. The most frequently reported AEs were under the System Organ Class (SOC) *Infections and Infestations* (5.3% of participants), *General disorders and administration site conditions* (2.9%), and *Nervous system disorders* (2.9%). By Preferred Terms (PTs), the most frequently reported unsolicited AEs within 28 days post-vaccination were headache (2.1%), respiratory tract infection (1.8%), and pyrexia (1.1%).

Clinical Reviewer Comment: The open label nature of this study and lack of comparator group limits the interpretability of safety data presented. However, generally, the rates and types of unsolicited AEs were comparable to those seen after Dose 1 and/or Dose 2 of the 2-dose series. No new safety concerns were identified.

6.1.12.5 Medically Attended Adverse Events

Through the data cutoff of June 5, 2023, 12.4% (n=47) of participants reported medically attended adverse events (MAAEs). There were 7 events (1.8%) considered by the investigator to be related to study vaccine. These 7 events were all events consistent with vaccine reactogenicity.

6.1.12.6 Adverse Events Of Special Interest (AESIs)

Participants are 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). As of the data cutoff of June 5, 2023, no AESIs were reported.

6.1.12.7 FDA Standard MedDRA Queries

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.

SMQ Hypersensitivity

As of the data cutoff, two participants reported events under the *SMQ Hypersensitivity*: cases of allergic dermatitis and contact dermatitis, with onset 20 and 3 days post-vaccination, respectively. Both events were assessed by the investigator as not related to study vaccine.

Cardiac-related *SMQs*

To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (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 (Appendix B). As of the data cutoff, there were no events identified through this search clinically concerning for myocarditis or pericarditis.

6.1.12.8 Serious Adverse Events (SAEs)

As of the data cutoff, SAEs were reported in 3 mRNA-1273.222 recipients (0.8%), summarized below:

- A 14-year-old female with a history of depression and anxiety experienced worsening of depression 27 days following vaccination. The investigator considered the event not related to study vaccination.

- A 12-year-old male with no reported medical history developed hypertension the day of vaccination. The participant's pre-vaccination blood pressure was 106/58 mmHg and was found to have asymptomatic hypertension (161/101 mmHg) 30 minutes following vaccination. The participant was monitored at the site for 3 hours and blood pressure remained elevated with no other changes in vital signs and no evidence of hypersensitivity. He was subsequently transferred to a children's hospital, where cardiac and renal work-up revealed left ventricular hypertrophy, bilateral nephrolithiasis and renal sinus dilatation. He was diagnosed with arterial hypertension and suspected to have had longstanding disease given the findings of end-organ damage. The investigator considered the event not related to study vaccination.

- A 14-year-old female developed dengue fever 69 days post-vaccination. The investigator considered the event not related to study vaccination.

Clinical Reviewer Comment: The reviewer agrees with the investigator's assessments for the 3 SAEs described above that the events were not likely related to the study vaccine.

6.1.12.9 Deaths

There were no deaths among Study P203 Part 3 participants through the data cutoff.

6.1.12.10 Dropouts and/or Discontinuations

See Section 6.1.12.2. No participant discontinued the study due to an AE.

6.1.13 Study Conclusions

The primary evidence to support effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in vaccine-naïve, baseline SARS-CoV-2 positive adolescents 12-17 years of age was a comparison of the immune responses generated following the single dose of mRNA-1273.222 in adolescents to immune responses after a 2-dose series of mRNA-1273 in a clinically relevant young adult subgroup (18-25 years) from Study P301, for whom VE had been previously demonstrated. The study met the pre-specified success criteria for the two co-primary endpoints of superiority of the GMC ratio against Omicron BA.4/BA.5 and noninferiority of the GMC ratio against the Original Wuhan strain (D614G). An analysis of the safety data through the data cutoff of June 5, 2023, with a median duration of follow-up of 35 days post-vaccination, revealed no new safety concerns. As of the data cutoff, there were no cases of myocarditis or pericarditis and no vaccine-related SAEs reported. Data on effectiveness of a single dose (50 µg) in COVID-19 vaccine-naïve adolescents can be extrapolated to support the effectiveness of a single dose (50 µg) in COVID-19 vaccine-naïve adults due to the comparable efficacy and immunogenicity results observed after a 2-dose series of Spikevax (Original monovalent) between adolescent participants and adult participants (see Section 6.2 and original Spikevax BLA memo). The data generated from this study support the safety and effectiveness of a single 50 µg dose of SPIKEVAX including Spikevax (2023-2024 Formula) in vaccine-naïve, baseline SARS-CoV-2 positive individuals 12 years of age and older. The data to support the safety and effectiveness of a single 50 µg dose of SPIKEVAX including Spikevax (2023-2024 Formula) in previously COVID-19 vaccinated individuals 12 years of age and older are addressed in the following sections (Sections 6.2, 6.3, 6.4, 6.5, 6.6). Together these data provide evidence to support the use of SPIKEVAX, including Spikevax (2023-2024 Formula), as a single dose in individuals 12 years of age and older, irrespective of previous COVID-19 vaccination status.

6.2 Study P203 (Part A and B): Adolescent 2-dose Series

NCT04649151

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 years of age

Study Overview: Study P203 was designed to evaluate the safety and effectiveness of a 2-dose primary series of mRNA-1273 (100 µg each, 1 month apart) in an adolescent population 12 to <18 years of age in Part A of the study. After the EUA of a non-study COVID-19 vaccine for adolescents in the U.S., Study P203 was amended to include

open label Part B that allowed placebo recipients from Part A to be unblinded and offered a 2-dose primary series of mRNA-1273. Study P203 enrollment initiated on December 9, 2020, and data cut off for all participants was January 31, 2022, with a total of 3733 participants randomized. Data from both parts serve to support the safety and effectiveness of the 2-dose primary series (100 µg each) in adolescents.

6.2.1 Objectives and Endpoints

Primary Objectives/Endpoints:

1. To evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.

   Endpoints:
   - Solicited local and systemic ARs through 7 days after each injection
   - Unsolicited AEs through 28 days after each injection
   - MAAEs through the entire study period
   - SAEs through the entire study period
   - AESIs through the entire study period
   - Vital sign measurements
   - Physical exam findings

2. To infer effectiveness of mRNA-1273 (100 µg, 2 doses 28 days apart) by establishing noninferiority of antibody responses after Dose 2 in P203 vaccine recipients compared to those in young adult (18-25 years of age) mRNA-1273 recipients from the clinical endpoint efficacy study (P301).

   Endpoints:
   - Geometric mean (GM) value of Day 57 nAb levels against D614G in adolescents in Study P203 as compared to Day 57 response against D614G in young adults in P301.
     - Statistical Criterion for Success: the lower bound of the 95% CI of the GMT ratio >0.67, and the GMT ratio point estimate >0.8.
   - Seroresponse rate (SRR) from baseline at Day 57 against D614G in adolescents in Study P203 as compared to SRR from baseline at Day 57 against D614G in young adults in P301.
     - Statistical Criterion for Success: The lower bound of the 95% CI of the seroresponse rate difference > -10%, and the seroresponse rate difference point estimate > -5%.

Secondary Objectives/Endpoints:

1. To evaluate immune response persistence by the level of SARS-CoV-2 S2P-specific bAb through 1 year after Dose 2 of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.

   Endpoints:
   - The GM value of SARS-CoV-2-S-2P-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).

2. To evaluate immune response persistence by the level of nAb through 1 year after Dose 2 of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.

   Endpoints:
   - Solicited The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2).

3. To evaluate the incidence of symptomatic or asymptomatic SARS-CoV-2 infection in participants receiving 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart and placebo recipients.

   Endpoints:
   - The incidence of SARS-CoV-2 infection counted starting 14 days after the second dose mRNA1273. SARS-CoV-2 infection defined as participants with negative SARS-CoV-2 at baseline (bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive, as measured by Roche Elecsys at Day 57 or later), OR Positive reverse transcription-polymerase chain reaction (RT-PCR) counted starting 14 days after second dose of IP systemic ARs through 7 days after each injection.

4. To evaluate the incidence of COVID-19, defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2, after vaccination with 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart or placebo.

   Endpoints:
   - The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of mRNA1273 with COVID-19 is defined as symptomatic disease based on the following criteria:
     - Two of the following systemic symptoms:
       - fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); OR
       - The participant must have experienced at least 1 of the following respiratory signs/symptoms: cough, shortness of breath, or difficulty breathing, OR
       - clinical or radiographical evidence of pneumonia; AND
       - The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

<u>Exploratory Objectives:</u>

- Part A
  - To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
  - To describe the ratio of binding antibodies and neutralizing antibodies.
  - To characterize the clinical profile and immune response of participants with COVID-29 or SARS-CoV-2 infection.

    - To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline.
- Part B
    - To evaluate the safety of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.
    - To evaluate SARS-CoV-2 or COVID-19 incidence after 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.

6.2.2 Design Overview

Study P203 is a randomized, observer-blind, placebo-controlled study conducted in the U.S. to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 administered as 2-dose primary series 28 days apart in healthy adolescents 12 through 17 years of age. Study P203 Part A started on December 9, 2020. Participants (n=3,733) were randomized 2:1 to receive intramuscular injections of either 100 µg of mRNA-1273 (n=2,490) or placebo (n=1,243) on Day 1 and Day 29. Vaccine effectiveness was inferred from the comparison of immune responses of adolescents in Study P203 to those of young adults 18 to 25 years of age from Study P301, which are the most clinically relevant study population subgroup where clinical efficacy has been demonstrated.

The study protocol was amended on March 23, 2021 to include an open-label phase (Part B), prompted by authorization of a non-study COVID-19 vaccine in the U.S. and participant requests for individual unblinding. Eligible study participants were informed of the authorized and available COVID-19 vaccine and could request a Participant Decision Visit and unblinding to learn their treatment assignment. Participants transitioned to Part B of the study at the time of unblinding. Participants who received placebo in Part A and desired to remain in the study were offered vaccination with mRNA-1273 (2 doses 28 days apart, 100 µg) in Part B, starting October 6, 2021.

> *Reviewer Comment: The P203 protocol was amended over time to add study populations, interventions, and analyses. These modifications were appropriate changes to reflect the evolution of the COVID-19 pandemic and to provide available effective vaccines to all eligible participants.*

6.2.3 Population

The study enrolled adolescents 12 to <18 years of age who had no known history of SARS-CoV-2 infection. Pertinent exclusion criteria included:

- Travel outside the U.S. within 28 days of screening Visit Day 0
- Prior administration of an investigational CoV vaccine
- Current treatment with an investigational agent for prophylaxis against COVID- 19
- Current use of any inhaled substances to include tobacco, cannabis, or vaping

6.2.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273 is a nucleoside modified mRNA that encodes for the full-length spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-2P spike protein into a prefusion conformation, and encapsulated in lipid particles.

Each 0.5mL injection contained 100 µg of mRNA-1273

Lots: 7006320005 and 7006320007

The placebo was a 0.9% sodium chloride solution for injection (0.5 mL).

Lots: DK0883 and 10097DK

6.2.5 Directions for Use

The investigational product (mRNA-1273 or placebo) was administered as an intramuscular injection into the deltoid muscle, preferentially to the nondominant arm. The second dose was to be administered in the same arm as the first dose.

6.2.6 Sites and Centers

Study P203 was conducted at 25 clinical sites, all within the U.S.

6.2.7 Surveillance/Monitoring

Immunogenicity

Blood samples were collected from all participants pre-vaccination on Day 1 (baseline), on Day 57 (28 days after Dose 2), and on Days 209 and 394 (6 and 12 months after Dose 2). Serum from a subset of participants (Immunogenicity Subset) was evaluated for the study's immunogenicity endpoints. Immunogenicity assessments included the following:

- For the analyses of the primary immunogenicity endpoints, serum nAb levels against SARS-CoV-2 were measured by PsVNA validated at Duke University. The assay measured neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein (D614G form of the U.S.A.-WA1/2020 Wuhan strain). Neutralization was measured as the serum dilution at which the relative luminescence unit (RLU) value is reduced by 50% (ID50) relative to mean RLU value in virus-control wells.
- For the analyses of long-term immunogenicity, serum nAb concentrations against SARS-CoV-2 was measured using a validated pseudovirus neutralization assay against the D614G strain conducted at PPD Vaccine Laboratories. nAb levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses.
- SARS-CoV-2 binding antibodies (bAb) were measured using MesoScale Discovery (MSD) electrochemiluminescence assays against the D614G strain as well as against Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1], and Delta [B.1.617.2] variants.
- Serum Ab directed against the nucleocapsid protein were measured using Roche Elecsys immunoassay.

Efficacy

Participants were followed for potential cases of COVID-19 to assess for vaccine efficacy (VE) against laboratory-confirmed COVID-19. Definitions of COVID-19 cases and SARS-CoV-2 infection used in Study P203 are presented in Appendix C. Surveillance for COVID-19 symptoms was conducted via a combination of telephone calls and electronic diary (e-diary) prompts from enrollment through the end of the

study. Participants with symptoms of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms, which could be of any duration) returned to the study site or were visited at home for collection of a nasopharyngeal (NP) swab sample for RT-PCR testing, to be collected within 72 hours of symptom onset. A blood sample for immunologic analysis of SARS-CoV-2 infection was also collected. NP samples were tested for SARS-CoV-2 at a central laboratory using an authorized RT-PCR test whenever possible, or other sufficiently validated nucleic acid amplification-based test (NAAT) conducted in a clinical laboratory improvement amendments (CLIA)-certified laboratory. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory. Any confirmed symptomatic SARS-CoV-2 infection occurring in participants was captured as a MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome and a convalescent visit was scheduled approximately 28 days (+7 days) after diagnosis.

To assess VE to prevent asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection regardless of symptoms, NP or nasal swab samples were collected and tested for the presence of SARS-CoV-2 by RT-PCR prior to dosing on Day 1 and Day 57. An additional NP or nasal swab was collected 6 months after Dose 2. Additionally, blood was collected for evaluation of bAb to the SARS-CoV-2 nucleocapsid protein at the immunogenicity assessment timepoints.

Safety

Safety assessments included the following:

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using an e-diary along with daily temperature and a medication log.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through the end of the study period or withdrawal from the study.
- MAAEs from Day 1 through the end of the study period or withdrawal from the study.
- SAEs from Day 1 through the end of the study period or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through the entire study period.
- Pregnancy and accompanying outcomes.

Safety follow-up calls occurred every four weeks between Day 85 to 197 and Day 223 to 363. 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.

Reviewer Comment: The study initially specified for participants to be followed for a longer duration (12 months). However, Study P203 protocol was modified after the

authorization of a non-study COVID-19 vaccine for this adolescent age group, to allow for treatment unblinding and to transition to the open-label Part B phase of the study. As a result, the median duration from second dose of blinded follow-up for all study participants was 112 days and the median duration of total safety follow-up for mRNA-1273 recipients, including both blinded and open-label follow-up after the second dose was 312 days.

6.2.8 Endpoints and Criteria for Study Success

See Sections 6.1.1 and 6.1.9.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity Analyses

The primary objective of the study was to infer effectiveness of mRNA-1273 (100 µg, 2 doses 28 days apart) based on non-inferiority (NI) of the nAb geometric mean titer (GMT) levels and SRRs obtained 28 days after Dose 2 of mRNA-1273 in adolescents in P203 as compared to young adults (18-25 years) in P301.

The protocol specified success criteria for the co-primary endpoints were:

- Co-primary endpoint 1: GMT
  The GMT ratio (adolescents to young adults) is non-inferior if the lower bound (LB) of the 95% CI >0.67 (based on NI margin of 1.5) AND a point estimate of GMT >0.8.

- Co-primary endpoint 2: SRR
  The difference in the percentages of SRRs (adolescents minus young adults) is non-inferior if the LB of the 95% CI >-10% AND a point estimate of difference in percentages of SRRs >-5%.

  Seroresponse was defined as a change from below LLOQ to greater than or equal to the LLOQ, or at least a 4-fold rise in participants ≥LLOQ at baseline.

Reviewer Comment: *During the original analysis for the EUA of a primary vaccine series in adolescents, CBER raised concerns that the Applicant's seroresponse definition may not be sufficient to demonstrate vaccine effect. At that time, the seroresponse was set as a ≥3.3-fold rise in titer from baseline. CBER commented to the Applicant that a change to ≥LLOQ from <LLOQ may simply result from assay variability, while a ≥3.3-fold rise in titer from baseline may only rule out differences due to assay variability and not necessarily indicate a meaningful immunologic response to vaccination. The Applicant made a protocol amendment that applied a conventional seroresponse definition that included a ≥4-fold rise, which did not change the number of responders in each group, the overall results, nor the corresponding 95% CI.*

Efficacy Analyses

VE is defined as 1 – ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio will be calculated using the exact method conditional upon the total number of cases adjusted by the total person-time.

The incidence rate will be calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

Person-time is defined as the total time from randomization date to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earlier.

Safety Analyses

Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event. Only the maximum severity was reported. Subgroup analyses were provided based on age group (12-15 years, 16-17 years), sex (male, female), pre-booster SARS-Cov-2 status, race, and ethnicity.

6.2.10 Study Population and Disposition

A total of 3,733 participants were randomized to receive either mRNA 1273 or placebo in Part A of the study. The study data submitted to support the use of a 2-dose primary series of mRNA-1273 in adolescent populations include data from participants who remained in blinded Part A, but also data from participants who elected to be unblinded at the Participant Decision Visit (Day 209) and receive mRNA-1273 vaccination in open-label period of the study, Part B. P203 study enrollment began on December 9, 2020, and the data cutoff date was January 31,2022.

6.2.10.1 Populations Enrolled/Analyzed

For each trial participant, there are 2 periods in the study:

- Part A: enrollment into the blinded phase until the date of study group unblinding
- Part B: the time in the study after unblinding

The primary immunogenicity, efficacy, and safety analyses presented are based on data from the blinded Part A portion of the study. Part B contributed to the long-term safety and long-term immunogenicity data.

Populations used for the study analyses are defined in Table 12. Immunogenicity analyses were primarily based on the Per Protocol (PP) Immunogenicity Subset. Efficacy analyses were based on the PP set for Efficacy. Safety analyses were based on the Safety Set, except for analyses of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 12. Analysis Populations

Population	Description
Full Analysis Set (FAS)	All randomized participants who received at least one dose of Investigational Product (IP).
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing who have baseline (Day 1) SARS-CoV-2 status available and have baseline and at least one post-dose antibody assessment for the analysis endpoint.

Population	Description
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing who received planned doses of study vaccination per schedule, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, complied with immunogenicity testing schedule, and had no major protocol deviations that impact key or critical data. Participants seropositive at baseline were excluded. The PP Immunogenicity Subset was used for analyses of immunogenicity unless otherwise specified.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, and had no major protocol deviations that impact key or critical efficacy data.
Modified Intent-to-treat Set (mITT)	All participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on binding antibodies (bAb) specific to SARS-CoV-2 nucleocapsid) at baseline.
mITT1 Set	All participants in the mITT Set excluding those who received the wrong treatment.

Source: FDA-generated table

6.2.10.1.1 Demographics

The Per Protocol Immunogenicity Set (PPIS) (Table 13), which contributed to the co-primary immunogenicity endpoints for the study, included 340 adolescent (12-17 years) participants from Study P203 and 295 adults (18-25 years) participants from Study P301 (18-25 years). In the adolescent population, 29.7% were 16-17 years of age and 70.3% were 12-15 years of age and equal distribution of males and females. Most adolescent participants were White (83.5%) and non-Hispanic or Latino (89.4%) and were less racially and ethnically diverse compared to young adult comparator participants. In addition, a lower proportion of adolescent participants were considered obese, defined as BMI ≥95th percentile of the World Health Organization (WHO) growth reference data in Study P203, compared to adult comparator participants, defined as BMI ≥30 kg/m^2 in Study P301.

Table 13. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age (Study P203 Part A; PPIS) and 18 Through 25 Years of Age (Study P301; PPIS)

Characteristic	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%) N=340	P301 18-25 Years mRNA-1273 100 µg Primary Series n (%) N=295
Sex, n (%)	--	--
Female	162 (47.6)	153 (51.9)
Male	178 (52.4)	142 (48.1)
Age	--	--
Median (years)	14.0	23.0
12 to <16 years, n (%)	239 (70.3)	-
16 to <18 years, n (%)	101 (29.7)	-
Race, n (%)	--	--
American Indian or Alaska Native	0	3 (1.0)

Characteristic	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%) N=340	P301 18-25 Years mRNA-1273 100 µg Primary Series n (%) N=295
Asian	15 (4.4)	30 (10.2)
Black or African American	4 (1.2)	29 (9.8)
Multiracial	19 (5.6)	14 (4.7)
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.7)
Not reported	6 (1.8)	3 (1.0)
Other	7 (2.1)	8 (2.7)
Unknown	4 (1.2)	0
White	284 (83.5)	206 (69.8)
Ethnicity, n (%)	--	--
Hispanic or Latino	26 (7.6)	78 (26.4)
Not Hispanic or Latino	304 (89.4)	215 (72.9)
Not reported	9 (2.6)	0
Unknown	1 (0.3)	2 (0.7)
Obesity[a], n (%)	--	--
Non-obese	281 (82.6)	226 (76.6)
Obese	59 (17.4)	68 (23.1)
Missing	0	1 (0.3)

Source: sBLA 125752/68, Study P203 Part A, Table 14.1.3.5.
Notes: N=number of participants in the per-protocol immunogenicity set; n=number of participants in the category; PPIS=Per-Protocol Immunogenicity Subset
a. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m^2 for P301.

The Safety Set (Table 14) for Study P203 Part A consisted of a total of 3,726 participants, with 2,486 in the mRNA-1273 vaccine group and 1,240 in the placebo group. Across the two groups, 48.6% of participants were female and the median age was 14 years. The majority were White (83.8%), non-Hispanic or Latino (87.5%), and non-obese (85.7%). Among participants in the Safety Set, 5.8% had evidence of prior SARS-CoV-2 infection at baseline. The demographics and baseline characteristics were balanced between the treatment groups. The demographic characteristics of the PP Set for Efficacy (not shown) were comparable to those reported in the Safety Set.

Table 14. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age, P203 Part A, Safety Set

Characteristic	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%) N=2486	P203 Part A 12-17 Years Placebo n (%) N=1240
Sex, n (%)	--	--
Female	1203 (48.4)	608 (49.0)
Male	1283 (51.6)	632 (51.0)
Age	--	--
Median (years)	14.0	14.0
12 to <16 years, n (%)	1839 (74.0)	929 (74.9)
16 to <18 years, n (%)	647 (26.0)	311 (25.1)
Race, n (%)	--	--
American Indian or Alaska Native	12 (0.5)	7 (0.6)

Characteristic	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%) N=2486	P203 Part A 12-17 Years Placebo n (%) N=1240
Asian	142 (5.7)	80 (6.5)
Black or African American	83 (3.3)	42 (3.4)
Native Hawaiian or other Pacific Islander	3 (0.1)	0
White	2084 (83.8)	1040 (83.9)
Multiracial	118 (4.7)	50 (4.0)
Other	27 (1.1)	9 (0.7)
Not reported	11 (0.4)	11 (0.9)
Unknown	6 (0.2)	1 (<0.1)
Ethnicity, n (%)	--	--
Hispanic or Latino	280 (11.3)	152 (12.3)
Not Hispanic or Latino	2186 (87.9)	1076 (86.8)
Not reported	19 (0.8)	10 (0.8)
Unknown	1 (<0.1)	2 (0.2)
Obesity[a], n (%)	--	--
Non-obese	2035 (81.9)	1015 (81.9)
Obese	451 (18.1)	225 (18.1)
Baseline SARS-CoV-2 Status[b], n (%)	--	--
Negative	2171 (87.3)	1078 (86.9)
Positive	147 (5.9)	70 (5.6)
Missing	168 (6.8)	92 (7.4)

Source: sBLA 125752/68, Study P203 Part A, Table 14.1.3.2.
Notes: N=number of participants in the safety set; n=number of participants in the category
a. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m^2 for P301.
b. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

6.2.10.1.2 Subject Disposition

Disposition tables are presented below in Table 15 (immunogenicity populations), Table 16 (efficacy populations) and Table 17 (safety population) for Study P203, Part A (blinded phase).

A random sample of 374 adolescent mRNA-1273 recipients from P203 (Part A) and 340 young adult mRNA-1273 recipients from P301 were selected for inclusion in the Immunogenicity Subset. Placebo recipients were not included in the Immunogenicity Subset. The Per Protocol (PP) Immunogenicity Subset, used for the primary immunogenicity analyses, consisted of 340 adolescent participants and 295 young adult participants. Most exclusions from the PP Immunogenicity Subset were due to positive baseline SARS-CoV-2 status, reported at similar rates in adolescent and young adult groups (7.2% and 5.0%, respectively).

Table 15. Disposition of Participants 12 Through 17 Years of Age (Study P203 Part A) and 18 Through 25 Years of Age (Study P301), Immunogenicity Populations

Disposition	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%)	P301 18-25 Years mRNA-1273 100 µg Primary Series n (%)
Immunogenicity Subset	**N=374**	**N=340**
Per Protocol Immunogenicity Subset, n (%)	340 (90.9)	295 (86.8)
Excluded from PP Immunogenicity Subset, n (%)	34 (9.1)	45 (13.2)
Reason for exclusion[a], n (%)	--	--
Positive baseline SARS-CoV-2 status	27 (7.2)	17 (5.0)
Did not receive Dose 2 per schedule	0	16 (4.7)
Received Dose 2 out of window	7 (1.9)	2 (0.6)
Had no Immunogenicity Data at Day 57	0	9 (2.6)
Participants with HIV infection	0	1 (0.3)

Source: sBLA 125752/68, Study P203 Part A, Table 14.1.2.3
Notes: Percentages are based on the number of participants in the Immunogenicity Subset
A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.

As shown in the table below, the proportion of participants in each of the study populations used to assess the efficacy endpoints in P203 Part A were similar across study groups. There were a higher proportion of participants in the placebo group compared to the mRNA-1273 group who were excluded from the PP Set for Efficacy due to discontinuation of study treatment prior to Dose 2 (1.0% vs 0.1%, respectively), likely due to eligibility to receive alternate COVID-19 vaccine under EUA.

Table 16. Disposition of Participants 12 Through 17 Years of Age, Study P203 Part A, Efficacy Populations

Disposition	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%)	P203 Part A 12-17 Years Placebo n (%)
Randomized	**N=2490**	**N=1243**
Full Analysis Set, n (%)	2486 (99.8)	1240 (99.8)
mITT1 Set, n (%)	2167 (87.0)	1076 (86.6)
Excluded from mITT1 Set, n (%)	323 (13.0)	167 (13.4)
Reason for exclusion[a]	--	--
Randomized but not dosed	4 (0.2)	3 (0.2)
Positive or missing baseline SARS-CoV-2 status	315 (12.7)	162 (13.0)
Received incorrect vaccination	4 (0.2)	2 (0.2)
Per-Protocol Set for Efficacy, n (%)	2142 (86.0)	1044 (84.0)
Excluded from PP Set for Efficacy	348 (14.0)	199 (16.0)
Reason for exclusion[a]	--	--
Randomized but not dosed	4 (0.2)	3 (0.2)
Positive or missing baseline SARS-CoV-2 status	315 (12.7)	162 (13.0)
Discontinued study treatment or participation without receiving Dose 2	3 (0.1)	13 (1.0)
Received incorrect vaccination	5 (0.2)	2 (0.2)
Received Dose 2 out of window	21 (0.8)	18 (1.4)

Disposition	P203 Part A 12-17 Years mRNA-1273 100 µg Primary Series n (%)	P203 Part A 12-17 Years Placebo n (%)
Randomized	**N=2490**	**N=1243**
Off-study COVID-19 vaccination received before Dose 2	0	1 (<0.1)

Source: sBLA 125752/68, Study P203 Part A, Table 14.1.2.4, 14.1.2.5
Abbreviations: mITT1=modified intent-to- treat-1; PP=Per-protocol.
a. A participant who has multiple reasons for exclusion is listed under the reason appears earliest.

Study P203 (Part A) participant disposition data for the Safety Set are presented in the table below. There were a higher proportion of participants who discontinued from the placebo group (78.6%) than the mRNA-1273 group (8.7), the majority of which were due to study withdrawal to obtain an alternative COVID-19 vaccine.

Three participants (0.1%) in the mRNA-1273 group discontinued study vaccination due to an AE (discussed in Section 6.2.12.9), one of whom also withdrew from the study due to the AE.

Table 17. Disposition of Participants 12 Through 17 Years of Age, Study P203 Part A, Safety Set

Disposition	P203 Part A 12-17 Years mRNA-1273 n (%)	P203 Part A 12-17 Years Placebo n (%)
Safety Set	**N=2486**	**N=1240**
Received Dose 1 in Part A	2486 (100)	1240 (100)
Received Dose 2 in Part A	2480 (99.8)	1222 (98.5)
Solicited Safety Set	--	--
First dose	2482 (99.8)	1238 (99.8)
Second dose	2478 (99.7)	1220 (98.4)
Discontinued Study Vaccine in Part A (after Dose 1 and before Dose 2)	6 (0.2)	18 (1.5)
Reason for Discontinuation of Study Vaccine in Part A	--	--
Adverse Event	3(0.1)	0 (0)
Lost to Follow-up	2 (<0.1)	6 (0.5)
Withdrawal of Consent by Participant	1 (<0.1)	9 (0.7)
Other	0 (0)	2 (0.2)
Missing	0 (0)	1 (<0.1)
Discontinued from Study Prior to Unblinding	216 (8.7)	975 (78.6)
Reason for Discontinuation of Study	--	--
Adverse Event	1 (<0.1)	0 (0)
Lost to Follow-Up	55 (2.2)	13 (1.0)
Physician Decision	2 (<0.1)	0 (0)
Protocol Deviation	1 (<0.1)	2 (0.2)
Participant Received Another COVID-19 Vaccine Under EUA	37 (1.5)	646 (52.1)
Withdrawal of Consent by Participant	102 (4.1)	86 (6.9)
Other	18 (0.7)	228 (18.4)

Source: sBLA 125752/68, Study P203 Part A, Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.1.1.1.3
Abbreviations: EUA=Emergency Use Authoization

The following study disposition table is for the open-label phase of P203 (Part B). This group includes the participants randomized to the mRNA-1273 group in Part A, the crossover placebo-mRNA-1273 group who were participants who received placebo in Part A and received mRNA-1273 in Part B, and the placebo group who were participants who received placebo in Part A and continued in open-label follow-up but did not receive mRNA-1273 in Part B. There was a higher rate of study discontinuation in the placebo group (96.2%) than the mRNA-1273 group (17.5%); the majority discontinuations were withdrawals by the participant due to eligibility for an alternative COVID-19 vaccine

Table 18. Disposition of Participants 12 Through 17 Years of Age, Open-Label Phase, P203 Part B, Safety Set

Disposition	P203 Part B 12-17 Years mRNA-1273 n (%) N=2486	P203 Part B 12-17 Years Crossover mRNA-1273 n (%) N=91	P203 Part B 12-17 Years Placebo n (%) N=131
Continued in open-label phase	2177 (87.6)	91 (100)	131 (100)
Received first injection in Part B	NA	91 (100)	NA
Received second injection in Part B	NA	79 (86.8)	NA
Discontinued Study Vaccine in Part B (after receipt of crossover Dose 1 of mRNA-1273)	NA	1 (1.1)	NA
Discontinued Study during Part B open-label phase	436 (17.5)	1 (1.1)	126 (96.2)
Reason for Discontinuation of Study	--	--	--
Adverse Event	0	0	0
Lost to Follow-Up	7(0.3)	0	0
Physician Decision	1 (<0.1)	0	0
Protocol Deviation	19 (0.8)	0	0
Participant Received Another COVID-19 Vaccine Under EUA	316 (12.7)	0	49 (37.4)
Withdrawal of Consent by Participant	68 (2.7)	1 (1.1)	12 (9.2)
Other	25 (1.0)	0	65 (49.6)

Source: sBLA 125752/68, Study P203 Part A and B,Table 14.1.1.1.3
Note that crossover placebo-mRNA-1273 participants in Part B may have received Dose 2 or discontinued from the study after the data cutoff date of 31 Jan 2022, and therefore, not all participants who received Dose 2 or discontinued study vaccine are summarized in the source table.
mRNA-1273: participants who received mRNA-1273 in Part A
Crossover Placebo-mRNA-1273: participants who received placebo in Part A and received mRNA-1273 in Part B
Placebo: participants who received placebo in Part A and continued in open-label follow-up but did not receive mRNA-1273 in Part B
Note: Numbers of Discontinued Study during Part B open-label phase for mRNA-1273 group are calculated by subtracting numbers of Discontinued from Study Prior to Unblinding from numbers of Discontinued from Study booster Dose

Follow-up Duration for Participants 12 Through 17 Years of Age

Participants 12-17 years of age began enrollment into Study P203 on December 9, 2020. As of the May 31, 2021, data cutoff for the blinded phase, the median follow-up time after Dose 2 was 135 days for the mRNA-1273 group and 78 days for the placebo group. A total of 918 mRNA-1273 recipients had ≥6 months of blinded follow-up after Dose 2.

A later data cutoff, of January 31, 2022, was used to provide longer-term safety follow-up from the ongoing trial. Therefore, follow-up included blinded data collection through May 31, 2021, and unblinded (open-label) data collection through January 31 2022, of participants originally were randomized to placebo group, and then unblinded at the Participant Decision Visit and receive mRNA-1273 (crossover mRNA-1273 group). For participants in the original mRNA-1273 group, the median total duration of follow-up including both blinded and open-label phases was 312 days post Dose 2, and 2,378 participants (95.7%) were followed for at least 6 months since Dose 2.

6.2.11 Analysis of Vaccine Effectiveness

6.2.11.1 Analyses of Primary Endpoint

Vaccine effectiveness in the adolescents was inferred through immunobridging to the young adult data in Study P301 using the co-primary endpoints of GMT ratio and difference in percentages of SRRs at 28 days post-dose 2 (Table 19). The GMT ratio of adolescents in P203 to young adults in P301 was 1.1 (95% CI: 1.0, 1.3) which met the protocol-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >0.8. The difference in percentages of SRRs between adolescents and young adults was -0.2% (95% CI -2.1, 1.9) which met the pre-specified success criterion of a LL of the 95% CI>-10% and an SRR difference point estimate of >-5%.

Table 19. Geometric Mean SARS-CoV-2 Neutralizing Titers and Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID50) Against D614G at Day 57, Participants 12 Through 17 Years of Age (Study P203 Part A; PPIS) and 18 Through 25 Years of Age (Study P301; PPIS)

P203 Part A 12-17 Years 100 µg mRNA-1273 Primary Series	P301 18-25 Years 100 µg mRNA-1273 Primary Series	Endpoint	Met Success Criterion?
GMT (95% CI)[a] N1=340	**GMT (95% CI) [a] N1=295**	**Geometric Mean Ratio (12-17 Years/18-25 Years) (95% CI) [a]**	**--**
1401.7 (1276.2, 1539.5)	1299.9 (1175.4, 1437.5)	1.1 (0.9, 1.2)	Yes [e]
Seroresponse % (95% CI)[b,c] N1=340	**Seroresponse % (95% CI) [b,c] N1=295**	**Difference in Seroresponse Rate (12-17 Years/18-25 Years) % (95% CI)[d]**	**--**
98.8% (97.0, 99.7)	99.0% (97.1, 99.8)	-0.2% (-2.1, 1.9)	Yes[f]

Source: sBLA 125752/68, Study P203 Part A,Table 14.2.1.1.3.1 and Table 14.2.1.2.3.1
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean ratio; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification. N1= Number of subjects with non-missing data at the corresponding timepoint.
Notes: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)
Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available. The ULOQ for selected P301 participants tested previously was different.
a. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resulted least square (LS) means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b. Seroresponse at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on N1.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
e. Co-primary endpoint 1: Success criteria for GMT ratio: the lower bound of the 95% CI of the GMT ratio > 0.67, and the GMT ratio point estimate >0.8
f. Co-primary endpoint 2: Success criteria for difference in seroresponse rate: The lower bound of the 95% CI of the seroresponse rate difference > -10%, and the seroresponse rate difference point estimate > -5%

6.2.11.2 Subpopulation Analyses

The GMTs and SRRs for SARS CoV-2 neutralizing titers at Day 57 were similar between adolescents and young adults, and did not vary by demographic subgroup, though the small number of participants in some subgroups resulted in wide CIs and limit the interpretation of the results. In the small number of participants (n=27) who had positive SARS-CoV-2 status at baseline, there was a more robust immune response observed Day 57 (GMT 2982.6, 95% CI 2116.9, 4202.5) compared to participants (n=347) who were baseline SARS-CoV-2 negative (GMT 1412.2, 95% CI 1290.4, 1545.5).

6.2.11.3 Analyses of Secondary Endpoints

Vaccine Efficacy Against COVID-19

VE was descriptively analyzed as a secondary endpoint with the data cutoff date of May 31, 2021. The study evaluated the first occurrence of symptomatic COVID-19 in participants without evidence of previous SARS-CoV-2 at baseline, using two different case definitions: the P301 definition and the broader CDC case definition (see Appendix C). Using the P301 definition for participants 12-17 years, the observed VE against starting 14 days after Dose 2 was 100% (95% CI 61.2%, non-evaluable), with no cases in the mRNA-1273 group and 6 cases in the placebo group. Using the CDC case definition, the observed VE was 89.9% (95% CI: 51.0%, 98.9%), with 2 cases in the mRNA-1273 group and 9 in the placebo group. These results appear to be consistent with the VE observed from the adult efficacy study (P301); however, the small number of COVID-19 cases, especially using the P301 definition, resulted in large CIs.

During the study period in which COVID-19 cases were accrued, the Original Wuhan strain (with D614G mutation) and then the Alpha variant were the predominant circulating SARS-CoV-2 strains in the U.S. There were no cases of severe COVID-19 reported in the study.

VE by subgroup was not evaluated given the small number of cases in both groups. Among the approximately 6% of total study participants with evidence of prior SARS-CoV-2 infection at baseline, no participants developed COVID-19 starting 14 days after Dose 2.

Table 20. Vaccine Efficacy Against First Occurrence COVID-19 Starting 14 Days After Dose 2, Participants 12 Through 17 Years of Age, Study P203 Part A, Per-Protocol Set for Efficacy

Endpoint	P203 Part A 12-17 Years mRNA-1273 100 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI)[a,b] N=2,142	P203 Part A 12-17 Years Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI)[a,b] N=1,044	Vaccine Efficacy (95% CI)[c]
P301 definition	0 (0) 0 (NE, 6.1)	6 (0.6) 21.5 (7.9, 46.9)	100.0% (61.2, NE)
CDC definition	2 (<0.1) 3.3 (0.4, 11.9)	9 (0.9) 32.4 (14.8, 61.5)	89.9% (51.0, 98.9)

Source: BLA 125752/68, Study P203 Part A, Table 14.2.7.1.1.2, Table 14.2.8.1.1.2
Abbreviations: NE=non-evaluable; CI=confidence interval; n=cases
a. Person-years is defined as the total years from randomization date to the earliest date of the first occurrence of COVID-19, study discontinuation, unblinding, nonstudy COVID-19 vaccination, crossover dose, booster dose, data cutoff, or 31 May 2021.
b. Incidence rate is defined as the number of participants with an event before or on 31 May 2021 divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
c. Vaccine efficacy, defined as 1 – ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years

Vaccine Efficacy Against All SARS-CoV-2 Infection

VE was also evaluated against all SARS-CoV-2 infection, including symptomatic COVID-19 cases and asymptomatic SARS-CoV-2 infection. Asymptomatic SARS-CoV-2 infection is defined as absence of COVID-19 symptoms and either of the following: (a) binding antibody (bAb) levels against SARS-CoV-2 nucleocapsid (N) protein (as measured by Roche Elecsys) negative at Day 1 and becoming positive starting at Day 57 or later or (b) positive RT-PCR test at scheduled or unscheduled/illness visits. Per protocol, all participants in Study P203 had scheduled assessment of N-serology and RT-PCR testing at the Day 57 visit. Nasal swabs for RT-PCR were also collected from all study subjects at the Day 29 visit, prior to administration of Dose 2.

As shown in Table 21 below, a large proportion of cases reported across groups were asymptomatic SARS CoV-2 infections, including 20/22 cases in mRNA-1273 group and 16/25 cases in placebo group. The impact of these findings on VE point estimates may be difficult and are limited by wide 95% CIs. The efficacy analyses had limited follow-up time during a period when SARS-CoV-2 Alpha variant was the predominant circulating strain during the pandemic.

Table 21. Vaccine Efficacy Against SARS-CoV-2 Infection Starting 14 Days after Dose 2, Participants 12-17 Years of Age, Study P203 Part A, Per-Protocol Set for Efficacy

Endpoint	P203 Part A 12-17 Years mRNA-1273 100 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI) [a,b] N=2,142	P203 Part A 12-17 Years Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI) [a,b] N=1,044	Vaccine Efficacy[c] (95% CI)
SARS-CoV-2 infection, regardless of symptom	22 (1.0) 36.4 (22.8, 55.0)	25 (2.4) 91.5 (59.2, 135.0)	60.3% (26.6, 78.6)

Endpoint	P203 Part A 12-17 Years mRNA-1273 100 µg n (%) Incidence Rate per 1,000 Person-Years (95% CI) [a,b] N=2,142	P203 Part A 12-17 Years Placebo n (%) Incidence Rate per 1,000 Person-Years (95% CI) [a,b] N=1,044	Vaccine Efficacy[c] (95% CI)
Asymptomatic SARS-CoV-2 infection	20 (0.9) 33.1 (20.2, 51.0)	16 (1.5) 58.5 (33.5, 95.1)	43.5% (-16.5, 72.2)

Source: BLA 125752/68, P203 Part A, Table 14.2.6.1.1.2, and Table 14.2.5.1.1.2.
Abbreviations: n=cases; CI=confidence interval
a Person-years is defined as the total years from randomization date to the earliest date of the first occurrence of disease endpoint, study discontinuation, unblinding, nonstudy COVID-19 vaccination, crossover dose, booster dose, data cutoff, or 31 May 2021.
B Incidence rate is defined as the number of participants with an event before or on 31 May 2021 divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
C Vaccine efficacy, defined as 1 – ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Reviewer Comment: The interpretability of VE estimates against asymptomatic infection are limited and confounded by infrequent assessments for N-serology and RT-PCR at fixed timepoints during study conduct. It is unlikely that all cases of asymptomatic SARS-CoV-2 infection that occurred during the study were reported. Furthermore, onset time of asymptomatic infection was unlikely to be accurately assessed as detection of positive anti N-protein antibody at Study visit Day 57 does not preclude an earlier infection onset time point during the study, including timepoints after screening and prior to 14 days post-Dose 2.

This study was conducted entirely in the U.S. starting on December 9, 2020 and with a May 31, 2021 data cutoff. Sequencing data were not available in this study, therefore additional information to characterize VE against circulating variants at the time of study conduct are not available, including against SARS CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351) or Delta (B.1.617.2).

6.2.11.4 Exploratory and Post Hoc Analyses

Long-term Analysis of Immunogenicity

Blood was collected from study participants for immunogenicity assessments on Day 1 (baseline), Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2). nAb results from Day 57 contributed to the analyses of the primary immunogenicity endpoints and are discussed in Section 6.1.11.1. Evaluation of nAb from timepoints after Day 57 are referred to as “long-term” analyses. For the long-term analyses, testing was conducted at PPD Laboratories using a validated pseudovirus nAb assay (VAC62) against D614G and reported as geometric mean concentration (arbitrary unit [AU]/mL), which differed from the Duke University nAb assay, reported as geometric mean titers, used for the analyses of the primary immunogenicity endpoints.

Analyses of nAb responses against D614G through Day 394, by baseline SARS-CoV-2 status, are shown in Table 22. Among participants in both subgroups, at 6 months post-Dose 2, the nAb GMC declined to approximately one-third of the Day 57 level, with a slight further decline observed through 1-year post-Dose 2. Overall, the kinetics of the nAb response over time appeared similar between the two subgroups.

Table 22. Long-term Analyses of Geometric Mean SARS-CoV-2 Neutralizing Concentrations as Measured by Pseudovirus nAb Assay (VAC62) Against D614G, Participants 12-17 Years, By Baseline SARS-CoV-2 Status, Study P203 Part A and Part B, Immunogenicity Subset (Long-term Analysis)

Timepoint	P203 12-17 Years 100 µg mRNA-1273 Baseline SARS-CoV-2 Status: Negative GMC (95% CI) N=369	P203 12-17 Years 100 µg mRNA-1273 Baseline SARS-CoV-2 Status: Positive GMC (95% CI) N=14
Baseline	n=369 11.2 (10.7, 11.8)	n=14 110.7 (56.0, 218.9)
Day 57	n=366 1868.4 (1758.8, 1984.7)	n=14 5823.2 (3322.6, 10205.6)
Day 209	n=366 625.4 (583.3, 670.4)	n=14 1717.8 (960.2, 3073.3)
Day 394	n=363 550.3 (489.9, 618.1)	n=14 1356.8 (856.7, 2148.9)

Source: BLA 125752/68, Study P203 Part A and Part B, Table 14.2.3.1.4.2
Abbreviations: CI=confidence interval; GMC=geometric mean concentration; nAb=neutralizing ant body; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification; N=number of participants in the Immunogenicity Subset (long-term analysis) with specified baseline SARS-CoV-2 status; n=number of participants with non-missing data at the timepoint
LLOQ: 10; ULOQ: 281600
Notes: Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

Among the baseline SARS-CoV-2 negative participants who contributed to the analyses shown above, 64 out of the 369 participants had documented SARS-CoV-2 infection during the study (at or before Day 394), the majority (54/64) of which occurred between Day 209 and Day 394. Excluding these 64 participants from the analysis, a more notable decline in nAb GMC was observed between Day 209 and Day 394, though much less than that observed between Day 57 and Day 209. Among the participants with documented SARS-CoV-2 infection post-vaccination and before Day 394, the nAb GMC at Day 394 was restored to levels above those observed at Day 57.

Table 23. Long-term Analyses of Geometric Mean SARS-CoV-2 Neutralizing Concentrations as Measured by Pseudovirus nAb Assay (VAC62) Against D614G, Participants 12 Through 17 Years, By SARS-CoV-2 Infection Status During the Study, Study P203 Part A and Part B, Per Protocol Immunogenicity Subset (Long-term Analysis)

Timepoint	P203 12-17 Years 100 µg mRNA-1273 SARS-CoV-2 Infection During Study: No GMC (95% CI) N=305	P203 12-17 Years 100 µg mRNA-1273 SARS-CoV-2 Infection During Study: Yes GMC (95% CI) N=64
Baseline	n=305 11.3 (10.7, 11.9)	n=64 11.0 (9.6, 12.6)
Day 57	n=302 1887.4 (1768.4, 2014.4)	n=64 1781.0 (1514.9, 2093.9)
Day 209	n=302 622.3 (582.1, 665.3)	n=64 639.9 (498.8, 820.9)
Day 394	n=299 387.8 (361.9, 415.4)	n=64 2823.1 (1940.4, 4107.4)

Source: BLA 125752/68, Study P203 Part A and Part B, Table 14.2.3.1.4.4
Abbreviations: CI=confidence interval; GMC=geometric mean concentration; nAb=neutralizing ant body; LLOQ=lower limit of quantification; ULOQ=upper limit of quantification; N=number of participants in the per protocol immunogenicity subset (long-term analysis) with specified SARS-CoV-2 infection status; n=number of participants with non-missing data at the timepoint LLOQ: 10; ULOQ: 281600
Notes: Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

Incidence of COVID-19 – Open-Label Phase (Part B)

VE after the data cutoff for the blinded phase of the study of May 31, 2021 could not be evaluated due to the attrition of the placebo group. In the open-label phase, incidence rate of COVID-19 by calendar month was evaluated for mRNA-1273 recipients in the PP Efficacy Set. Using the broader CDC COVID-19 case definition, the incidence rate was 0-1.0 per 1000 person-months during the months of June and July 2021, rising to 3.5-4.8 per 1000 person-months during the months of August through November 2021, which coincided with the predominance of the Delta variant in the U.S. Further sharp increases in COVID-19 incidence rates were observed in Dec 2021 (30.1 per 1000 person-months) and January 2022 (125.1 per 1000 person-months), coinciding with circulation of the Omicron variant.

> *Reviewer Comment: In Study P203 (Part A), January 2022 was a time point in the study that was ~9 months after mRNA-1273 recipients had received Dose 2 of their 2-dose series. Though the sample size was not large for the long-term immunogenicity analyses, gradual decline of nAb levels was observed between 6 months post-Dose 2 and 1 year post-dose 2. During December 2021/January 2022, the U.S. incidence of SARS-CoV-2 cases had significantly increased (35 times greater than previous months). While data from the long-term analyses suggest waning immunity following a two-dose series vaccination, greater infectivity and immune escape of the Omicron variant, dominant during this time point in the pandemic, were important factors in the observed trends. Subsequently, modified*

bivalent SARS-CoV-2 booster doses were authorized for use in August 2022 in the U.S. to target circulating SARS CoV-2 Omicron variants.

6.2.12 Safety Analyses

Safety analyses presented are derived from two study periods: the blinded placebo-controlled phase (Part A) and the open-label phase (Part B). Analyses of solicited adverse reactions and unsolicited AEs within 28 days will be based on data from Part A only, while SAEs, AESIs, SMQ searches, and AEs leading to discontinuation will be based on data from both parts of the study. A total of 2,577 participants received at least one dose of mRNA-1273 in the study (2,486 in Part A and 91 in Part B). As of the data cutoff date of January 31, 2022, the median duration of follow-up for these 2,577 participants, including both blinded and open-label follow-up, was 311 days.

6.2.12.1 Methods

See Section 6.1.7.

6.2.12.2 Overview of Adverse Events

Table 24 below provides an overview of solicited adverse reactions and unsolicited AEs reported during the blinded phase of the study (Part A), with a cutoff date of May 31, 2021.

As compared to the placebo group, a greater percentage of adolescent participants in the vaccine group experienced local and systemic solicited adverse reactions. The rate of unsolicited AEs, including related unsolicited AEs, was higher in the vaccine group compared to the placebo group. Overall, the proportions of MAAEs and SAEs were balanced between vaccine and placebo groups. SAEs were uncommon and no deaths were reported.

Table 24. Safety Overview, Blinded Phase P203 Part A, Participants 12 Through 17 Years of Age, Safety Set and Solicited Safety Set

Event Type	P203 Part A 12-17 Years mRNA-1273 100 µg n (%)	P203 Part A 12-17 Years Placebo n (%)
Solicited adverse reactions	**N1=2478-2485**	**N1=1220-1240**
Solicited local adverse reaction within 7 days after vaccination	2431 (97.8)	602 (48.5)
Dose 1	2339 (94.2)	455 (36.8)
Dose 2	2314 (93.4)	398 (32.6)
Grade 3 or 4 local adverse reaction (any dose)	344 (13.8)	4 (0.3)
Solicited systemic adverse reaction within 7 days after vaccination	2284 (91.9)	830 (66.9)
Dose 1	1701 (68.5)	687 (55.5)
Dose 2	2134 (86.1)	561 (46.0)
Grade 3 or 4 systemic adverse reaction (any dose)	415 (16.7)	58 (4.7)
Unsolicited adverse events	**N=2486**	**N=1240**
Unsolicited adverse event up to 28 days after any dose	582 (23.4)	237 (19.1)
Non-serious unsolicited AE[a]	579 (23.3)	236 (19.0)

Event Type	P203 Part A 12-17 Years mRNA-1273 100 µg n (%)	P203 Part A 12-17 Years Placebo n (%)
Related non-serious unsolicited AE	374 (15.0)	98 (7.9)
Severe non-serious unsolicited AE[a]	16 (0.6)	3 (0.2)
Related severe non-serious unsolicited AE	14 (0.6)	3 (0.2)
Medically attended adverse event[b]	337 (13.6)	136 (11.0)
Related MAAE	25 (1.0)	2 (0.2)
SAE[b]	9 (0.4)	3 (0.2)
Related SAE	0	0
AESI[b]	1 (<0.1)	1 (<0.1)
Deaths[b]	0	0
AE leading discontinuation of study vaccine[b]	3 (0.1)	0

Source: sBLA 125752/68, Study P203 Part A, Table 14.3.1.1.1.3, Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.3.1.7.1.1, Table 14.3.1.19.2.2, Table 14.3.1.20, Table 14.3.1.21.3.2.2, Table 14.3.1.13.2.3, Table 14.3.1.15
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; SAE=serious adverse event; N1=number of exposed participants who submitted any data for the event; N=number of participants in the Safety Set
Notes: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event. Unsolicited AE percentages are based on the number of safety participants.
a. Participants without any SAE and with any non-serious AE.
b. Through May 31, 2021, or the unblinding date, whichever came first

Table 25 below provides an overview of MAAEs, SAEs, AESIs, deaths, and AEs leading to discontinuation of study vaccine through the data cutoff of January 31, 2022. The analyses shown consist of AEs accrued through both the blinded phase (Part A) and the open-label phase (Part B) of the study among participants who received mRNA-1273 in the Part A (mRNA-1273 group) and participants who received placebo in Part A and crossed-over to receive mRNA-1273 in Part B (Crossover-mRNA-1273). For the crossover group, only AEs occurring after receipt of mRNA-1273 are included.

Table 25. Safety Overview, Blinded and Open-Label Phases (P203 Parts A and B), Participants 12 Through 17 Years of Age, Safety Set

Event Type	P203 12-17 Years mRNA-1273 100 µg n (%) N=2486	P203 12-17 Years Cross-over mRNA-1273 100 µg n (%) N=91
Medically attended adverse event[a]	991 (39.9)	23 (25.3)
Related MAAE	27 (1.1)	2 (2.2)
SAE[a]	21 (0.8)	1 (1.1)
Related SAE	0	0
AESI[a]	13 (0.5)	0
Deaths[a]	0	0
AE leading discontinuation of study vaccine[a]	3 (0.1)	0

Source: sBLA 125752/68, Study P203 Part A and B, Table 14.3.1.7.4.1
Abbreviations: AE=adverse event; AESI=adverse event of special interest; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants in the Safety Set
Notes: Unsolicited AE percentages are based on the number of safety participants.
b. For placebo-mRNA-1273 group, only AEs occurring after the cross-over mRNA-1273 first dose are included; for mRNA-1273 group, any AEs occurring after mRNA-1273 first dose are included through January 31, 2022

Reviewer Comment: Interpretation of safety data from mRNA-1273 recipients during

the open-label phase of the study was limited by the absence of a placebo group comparator.

6.2.12.3 Solicited Adverse Reactions

The frequency and severity of solicited local and systemic ARs with onset within 7 days after vaccination with either mRNA1273 or placebo are presented in the solicited safety set (Table 26 and Table 27 below). Solicited ARs were recorded daily by study participants using e-diaries, and from any verbally reported ARs during safety telephone calls and included the assessment of local injection site reactions (pain, erythema, swelling and axillary swelling/tenderness) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills). Solicited ARs were not collected for the open-label Part B portion of the study.

Overall, the incidence of solicited ARs was higher in participants who received mRNA-1273 compared to placebo. By order of frequency, ARs following administration of any dose of mRNA-1273 were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.4%), chills (49.1%), arthralgia (34.6%), axillary swelling/tenderness (34.5%), nausea/vomiting (29.3%), swelling at the injection site (27.6%), erythema at the injection site (25.7%), and fever (13.4%).

6.2.12.4 Solicited Local Reactions

Table 26 below provides rates of solicited local ARs by treatment group. Among mRNA-1273 recipients, the overall rates of local ARs were similar after Dose 1 and Dose 2; however, erythema and swelling were reported more frequently following Dose 2. Injection site pain was the most frequent solicited local AR in mRNA-1273 recipients after any dose. Solicited local ARs following any dose were mostly Grade 1 or Grade 2, with Grade 3 local ARs reported by 6.9% (Dose 1) and 8.9% (Dose 2) of mRNA-1273 recipients. No Grade 4 solicited local ARs were reported within 7 days following vaccination.

Among mRNA-1273 recipients, the median day of onset of local reactogenicity was Day 1 and the median duration was 3 days. A greater percentage of mRNA-1273 recipients reported symptoms persisting beyond Day 7 following Dose 1 (10.1%) as compared to following Dose 2 (4.4%).

Delayed solicited injection site reactions, defined as beginning after Day 7, after any injection were reported by 1.5% of mRNA-1273 recipients (all occurring after Dose 1) and one placebo recipient (<0.1%).

Table 26. Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, Participants 12 Through 17 Years of Age, Study P203 Part A, First [Second] Injection Solicited Safety Set

Event	P203 Part A 12-17 Years mRNA-1273 100 µg Dose 1 n (%) N=2482	P203 Part A 12-17 Years Placebo Dose 1 n (%) N=1238	P203 Part A 12-17 Years mRNA-1273 100 µg Dose 2 n (%) N=2478	P203 Part A 12-17 Years Placebo Dose 2 n (%) N=1220
Any local adverse reaction	N1=2482	N1=1238	N1=2478	N1=1220
Any	2339 (94.2)	455 (36.8)	2314 (93.4)	398 (32.6)

Event	P203 Part A 12-17 Years mRNA-1273 100 µg Dose 1 n (%) N=2482	P203 Part A 12-17 Years Placebo Dose 1 n (%) N=1238	P203 Part A 12-17 Years mRNA-1273 100 µg Dose 2 n (%) N=2478	P203 Part A 12-17 Years Placebo Dose 2 n (%) N=1220
Grade 3	171 (6.9)	1 (<0.1)	220 (8.9)	3 (0.2)
Pain[a]	N1=2482	N1=1238	N1=2478	N1=1220
Any	2310 (93.1)	431 (34.8)	2290 (92.4)	370 (30.3)
Grade 3	133 (5.4)	1 (<0.1)	126 (5.1)	3 (0.2)
Erythema (redness)[b]	N1=2482	N1=1238	N1=2478	N1=1220
Any ≥25 mm	329 (13.3)	8 (0.6)	484 (19.5)	11 (0.9)
Grade 3	22 (0.9)	0	72 (2.9)	0
Swelling (hardness)[b]	N1=2482	N1=1238	N1=2478	N1=1220
Any ≥25 mm	401 (16.2)	12 (1.0)	508 (20.5)	12 (1.0)
Grade 3	27 (1.1)	0	56 (2.3)	0
Axillary swelling or tenderness[a]	N1=2481	N1=1238	N1=2477	N1=1220
Any	576 (23.2)	101 (8.2)	519 (21.0)	61 (5.0)
Grade 3	11 (0.4)	0	7 (0.3)	0

Source: Source: sBLA 125752/68, Study P203 Part A, Table 14.3.1.1.1.1, Table 14.3.1.1.1.2.
Notes: N1=Number of exposed participants who submitted any data for the event. Any=Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
No grade 4 solicited local ARs were reported.
a. Grade 3 pain and axillary swelling or tenderness: any use of prescription pain reliever/prevents daily activity
b. Grade 3 erythema (redness) and swelling (hardness): >100 mm

6.2.12.5 Solicited Systemic Adverse Reactions

Table 27 below provides rates of solicited systemic ARs by treatment group. Among mRNA-1273 recipients, systemic ARs occurred more frequently after Dose 2 compared to Dose 1. Headache and fatigue were the most frequent solicited systemic ARs in vaccine recipients after any dose. Systemic ARs following any dose were mostly Grade 1 or Grade 2, with Grade 3 systemic ARs reported by 13.8% of mRNA-1273 recipients after Dose 2.

Among vaccine recipients, the median day of AR onset was Day 1 for local or systemic reactogenicity after Dose 1 or Dose 2. The overall median duration of systemic reactogenicity was 2 days. A greater percentage of mRNA-1273 recipients reported that symptoms persisted beyond Day 7 following Dose 1 (10.1%%) compared with Dose 2 (4.4%).

Table 27. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 17 Years of Age, Study P203 Part A, First [Second] Injection Solicited Safety Set

Event	P203 Part A 12-17 Years mRNA-1273 100 µg, Dose 1 n (%) N=2482	P203 Part A 12-17 Years Placebo, Dose 1 n (%) N=1238	P203 Part A 12-17 Years mRNA-1273 100 µg, Dose 2 n (%) N=2478	P203 Part A 12-17 Years Placebo, Dose 2 n (%) N=1220
Any systemic adverse reaction	N1=2482	N1=1238	N1=2478	N1=1220
Any	1701 (68.5)	687 (55.5)	2134 (86.1)	561 (46.0)

Event	P203 Part A 12-17 Years mRNA-1273 100 µg, Dose 1 n (%) N=2482	P203 Part A 12-17 Years Placebo, Dose 1 n (%) N=1238	P203 Part A 12-17 Years mRNA-1273 100 µg, Dose 2 n (%) N=2478	P203 Part A 12-17 Years Placebo, Dose 2 n (%) N=1220
Grade 3	108 (4.4)	36 (2.9)	341 (13.8)	25 (2.0)
Grade 4	0	0	3 (0.1)	1 (<0.1)
Fever	N1=2480	N1=1238	N1=2477	N1=1219
≥38.0°C	57 (2.3)	11 (0.9)	298 (12.0)	12 (1.0)
38.0°C to 38.4°C	34 (1.4)	8 (0.6)	161 (6.5)	7 (0.6)
38.5°C to 38.9°C	14 (0.6)	2 (0.2)	88 (3.6)	3 (0.2)
39°C to 40.0°C	9 (0.4)	1 (<0.1)	48 (1.9)	1 (<0.1)
>40.0°C	0	0	1 (<0.1)	1 (<0.1)
Headache[a]	N1=2480	N1=1238	N1=2478	N1=1220
Any	1106 (44.6)	477 (38.5)	1739 (70.2)	371 (30.4)
Grade 3	56 (2.3)	17 (1.4)	112 (4.5)	14 (1.1)
Grade 4	0	0	1 (<0.1)	0
Fatigue[b]	N1=2481	N1=1238	N1=2478	N1=1220
Any	1188 (47.9)	453 (36.6)	1679 (67.8)	353 (28.9)
Grade 3	33 (1.3)	18 (1.5)	188 (7.6)	10 (0.8)
Grade 4	0	0	0	0
Myalgia[b]	N1=2480	N1=1238	N1=2477	N1=1220
Any	670 (27.0)	205 (16.6)	1155 (46.6)	153 (12.5)
Grade 3	24 (1.0)	10 (0.8)	129 (5.2)	3 (0.2)
Grade 4	0	0	0	0
Arthralgia[b]	N1=2480	N1=1238	N1=2477	N1=1220
Any	371 (15.0)	143 (11.6)	716 (28.9)	113 (9.3)
Grade 3	15 (0.6)	5 (0.4)	57 (2.3)	2 (0.2)
Grade 4	0	0	0	0
Nausea/vomiting[c]	N1=2480	N1=1238	N1=2477	N1=1220
Any	281 (11.3)	109 (8.8)	591 (23.9)	106 (8.7)
Grade 3	2 (<0.1)	0	2 (<0.1)	0
Grade 4	0	0	1 (<0.1)	0
Chills[d]	N1=2480	N1=1238	N1=2477	N1=1220
Any	456 (18.4)	138 (11.1)	1066 (43.0)	97 (8.0)
Grade 3	4 (0.2)	1 (<0.1)	11 (0.4)	0
Grade 4	0	0	0	0
Use of antipyretic or pain medication	N1=2482	N1=1238	N1=2478	N1=1220
Any	748 (30.1)	118 (9.5)	1242 (50.1)	108 (8.9)

Source: sBLA 125752/68, Study P203 Part A, Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.1.5.3.1, Table 14.1.5.3.2.
Notes:
N1=Number of exposed participants who submitted any data for the event. Any=Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1). Medications were collected on the e-diary.
a..Headache grade 3: significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
b. Fatigue, myalgia, arthralgia grade 3: significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
c. Nausea/vomiting grade 3: prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
d. Chills grade 3: prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.

Reviewer Comment: Overall, solicited systemic reactions and use of antipyretic or pain medication use were reported more frequently after Dose 2 than Dose 1 of mRNA-1273 vaccine, suggestive of greater reactogenicity after Dose 2.

Subgroup Analyses of Solicited Adverse Reactions

Subgroup analyses were performed for solicited ARs, comparing mRNA-1273 and placebo groups by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the demographic subgroups, although some race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Solicited local and systemic reactions after vaccination among mRNA-1273 recipients by SARS-CoV-2 status at baseline are shown in Table 28. After Dose 1, the frequencies of solicited local ARs were similar between the two groups, except for axillary swelling or tenderness, which was higher among those with positive (39.5%) than those with negative (22.4%) SARS-CoV2 status at baseline. Solicited systemic ARs after Dose 1 were more frequently reported among participants with positive than with negative SARS-CoV-2 status at baseline, most notably for fever (19.0% vs 1.3%). Grade 3 systemic ARs were also more frequently reported after Dose 1 among baseline positive participants (14.3%) compared to baseline negative participants (3.8%). Rates of solicited systemic ARs among baseline positive participants after Dose 1 were similar to those reported after Dose 2 among baseline negative participants. In general, after Dose 2, the frequencies of solicited local and systemic ARs were similar among the two subgroups.

Table 28. Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose by Baseline SARS-CoV-2 Status, by Maximum Severity, mRNA-1273 Recipients 12 Through 17 Years of Age, Study P203 Part A, First [Second] Injection Solicited Safety Set

Event	P203 Part A 12-17 Years Baseline SARS-CoV-2 Negative Dose 1 n (%) N=2167	P203 Part A 12-17 Years Baseline SARS-CoV-2 Positive Dose 1 n (%) N=147	P203 Part A 12-17 Years Baseline SARS-CoV-2 Negative Dose 2 n (%) N=2162	P203 Part A 12-17 Years Baseline SARS-CoV-2 Positive Dose 2 n (%) N=146
Any local adverse reaction	N1=2167	N1=147	N1=2166	N1=146
Any	2051 (94.6)	131 (89.1)	2032 (93.8)	125 (85.6)
Grade 3 or above	144 (6.6)	13 (8.8)	198 (9.1)	10 (6.8)
Pain at injection site	N1=2167	N1=147	N1=2166	N1=146
Any	2027 (93.5)	128 (87.1)	2009 (92.8)	124 (84.9)
Grade 3 or above[a]	113 (5.2)	9 (6.1)	114 (5.3)	7 (4.8)
Erythema (redness)	N1=2167	N1=147	N1=2166	N1=146
Any ≥25mm	303 (14.0)	20 (13.6)	432 (19.9)	18 (12.3)
Grade 3 or above[b]	20 (0.9)	1 (0.7)	62 (2.9)	3 (2.1)
Swelling (hardness)	N1=2167	N1=147	N1=2166	N1=146
Any ≥25mm	359 (16.6)	24 (16.3)	448 (20.7)	22 (15.1)
Grade 3 or above[b]	21 (1.0)	4 (2.7)	50 (2.3)	2 (1.4)
Axillary swelling or tenderness	N1=2166	N1=147	N1=2165	N1=146
Any	485 (22.4)	58 (39.5)	465 (21.5)	25 (17.1)

Event	P203 Part A 12-17 Years Baseline SARS-CoV-2 Negative Dose 1 n (%) N=2167	P203 Part A 12-17 Years Baseline SARS-CoV-2 Positive Dose 1 n (%) N=147	P203 Part A 12-17 Years Baseline SARS-CoV-2 Negative Dose 2 n (%) N=2162	P203 Part A 12-17 Years Baseline SARS-CoV-2 Positive Dose 2 n (%) N=146
Grade 3 or above[a]	10 (0.5)	1 (0.7)	7 (0.3)	0
Any systemic adverse reaction	N1=2167	N1=147	N1=2166	N1=146
Any	1465 (67.6)	128 (87.1)	1868 (86.2)	122 (83.6)
Grade 3 or above	82 (3.8)	21 (14.3)	305 (14.1)	15 (10.3)
Fever	N1=2165	N1=147	N1=2165	N1=146
≥38.0°C	28 (1.3)	28 (19.0)	258 (11.9)	20 (13.7)
38.0°C to 38.4°C	18 (0.8)	16 (10.9)	135 (6.2)	13 (8.9)
38.5°C to 38.9°C	6 (0.3)	8 (5.4)	80 (3.7)	5 (3.4)
39°C to 40.0°C	4 (0.2)	4 (2.7)	42 (1.9)	2 (1.4)
>40.0°C	0	0	1 (<0.1)	0
Headache	N1=2165	N1=147	N1=2166	N1=146
Any	941 (43.5)	103 (70.1)	1528 (70.5)	90 (61.6)
Grade 3 or above[c]	44 (2.0)	11 (7.5)	97 (4.5)	7 (4.8)
Fatigue	N1=2166	N1=147	N1=2166	N1=146
Any	1006 (46.4)	103 (70.1)	1471 (67.9)	94 (64.4)
Grade 3 or above[d]	27 (1.2)	4 (2.7)	173 (8.0)	5 (3.4)
Myalgia	N1=2165	N1=147	N1=2165	N1=146
Any	559 (25.8)	63 (42.9)	1019 (47.1)	63 (43.2)
Grade 3 or above[d]	19 (0.9)	3 (2.0)	117 (5.4)	2 (1.4)
Arthralgia	N1=2165	N1=147	N1=2165	N1=146
Any	306 (14.1)	36 (24.5)	634 (29.3)	39 (26.7)
Grade 3 or above[d]	12 (0.6)	2 (1.4)	52 (2.4)	0
Nausea/vomiting	N1=2165	N1=147	N1=2165	N1=146
Any	237 (10.9)	30 (20.4)	523 (24.2)	29 (19.9)
Grade 3 or above[e]	2 (<0.1)	0	2 (<0.1)	1 (0.7)
Chills	N1=2165	N1=147	N1=2165	N1=146
Any	364 (16.8)	72 (49.0)	935 (43.2)	63 (43.2)
Grade 3 or above[f]	4 (0.2)	0	10 (0.5)	0

Source: Source: sBLA 125752/68, Study P203 Part A, Table 14.3.1.1.2.1, Table 14.3.1.1.2.2
Notes: N1=Number of exposed participants who submitted any data for the event; Any=Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
There were no grade 4 solicited local adverse reactions.
a. Injection site pain, axillary swelling or tenderness grade 3: prevents daily activity.
b. Erythema (redness) or swelling (hardness) grade 3: >100 mm.
c. Headache Grade 3: significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
d. Fatigue, myalgia, arthralgia grade 3: significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
e. Nausea/vomiting grade 3: prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
f. Chills grade 3: prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.

Reviewer Comment: The analyses of solicited systemic ARs by baseline status suggest that participants with prior infection have comparable rates of reactogenicity after Dose 1 as those reported after Dose 2 in baseline negative participants.

However, generalizability of these findings to the general population is limited by the small number of participants with positive SARS-CoV-2 status at baseline (N=147).

6.2.12.6 Unsolicited Adverse Events

In the blinded Part A portion of the study, through the data cutoff of May 31, 2021, 96% of study participants had at least 28 days of follow-up after Dose 2.

Through the January 31, 2021, data cutoff for Study P203, 97.3% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 312 days after Dose 2. Overall, in the blinded phase of the study, rates of unsolicited AEs within 28 days after any dose were slightly higher among vaccine recipients (23.4%) compared to placebo recipients (19.1%). This observed difference was mostly driven by events classified under the SOC *General disorders and administration site conditions*, the majority of which included injection site adverse reactions, consistent with the overall findings for local reactogenicity reported on the e-diary by participants. By PT, *Injection site lymphadenopathy* was most frequently reported unsolicited AE (5.4% of vaccine recipients vs 0.5%) of placebo recipients) that was not a protocol-specified injection site reaction captured by the e-diary for this study.

In the blinded phase, during the 28-day follow-up period following any dose, lymphadenopathy-related events that were not necessarily captured in the 7-day e-diary were reported by 5.9% of vaccine recipients and 0.6% of placebo recipients. These events included lymphadenopathy, vaccination-site lymphadenopathy, and injection-site lymphadenopathy which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected group.

Rates of unsolicited AEs were generally similar across subgroups based on sex, race, ethnicity, and baseline SARS-CoV-2 status, though these analyses were limited by the low number of participants in several subgroups.

Given the small number of participants (N=91) who crossed-over to receive mRNA-1273 in the open-label phase (Part B) of the study, and the lack of a comparator group, unsolicited AEs within 28 days of any dose was not assessed for the open-label phase.

Medically Attended Adverse Events

In the blinded phase, within 28 days after any dose, MAAEs were reported at similar rates among mRNA-1273 recipients and placebo recipients (7.4% and 6.9%, respectively). Related MAAEs within 28 days were reported by 1.0% of mRNA-1273 recipients and 0.2% of placebo recipients. The majority of these events assessed as related were events consistent with local and systemic reactogenicity.

MAAEs through the data cutoff for the blinded phase of May 31, 2021 were reported by 13.6% of mRNA-1273 recipients and 11.0% of placebo recipients.

6.2.12.7 Adverse Events of Special Interest (AESIs)

This study was amended to specify designated AEs as AESIs that were considered to be possibly associated with COVID-19 or of interest in COVID-19 vaccine safety surveillance (Appendix A). Through the data cutoff of January 31, 2022, including both the blinded and open-label phases, AESIs were reported by 13 mRNA-1273 recipients.

These events included anosmia and ageusia (in 9 participants; associated with COVID-19 or viral infection), appendicitis (n=2), events of seizure and idiopathic generalized epilepsy reported in a participant with 285 days post-Dose 2 (discussed in SAE section), and an event of aseptic meningitis in a participant with recent Chiari decompression surgery (see SAE section). None of these events were considered related to study product by the investigator.

Reviewer Comment: This reviewer agrees with the investigator that these events were not related to the study vaccine.

6.2.12.8 FDA Standard MedDRA Queries

FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following Dose 1 through the data cutoff. SMQs were conducted on AE PTs that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in imbalance between the two treatment groups, and which captured events considered clinically relevant by the FDA, will be discussed.

SMQ Hypersensitivity

In the blinded phase, within 28 days after any vaccination, events under the narrow scope SMQ *Hypersensitivity* were reported by 1.3% of vaccine recipients (n=32) compared to 0.6% of placebo recipients (n=7). The most frequently reported events in vaccine recipients were classified under PTs of urticaria 6 (0.2%), injection site urticaria 4 (0.2%), and injection site rash 4 (0.2%). Sixteen events occurred with 7 days of vaccination, and most of them resolved within 1-3 days. All events in vaccine recipients were Grade 1 or 2, and none were considered serious. Based on FDA's review, these events are likely related to vaccination due to the temporality with vaccination and clinical plausibility. There were no reports of anaphylaxis related to vaccination.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (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 (Appendix B). Analysis of the data through the May 31, 2021, data cutoff for the blinded phase identified 13 events (0.5%) among mRNA-1273 recipients and 3 events (0.2%) among placebo recipients. Analysis of the data through the later data cutoff of January 31, 2022 identified an additional 11 events among participants who received mRNA-1273 in either the blinded phase or the open-label cross-over phase. Events identified through this search, including both the blinded and open-label phases, include Dyspnea (all considered not related to investigational product, all mild or moderate severity in 8 vaccine recipients, 0 placebo recipients), Syncope (all considered not related to investigational product, all mild or moderate severity in 14 vaccine recipients, 3 placebo recipients), Chest pain (considered related to investigational product, moderate severity in 1 vaccine recipient, 0 placebo recipients), Palpitations (considered not related to investigational product, moderate severity in 1 vaccine recipient, 0 placebo recipients).

Of the events identified, one was adjudicated by the Cardiac External Adjudication Committee (CEAC) to be a probable case of acute myocarditis. A summary of this event is included below:

1. A 14-year-old male had received placebo in Part A of the study and after unblinding, consented to receive mRNA-1273 in Part B. One day after receipt of Dose 2 of mRNA-1273, the participant experienced chest pain described as “like heart being squeezed” and “heart was going to explode” which was exacerbated with deep inhalation. He was seen by the investigator the following day with grossly normal physical exam, but an electrocardiogram (EKG) was remarkable for ST segment elevation with right axis deviation. Mild myocarditis was suspected, and the participant was advised to maintain hydration, avoid physical activity, and to take ibuprofen twice a day. Symptoms resolved 8 days after onset. The participant was evaluated 5 months later by pediatric cardiology with normal examination and evaluation by EKG and echocardiogram. The CEAC per protocol-defined procedure adjudicated the event to be a probable case of acute myocarditis.

Reviewer Comment: This reviewer agrees with the investigator that this event was related to study vaccine and agrees with CEAC adjudication that this case represents vaccine-associated myocarditis. Postmarketing data with authorized or approved monovalent mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis, most notably in young adult males.

6.2.12.9 Serious Adverse Events

In the blinded phase, through the data cutoff of May 31, 2021, SAEs were reported in 9 mRNA-1273 recipients (0.4%) and 3 placebo recipients (0.2%). Two additional SAEs were reported by one each of mRNA-1273 (event of depression) and placebo (event of epilepsy) recipients in the blinded phase but after the May 31, 2021 data cutoff. None of these events were assessed as related to study vaccine by the investigator.

The following SAEs occurred in mRNA-1273 recipients in the blinded phase:

1. Six participants (12-16 years of age) were hospitalized for depression and/or suicidal ideation (range of onset relative to vaccination: Days 31 to 343).
2. One 15-year-old participant was hospitalized for appendicitis on Day 4.
3. One 16-year-old participant experienced drug induced-liver injury on Day 14. The participant reported medication use with trimethoprim/sulfamethoxazole for a Bartholin’s gland cyst that was diagnosed on Day 8. The event was considered resolved on Day 35. The second dose was not administered due to the physician decision to discontinue the participant from the study and further dosing. The participant was diagnosed with hepatitis, most-likely drug-induced liver injury secondary to trimethoprim-sulfamethoxazole and the investigator did not believe this was related to the study product.
4. One 14-year-old participant was admitted to the hospital for surgical repair of pectus excavatum on Day 58.
5. One 17-year-old participant was hospitalized for sunburn with second and third-degree burns on Day 95.

The following SAEs occurred in placebo recipients in the blinded phase:
The SAEs that occurred in placebo recipients include a participant with a history of renal stones hospitalized for hydronephrosis/obstructive nephropathy, a participant

hospitalized for appendicitis; a participant hospitalized for suicide attempt, and a participant with epilepsy. These events were assessed as unrelated to study vaccination by the investigator. This reviewer agrees none of these events are related to placebo.

> *Reviewer Comment: For the cases of depression and/or suicidal ideation among mRNA-1273 recipients, given the past medical history, current events in the participants daily life, and as rates of these events were similar in the vaccine and placebo groups, this reviewer agrees there is no nexus that would suggest a causal relationship to mRNA-1273. This reviewer also agrees with the investigator's assessments that the remaining SAEs were not related to the study vaccine.*

The following SAEs occurred in mRNA-1273 recipients in the open-label phase:
An additional 12 mRNA-1273 recipients reported SAEs during the open-label phase, as of the data cutoff date of January 31, 2022. These events included hospitalizations for psychiatric disorders in the context of pre-existing diagnoses or precipitating factors, hospitalization for appendicitis, hospitalization after surgical correction for a pre-existing Arnold-Chiari malformation, hospitalization for idiopathic generalized epilepsy 285 days after Dose 2, hospitalization after motor vehicle trauma, and hospitalization for murine typhus. These events had prior medical history that would be consistent with the diagnoses during the study period. The investigators assessed these events as unrelated to study product given the clinical history and presentation.

> *Reviewer Comment: This reviewer agrees with the investigator's assessments that none of the SAEs reported among mRNA-1273 recipients during the open-label phase of the study was related to study vaccine.*

6.2.12.10 Adverse Events Leading to Discontinuation of Study Vaccine or Study Withdrawal

There were three total participants that reported an AE leading to discontinuation of vaccine. One mRNA-1273 recipient was discontinued from study vaccine and withdrew from the study due to drug induced liver injury as described above in Section 6.1.12.9. Another participant received one mRNA-1273 dose and later was found to have symptomatic COVID-19. In the electronic case report form, it was noted that a second dose of vaccine was not given based on parental preference to not administer a second dose with 90 days of the COVID-19 diagnosis. The investigators did not assess these two AEs as related to study product. Another participant was discontinued from further vaccination after reporting throat tightness 1 minute after the first dose of mRNA-1273. The investigator characterized this event as mild, which did not require any interventions and resolved after 10 minutes. The investigator assessed the event of throat tightness as related to mRNA-1273.

> *Reviewer Comment: Though the event of feeling throat tightness occurred 1 minute after receipt of Dose 1 of mRNA-1273, additional information was not available on this event and the participant was lost to follow-up. Because the participant reported minimal symptoms and did not require any medical assistance, with full resolution shortly after onset, the event does not appear to be consistent with anaphylaxis, however this reviewer agrees with the investigator's assessment that this event was related to mRNA-1273. This reviewer also agrees with the investigator's assessments that the two other AEs leading to discontinuation (events of liver injury and symptomatic COVID-19) were not related to mRNA-1273.*

6.2.13 Study Conclusions

In P203, a randomized, blinded, placebo-controlled, Phase 2/3 study, the 2-dose series (100 µg each) of Spikevax (Original monovalent) in vaccine naïve adolescents 12 through 17 years of age induced nAb GMTs and SRR that were non-inferior to those in young adults 18-25 years of age in Study P301, in whom clinical VE was demonstrated. In adolescents, VE against COVID-19 starting 14 days or more after Dose 2 was similar to that observed in adults in Study P301, though this was based on a small number of cases. Reactogenicity and safety profiles from adolescents in P203 were consistent with observations from the adult study (P301) and postmarketing experience. There was one case of vaccine-related myocarditis observed in the study. Taken together, data from Study P203 Part A, B and C support the safety and effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously vaccinated individuals 12-17 years of age.

6.3 Study P203 (Part C): Adolescent Booster Dose

NCT04649151

Title: A Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 to <18 years of age.

Study Overview: Study P203 was amended to include an open label booster, phase Part C-1 (Booster Phase or Part C) to evaluate a single 50 µg booster dose of original monovalent prototype (mRNA-1273) vaccine in adolescents 12 through 17 years (<18 years) at the time of enrollment in the primary phase (2-dose primary series, 100 µg each) of Study P203. A contemporaneous comparator vaccine group was not included in the design of the Booster Phase, and study participants were not blinded. Evaluation of mRNA-1273 booster dose was prompted to address public health needs associated with a rise in SARS-CoV-2 Delta variant cases during the pandemic. Participants were vaccinated with mRNA-1273 booster dose at least 5 months after receipt of primary series Dose 2. The study was conducted from December 27, 2021 to the data-cut off on August 15, 2022 and included 1405 vaccinated adolescents.

6.3.1 Objectives and Endpoints

Primary Objectives/Endpoints:

1. To evaluate the safety of the 50 µg booster dose (BD) of mRNA-1273

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

2. To infer effectiveness of the 50 µg of mRNA-1273 booster by establishing noninferiority of antibody responses after the booster dose compared to the primary series of mRNA-1273 based on Geometric Mean (GM) values of serum

antibody and SRR post-booster in Study P203 compared with primary series from young adult (18-25 years of age) recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301).

Reviewer Comment: In Amendment 5 to this protocol (mRNA-1273-P203), dated October 11, 2022, the Applicant changed Geometric Mean Titer (GMT) to Geometric Mean (GM) value for the co-primary endpoints in Part C of Study P203. Geometric Mean Concentrations (GMCs) were ultimately used for their analyses.

Endpoints:

- Geometric mean value of post-booster neutralizing antibody levels against D614G strain in Study P203 as compared to post-primary series (post-Dose 2) against D614G strain in the young adults in Study P301
- Seroresponse rate of post-booster from baseline (pre-Dose 1) as compared to post-Dose 2 from baseline (pre-Dose1) against D614G strain in the young adults in Study P301

Success Criteria

- Co-primary Endpoint 1: GMC
  The GMC ratio (adolescent booster/young adult primary series) is non-inferior if the lower bound (LB) of the 95% CI >0.667 (based on the noninferiority margin of 1.5) and the GMC ratio point estimate ≥0.8.

- Co-primary Endpoint 2: SRR
  The difference in the percentages of SRRs (adolescent booster minus young adult primary series) is non-inferior if the LB of the 95% CI ≥-10%.

Secondary Objectives/Endpoints:

1. To evaluate immune response elicited by the 50 µg prototype booster of mRNA-1273 against variant(s) of interest

Endpoints:

- Geometric mean value of post-booster (post-Dose 3) neutralizing antibodies against circulating strain as compared to post primary series (post-Dose 2) against circulating strain
- Seroresponse rate of post-booster/Dose 3 from baseline (pre-Dose 1) as compared to post Dose 2 from baseline (pre-Dose 1) against circulating strain using 4-fold rise definition

Reviewer Comment: For the key secondary endpoint evaluating mRNA-1273 immunogenicity testing and analysis for neutralizing antibodies (GM level and SRR) against the circulating strain were not performed for the CSR addendum submitted with this sBLA. This approach was considered acceptable because the 2022 updated bivalent booster mRNA-1273.222 was widely authorized for use and included antigenic components from the dominant circulating BA.4/BA.5 Omicron variants.

Exploratory Objectives/Endpoints:

1. To evaluate the incidence of SARS-CoV-2 infection or COVID-19 after vaccination with mRNA-1273

Endpoints:

- The incidence of SARS-CoV-2 infection (symptomatic or asymptomatic infection) counted starting 14 days after booster dose of mRNA-1273
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after booster dose in participants with negative SARS-CoV-2 at baseline or pre-booster
- The incidence of the first occurrence of symptomatic COVID-19 starting 14 days after booster dose of mRNA-1273

6.3.2 Design Overview

Study P203 is a Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 through 17 years of age. The primary phase of the study (Parts A and B) evaluated a 2-dose primary series of mRNA-1273 and are described in Section 6.2. In response to the global surge in COVID-19 cases due to the emergence of SARS CoV-2 Delta variant, the P203 protocol was amended in November 2021 to include a booster phase, to evaluate a booster dose of mRNA-1273. Part C of Study P203 was an open-label phase to evaluate the safety and immunogenicity of a 50 µg booster dose of mRNA-1273 in participants 12 through 17 years.[4]

Participants 12 through 17 years who completed a 2-dose primary series of mRNA-1273 (100 µg dose administered 28 days apart) in Part A or Part B of P203 were offered a 50 µg booster dose at least 5 months after completion of the primary series. Dosing started for Part C on December 27, 2021. A total of 1405 participants from Parts A or B were administered a booster dose (BD) in Part C of the study at least 5 months after completing the primary series in Parts A or B. Participants follow-up was planned for 1-year post-booster dose vaccination; however, the study was stopped early after the EUA of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to authorize its use in adolescents 12-17 years of age.

> *Reviewer Comment: Despite the early termination of Study P203 Part C, at the time of data cutoff (August 15, 2022) 1204/1405 (85.7%) of study participants had ≥6 months of safety follow-up. These safety data are supplemented with studies in older age cohorts with large safety populations, which taken together, provide an acceptable safety database for this vaccine in adolescents 12 through 17 years.*

6.3.3 Population

See original Spikevax BLA memo for further details on eligibility criteria for Study P203. Adolescent participants 12 through 17 years at the time of enrollment in Study P203

4 In Study P203, only the birth year and month were collected, and they were only collected once at the time of enrollment (time of first dose of primary series). To estimate the age of participants at the time of BD, the Applicant imputed 15 as a birth date and then calculated the following statistics: mean=15.5, median=15, min=13, and max=19 for the Safety Set; and mean=15.3, median=15, min=13, and max=19 for the PPIS-Negative.

Parts A or B, were eligible to be enrolled in the Booster Phase (Part C), if they were at least 5 months from their last mRNA-1273 dose.

6.3.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273 is a nucleoside modified mRNA that encodes for the full-length spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-2P spike protein into a prefusion conformation, and encapsulated in lipid particles.

Each 0.25 mL injection contained 50 µg of mRNA-1273.

Lots: 7006320007 and 7007421002

6.3.5 Directions for Use

mRNA-1273 was administered as an intramuscular injection into the deltoid muscle, preferentially to the nondominant arm.

6.3.6 Sites and Centers

Study P203 Part C (Booster Phase) was conducted at 25 study sites in the U.S.

6.3.7 Surveillance/Monitoring

Immunogenicity

Blood samples were collected from a random subset of participants (Immunogenicity Subset) for immunogenicity assessments at pre-BD baseline and on Days 29, 181, and 361 post-BD. Immunogenicity assessments included the following:

- Serum nAb levels against SARS-CoV-2 strain D614G as measured by PsVNA. Immunogenicity analyses for the Booster Phase were based on nAb concentrations measured using a validated pseudovirus neutralization assay against D614G conducted at PPD Vaccine Laboratories. nAb concentrations were measured in both the group of adolescent booster dose recipients in P203 Part C and the P301 comparator group of young adults. nAb levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses. This differed from the Duke pseudovirus neutralization assay used previously for other parts of P203 and Study P301 which reported results as 50% inhibitory dose (ID50) neutralization titers.
- Serum bAb were measured by an MSD-ECL Multiplex ligand-binding assay (b) (4) specific to the SARS-CoV-2 S-protein (D614G as well as Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1], and Delta [B.1.617.2] variants), RBD, and N-protein were measured by multiplex assay.

Reviewer Comment: Immunogenicity assessments were planned for Days 29, 181, and 361 post-BD, but only immunogenicity at Day 29 was submitted to this sBLA. As mentioned previously, this study was stopped early after the authorization of the bivalent booster on August 31, 2022.

COVID-19 Surveillance

Surveillance for COVID-19 symptoms was conducted via a combination of biweekly telephone calls and electronic diary (e-diary) prompts from enrollment through the end of the study. Definitions of COVID-19 cases and SARS-CoV-2 infections used in Study

P203 are presented in Appendix C. A study illness visit or consultation was arranged as soon as possible, and within 72 hours, to collect NP or nasal swabs for any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

NP or nasal swab samples were tested for SARS-CoV-2 at a central laboratory using an authorized RT-PCR test whenever possible, or other sufficiently validated NAAT conducted in a clinical laboratory improvement amendments (CLIA)-certified laboratory. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory. Any confirmed symptomatic SARS-CoV-2 infection occurring in participants was captured as a MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome and a convalescent visit was scheduled approximately 28 days (+7 days) after diagnosis.

Safety

Safety assessments included the following:

- Solicited local and systemic ARs that occurred during the 7 days following BD (starting on the day of vaccination and followed by 6 subsequent days). Solicited ARs were recorded using e-diaries.
- Unsolicited AEs observed or reported during the 28 days following BD (starting the day of vaccination and followed by 27 subsequent days)
- AEs leading to discontinuation from study participation from time of BD through the last day of study participation.
- MAAEs from time of BD through the entire study period.
- SAEs from time of BD through the entire study period.
- AESIs through the entire study period.
- Vital sign measurements.
- Physical examination findings.
- Details of all pregnancies in female participants from the time of BD until the end of their participation in the study.

Safety follow-up visits or calls occurred on Days 4, 8, 15, 22, 29, 271, and 361. 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.

Following the EUA of COVID-19 vaccines, post-authorization safety data suggested a possible association between myocarditis and/or pericarditis and COVID-19 mRNA vaccines. Therefore, the Applicant developed supplemental safety monitoring plans to identify unrecognized myocarditis/pericarditis cases in the clinical studies. Enhanced surveillance was implemented by modifying the safety script used in routine safety calls, which specifically solicited for symptoms associated with myocarditis/pericarditis.

All potential cases of myocarditis and pericarditis, as identified by the investigator or Applicant, were reviewed by an independent Cardiac Event Adjudication Committee (CEAC) to determine whether the case met the CDC criteria (Appendix D) 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.

6.3.8 Endpoints and Criteria for Study Success

See Sections 6.1.1 and 6.1.9.

For the key secondary endpoint planned in the protocol, the immunogenicity testing and analyses for neutralizing antibodies (GM level and SRR) against the circulating strain were not performed for the CSR addendum submitted with this sBLA because Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized for use and included antigenic components from the dominant circulating Omicron BA.4/BA.5 variants.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity Analyses

In the Booster Phase, the non-inferiority (NI) of the GMC levels and SRR against the Original SARS CoV-2 strain in BD adolescents in Study P203 at 28 days after BD compared with young adults (18-25 years) in Study P301 at Day 57 (28 days after Dose 2 in the primary series) was assessed.

The protocol specified success criteria for the co-primary endpoints were:

Co-primary Endpoint 1: GMC
The GMC ratio (adolescent booster/young adult primary series) is non-inferior if the lower bound (LB) of the 95% CI >0.667 (based on the noninferiority margin of 1.5) and the GMC ratio point estimate ≥0.8.

Co-primary Endpoint 2: SRR
The difference in percentages of the SRRs (adolescent booster minus young adult primary series) is non-inferior if the LB of the 95% CI ≥-10%.

The primary immunogenicity objective for the Booster Phase is met if NI for both co-primary endpoints of GMC ratio and difference in SRR are demonstrated. The GMC ratio with 95% CI to compare post-BD GMC in adolescents with post-Dose 2 GMC in young adults was computed based on the t-distribution of mean difference in the log transferred values and then back-transformed to the original scale. The SRR at the analysis time point was computed with 2-sided 95% Clopper-Pearson CI, and the SRR difference with 2-sided 95% CI (using Miettinen-Nurminen score method) was calculated. The seroresponse at participant level was defined as antibody measures change from pre-Dose 1 below the LLOQ to ≥4 × LLOQ, or at least a 4-fold-rise if pre-Dose 1 was ≥LLOQ.

Analysis Timing

Study P203 Part C was terminated early following the August 31, 2022, EUA for the bivalent booster in adolescents 12-17 years of age. For this sBLA, a CSR Addendum was submitted for Study P203 Part C, which includes additional data up to the final data cutoff date of August 15, 2022.

Safety Analyses

Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event. Only the maximum severity was reported. Subgroup analyses were provided based on age

group (12-15 years, 16-17 years), sex (male, female), pre-booster SARS-Cov-2 status, race, and ethnicity.

6.3.10 Study Population and Disposition

This sBLA submission includes data from the start of enrollment for the Booster Phase Part C on December 27, 2021, through the data cutoff date of August 15, 2022. A total of 1,405 participants received a booster dose in this phase of the study: 1,356 of whom received their primary series in Part A and 49 of whom received their primary series during the Part B cross-over phase. The study analyses discussed below will be based on this combined total of 1,405 participants.

6.3.10.1 Populations Enrolled/Analyzed

The analyses population used for study analyses are defined in Table 29. Immunogenicity analyses were conducted on the Per Protocol Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative (PPIS-Neg). Safety analyses were conducted on the Safety Set except for summaries of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 29. Analysis Populations, Study P203 Booster Phase Part C

Population	Description
Safety Set	All participants who received a BD.
Solicited Safety Set	All participants who received BD and contributed any solicited AR data (i.e., had at least one post-booster solicited safety assessment).
FAS	All participants who received at least 1 BD.
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing that consisted of: • Participants with baseline SARS-CoV-2 status available, and • Participants with baseline (pre-Dose 1), and at least 1 • post-booster antibody assessment for the analysis endpoint.
PP Immunogenicity Subset (PPIS)	All participants in the Immunogenicity Subset who met all the following criteria: • Received 2 doses of mRNA-1273 in the Blinded Phase per schedule • Received BD • Had a negative SARS-CoV-2 status at baseline (pre-Dose 1 of the Blinded Phase) • Had BD-Day 1 and BD-Day 29 antibody assessment for the analysis endpoint • Had no major protocol deviations that impacted key or critical data
PP Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative (PPIS-Neg)	Participants who were in the PPIS and were pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster), i.e., RT-PCR result was not positive if available at BD-Day 1 and a negative binding antibody specific to SARS-CoV-2 N-protein (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before BD-Day 1.

Source: FDA-generated table
Abbreviations: BD=booster dose; AR=adverse reaction; FAS=full analysis set; RT-PCR=reverse transcription-polymerase chain reaction

6.3.10.1.1 Demographics

The PPIS-Neg analyses population, which contributed to the co-primary immunogenicity endpoints for the study, included 264 adolescent participants who received 100 µg mRNA-1273 2-dose primary series (each dose 100 µg) and 50 µg booster dose in Study P203; and for the comparator group, included 295 young adult participants who received the 2-dose primary series (each dose 100 µg) of mRNA-1273 in Study P301 (Table 30). In the adolescent population, 17.4% were 16-17 years of age and 82.6% were 12-15 years of age. Both sexes were equally represented. In Study P203, 22.3% of adolescent participants were non-White and/or Hispanic compared to 50.5% of adult participants who were non-White and/or Hispanic participants in Study P301. There was a lower percentage of participants from P203 who were obese as compared to those from P301. Participant demographics were collected at the time of enrollment to primary phase of Study P203 as part of the initial Screening Visit and, other than height and weight, were not updated at the time of booster dose administration. In Study P203, only the birth year and month were collected, and they were only collected once at the time of enrollment (time of first dose of primary series). The Applicant imputed a birth date of 15 to estimate ages at the time of BD administration. Baseline characteristics were generally similar between participants in the PPIS-Neg and PPIS (not shown).

In the PPIS-Neg for participants 12-17 years, the median duration between Dose 2 of primary series to receipt of the booster dose was 295 days (~10 months). The minimum requirement for enrollment in the Booster Phase was at least 5 months after Dose 2 of the primary series.

Table 30. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age, Study P203 Part C (PPIS-Neg) and 18 Through 25 Years of Age, Study P301 (PPIS)

Characteristics	P203 12-17 years mRNA-1273 50 µg Booster Dose n (%) N=264	P301 18-25 years mRNA-1273 100 µg Primary Series n (%) N=295
Sex, n (%)	--	--
Female	130 (49.2)	152 (51.5)
Male	134 (50.8)	143 (48.5)
Age[a]	--	--
Median (Years)	15.0	23.0
13 to <16 years, n (%)	218 (82.6)	--
16 to ≤19 years, n (%)	46 (17.4)	--
Race, n (%)	--	--
American Indian or Alaska Native	0	3 (1.0)
Asian	9 (3.4)	30 (10.2)
Black	4 (1.5)	29 (9.8)
Multiracial	15 (5.7)	14 (4.7)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
Not reported	1 (0.4)	3 (1.0)
Other	3 (1.1)	8 (2.7)
White	232 (87.9)	206 (69.8)
Ethnicity, n (%)	--	--

Characteristics	P203 12-17 years mRNA-1273 50 µg Booster Dose n (%) N=264	P301 18-25 years mRNA-1273 100 µg Primary Series n (%) N=295
Hispanic or Latino	33 (12.5)	77 (26.1)
Non-Hispanic or non-Latino	229 (86.7)	216 (73.2)
Not reported	2 (0.8)	0
Unknown	0	2 (0.7)
Obesity[b], n (%)	--	--
Obese	47 (17.8)	67 (22.7)
Non-Obese	217 (87.2)	227 (76.9)
Missing	0	1 (0.3)
Time Since Primary Series Dose 2 to Booster Dose	--	--
Median (Days) (min, max)	295 (274, 357)	--

Source: sBLA 125752/68, Study P203 Part C, Table 14.1.3.14.3
Notes: N=total number of participants in the analysis set; n=number of participants fulfilling the item; PPIS-Neg=Per Protocol Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative
a. In Study P203, only the birth year and month were collected, and they were only collected once at the time of enrollment (time of first dose of primary series). To estimate the age of participants at the time of BD, the Applicant imputed 15 as a birth day and then calculated the following statistics: mean=15.3, median=15, min=13, and max=19 for the PPIS-Negative.
b. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m^2 for P301.
Participant demographics for P203 Part C are based on those collected at the time of enrollment to Study P203.

The demographic characteristics of the Safety Set for booster recipients in P203 are shown in Table 31 below. In the Safety Set, 6.7% of participants had evidence of prior SARS-CoV-2 infection at baseline (pre-Dose 1 of primary series) and 42.5% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 31. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age, Study P203 Part C Booster Phase, Safety Set

Characteristic	Study P203 Part C 12-17 Years mRNA-1273 50 µg BD n (%) N=1405
Sex, n (%)	--
Female	682 (48.5)
Male	723 (51.5)
Age[a]	--
Median (Years)	14.0
12 to <16 years, n (%)	1126 (80.1)
16 to <18 years, n (%)	279 (19.9)
Race, n (%)	--
White	1193 (84.9)
Black	44 (3.1)
Asian	69 (4.9)
American Indian or Alaska Native	7 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	73 (5.2)
Other	10 (0.7)
Not reported	4 (0.3)

Characteristic	Study P203 Part C 12-17 Years mRNA-1273 50 µg BD n (%) N=1405
Unknown	4 (0.3)
Ethnicity, n(%)	--
Hispanic or Latino	188 (13.4)
Non-Hispanic or non-Latino	1206 (85.8)
Not reported	11 (0.8)
Obesity[b], n (%)	--
Obese	278 (19.8)
Non-Obese	1127 (80.2)
Baseline (pre-Dose 1) SARS-CoV-2 status[c], n (%)	--
Positive	94 (6.7)
Negative	1238 (88.1)
Missing	73 (5.2)
Pre-booster SARS-CoV-2 status[d], n (%)	--
Positive	597 (42.5)
Negative	752 (53.5)
Missing	56 (4.0)
Time Since Primary Series Dose 2 to Booster	--
Median (Days) (min, max)	315 (63, 514)

Source: sBLA 125752/68, Study P203 Part C, Tables 14.1.6.5.1, 14.1.3.14.1
Abbreviations: BD=booster dose; min=minimum; max=maximum; N=total number of participants in the analysis set; n=number of participants fulfilling the item; SD=standard deviation.
Notes:
a. In Study P203, only the birth year and month were collected, and they were only collected once at the time of enrollment (time of first dose of primary series). To estimate the age of participants at the time of BD, the Applicant imputed 15 as a birth day and then calculated the following statistics: mean=15.5, median=15, min=13, and max=19 for the Safety Setb. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m^2 for P301.
Participant demographics for P203 Part C are based on those collected at the time of enrollment to Study P203
c. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive
RT-PCR test or positive Elecsys result at Day 1 in Part A. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1 in Part A.
d. Pre-booster SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at BD-Day 1 in Part C. Negative is defined as negative RT-PCR test and negative Elecsys result at BD-Day 1 in Part C.

Reviewer Comment: The large increase in baseline seropositivity pre-single dose relative to pre-two-dose series in the original study (42.5% versus 15.6%) is likely a reflection of the Omicron surge that took place during winter 2021-2022, which coincided with study enrollment of the Booster Phase.

6.3.10.1.2 Participant Disposition

Participant disposition for P203 Booster Phase Part C is presented below in Table 32 by analyses population. Discontinuation was rare and occurred in 3.4% of participants in the Booster Phase-Part C. The most common reason for discontinuation was withdrawal of consent, reported in 2.1% of participants. No participant discontinued due to an AE. Among the 1,405 participants in the Safety Set, 1,351 participants (96.2%) were included in the Solicited Safety Set. As of the data cutoff of August 15, 2022, a total of 1,204 participants (85.7%) have had at least 6 months of safety follow-up post-BD.

The Immunogenicity Subset included 374 participants, of which 327 participants were included in the Per Protocol Immunogenicity Subset and 264 were included in the PP Immunogenicity Subset-Pre-booster SARS-CoV-2 Negative (PPIS-Neg). The most common reason for exclusion from the PP Immunogenicity Subset was no immunogenicity data at 28 days post-BD (7.5%).

Table 32. Disposition of Adolescent Participants 12-17 Years in Study P203, Booster Phase Part C, All Enrolled

Disposition	Study P203 Part C 12-17 Years mRNA-1273 50 µg BD n (%)
Full Analysis Set	**N=1405**
Discontinued from study[a]	49 (3.5)[b]
Reason for discontinuation of study[a]	--
Lost to follow up	12 (0.9)
Withdrawal of consent by participant	30 (2.1)
Protocol deviation	2 (0.1)
Received another COVID-19 vaccine under EUA	1 (<0.1)
Other[c]	4 (0.3)
Safety Set	**N=1405**
Completed 6 months safety follow-up post BD[d]	1204 (85.7)
Solicited Safety Set[d]	1351 (96.2)
Immunogenicity Subset	**N=374**
PP Immunogenicity Subset[e]	327 (87.4)
Excluded from PP Immunogenicity Subset	47 (12.6)
Reason for exclusion from the PP Immunogenicity Subset	--
Positive baseline SARS-CoV-2 status in Part A	14 (3.7)
Had no Immunogenicity data at BD-Day 29	28 (7.5)
Had no Immunogenicity at BD-Day 1	5 (1.3)
PP Immunogenicity Subset-Pre-booster SARS-CoV-2 Negative (PPIS-Neg)[e]	264 (70.6)
Excluded from PPIS-Neg	63 (16.8)
Reason for exclusion from PPIS-Neg	--
Positive pre-booster SARS-CoV-2 status	51 (13.6)
Missing pre-booster SARS-CoV-2 status	12 (3.2)

Source: sBLA 125752/68, Study P203 Part C, Tables 14.1.1.1.5, 14.1.2.7.1, 14.1.2.1.5 , 14.1.6.5.1
Abbreviations: BD=booster dose; PP=per-protocol
Notes:
a. Percentages are based on the number of subjects in the Full Analysis Set Part C
b. One (<0.1%) participant was erroneously reported to have completed the study but had in fact withdrawn from study (clarified by site after database lock)
c. "Other" reasons for discontinuation from study included the participant's school schedule interfering with study visits, participant receiving a Pfizer COVID booster vaccine, and participant moving to another location and being unable to follow-up
d. Percentages are based on the number of subjects in the Immunogenicity Subset Part C
e. Percentages are based on the number of subjects in the Safety Set

6.3.11 Analyses of Vaccine Effectiveness

6.3.11.1 Analyses of Primary Endpoint

Vaccine effectiveness of the mRNA-1273 booster dose in the adolescent population was inferred based on the evaluation of nAb GMC and SRR against the Original SARS-

CoV-2 strain (D614G) elicited after a booster dose in P203 Part C compared to those after the primary series in young adults from Study P301, in whom efficacy was previously demonstrated. The co-primary endpoints, described in Section 6.1.8, were assessed in participants without evidence of prior SARS-CoV-2 infection pre-booster (PPIS-Neg) for the adolescent group and without evidence of prior SARS-CoV-2 infection pre-primary series (PPIS) for the young adult group.

Results for the co-primary endpoint of GMC ratio (adolescents/young adults) are displayed in Table 33, below. The GMC ratio was 5.1 (95% CI 4.5, 5.8) which met the pre-specified success criteria of a lower bound (LB) of the 95% CI >0.667 and a point estimate ≥0.8.

Table 33. Geometric Mean Antibody Concentration (GMC) as Measured by Pseudovirus Neutralizing Antibody Assay Against D614G at 28 Days Post-Booster Dose, Adolescent Participants 12-17 Years, Study P203 Part C, PPIS-Neg Compared to 28 Days Post-Primary Series, Young Adult Participants 18-25 Years, Study P301, PPIS

Study P203 Part C 12-17 Years mRNA-1273 50 µg BD GMC [95% CI][a] N1=264	Study P301 18-25 Years mRNA-1273 100 µg Primary Series GMC [95% CI][a] N1=294	GMC Ratio [95% CI][a]	Met Success Criterion[b]
7102.0 [6553.2, 7696.8]	1400.4 [1272.7, 1541.0]	5.1 [4.5, 5.7]	Yes

Source: sBLA 125752/68, Study P203 Part C, Tables 14.2.1.1.3.5.1.1
Abbreviations: BD=booster dose; CI=confidence interval; GMC=geometric mean concentration; N1=Number of subjects with non-missing data at baseline and the corresponding timepoint; nAB=neutralizing ant body
Notes:
LLOQ: 10, ULOQ: 281600
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
a. The log-transformed ant body levels are analyzed using t-test method with the group variable (adolescents in P203 and young adults in P301) and 95% CI is calculated based on the t-distribution of the difference in the log-transformed values for GM value. The resulted means and 95% CI are back transformed to the original scale for presentation.
b. Success criterion: the lower bound of the 95% CI of the GMC ratio is > 0.667and point estimate ≥0.8.

Among the adolescent booster dose recipients in Study P203 who were included in the PPIS-Negative Subset, the GMC observed at 28 days post-booster dose was approximately 18-fold higher compared to the GMC observed immediately pre-booster, and approximately 4-fold higher compared to the GMC observed at 28 days post-primary series.

Results for the co-primary endpoint of difference in percentages of SRRs (pre-Dose 1 primary series to post-booster dose) between adolescents and young adults are displayed in Table 34, below. The difference in percentages of SRRs was 0.7% (95% CI -0.8, 2.4) which met the pre-specified success criterion of a LB of the 95% CI ≥ -10%.

Table 34. Seroresponse Rate (SRR) as Measured by Pseudovirus Neutralizing Antibody Assay Against D614G at 28 Days Post-Booster Dose (from pre-Dose 1), Adolescent Participants 12-17 Years (Study P203 Part C, PPIS-Neg) Compared to 28 Days Post-Primary Series, Young Adult Participants 18-25 Years (Study P301, PPIS)

Study P203 Part C 12-17 Years 50 µg Booster Dose SRR[a] % [95% CI][b] N1=264	Study P301 18-25 Years 100 µg Primary Series SRR[a] % [95% CI][b] N1=294	Difference in SRR % (Adolescents minus Young Adults) [95% CI][c]	Met Success Criterion[d]
100% [98.6, 100.0]	99.3% [97.6, 99.9]	0.7% [-0.8, 2.4]	Yes

Source: sBLA 125752/68, Study P203 Part C, Tables 14.2.1.2.3.5.1.1
LLOQ: 10, ULOQ: 281600
Abbreviations: CI=confidence interval; N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint; nAb=neutralizing antibody; SRR=seroresponse rate
a. Seroresponse from pre-Dose 1 baseline at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on N1
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
d. Success criterion: the lower bound of the 95% CI in SRR difference is ≥-10%.

Because the seroresponse definition for P203 Part C participants was based on the change from pre-Dose 1 of the primary series, FDA requested a post hoc analysis using a revised seroresponse definition based on the proportion of adolescent participants achieving a ≥4-fold rise in nAb concentrations from the pre-booster time point (BD Day 1) to assess for the change in nAb concentration attributable solely to the booster dose. For this descriptive post hoc analysis, seroresponse following booster was defined as follows:

- Seroresponse for participants with pre-booster nAb concentrations <LLOQ, as a post-booster nAb concentration ≥4 x LLOQ,
- Seroresponse for participants with pre-booster nAb concentrations ≥LLOQ, as ≥4-fold rise in those with pre-booster nAb concentration.

In this post hoc analysis, the percentage difference between this adolescent SRR in Study P203 and the young adult SRR in Study P301 was -2.7% (95% CI: -5.8, -0.5), which also would have met the NI criterion (lower bound of the 95% CI of the SRR difference >-10%). The lower SRR observed among booster recipients 12-17 years using this revised seroresponse definition was likely due to the substantially higher pre-booster GMC in participants 12-17 years (398.9 AU/mL) compared to the pre-Dose 1 GMC in participants 18-25 years (11.1 AU/mL), making it more difficult comparatively for participants 12-17 years to achieve the 4-fold rise required to demonstrate seroresponse.

6.3.11.2 Subpopulation Analyses

Most of the study participants in Study P203 Part C were White and Non-Hispanic; therefore, subgroup analyses by race and ethnicity were not conducted because the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results. The GMC ranges post-booster were similar among adolescents 12-15 years and 16-17 years. When these two age subcohorts were analyzed separately against young adults from P301, the GMC ratios, SRR, and associated 95% CIs would have met study success criteria for both age cohorts.

Subgroup analyses by sex were comparable between males and females. nAb GMCs were notably higher after booster vaccination in participants 12-17 years with evidence of prior SARS-CoV-2 infection pre-booster compared to those with negative SARS-CoV-2 status pre-booster.

6.3.11.3 Analyses of Secondary Endpoints

For the key secondary endpoint planned in the protocol, the immunogenicity testing for nAb GMC and SRR against current circulating strains were not performed for this sBLA submission because the study vaccine, mRNA-1273, encoded the Original Wuhan strain, and was no longer authorized for use in the U.S. Furthermore, this 2023-2024 Formula sBLA considers the effectiveness of a vaccine encoding the XBB.1.5 S protein.

6.3.11.4 Dropouts and/or Discontinuations

6.3.11.5 Exploratory and Post Hoc Analyses

COVID-19 Incidence Rates

Study P203 Part C was not designed to assess the efficacy of a booster dose in preventing COVID-19 disease. Additionally, the booster and non-booster groups were not randomized, were highly dynamic (with those in the non-booster group receiving the booster) and were subject to varying degrees of community transmission. As such, any meaningful comparison between the booster and non-booster groups is significantly limited. No cases of severe COVID-19 were reported.

Excluding Participants with Post-boost SARS-CoV-2 Infection

In the PPIS-Neg subset (N=264), 40 participants were diagnosed with SARS-CoV-2 infection during the interval between receipt of BD and BD-Day 29 (based on positive RT-PCR or positive Elecsys anti-SARS-CoV-2 assay). A sensitivity analysis of the co-primary endpoints of GMT ratio and percentage difference in SRR, excluding these 40 participants with evidence of post-BD infection, showed no meaningful change in the overall results. The study would still have met the pre-specified success criteria for both co-primary endpoints.

Booster Interval

In those participants (n=49) who received placebo initially in the blinded Primary Phase, and then were unblinded to receive the mRNA-1273 2-dose primary series followed by 50 µg mRNA-1273 booster dose (Placebo-mRNA-1273-Booster group), the median time from primary series Dose 2 to BD was 185 days, with 60% receiving the BD between 168 and 223 days following Dose 2 of the primary series. In those participants (n=1356) who received mRNA-1273 initially in the blinded Primary Phase, and then unblinded to receive the 50 µg mRNA-1273 booster dose (mRNA-1273-Booster group), the median time from primary series Dose 2 was 316 days, with 98% receiving the BD between 280 and 391 days following Dose 2 of the primary series. An analysis of the impact of time interval on immunogenicity is challenging given the relatively minimal variation in the time interval between Dose 2 of the primary series and the BD between participants.

6.3.12 Safety Analyses

There were 1405 participants included in the Safety Set, of which 1204 (85.7%) completed at least 6 months of safety follow-up post-BD by the data cutoff of August 15, 2022. The median duration of safety follow-up was 204 days from BD.

6.3.12.1 Methods

See Section 6.1.7 above.

6.3.12.2 Overview of Adverse Events

Table 35 below summarizes AEs among booster dose recipients in the Booster Phase of Study P203. The proportion of participants who reported at least one solicited local and systemic ARs within 7 days post-booster dose were reported by 91.5% and 75.9% of study participants, respectively.

Among booster recipients, 14.9% (n=209) reported unsolicited AEs occurring within 28 days following booster administration, while severe unsolicited AEs were rare, reported in 0.3% (n=4) of participants (events of vomiting, fatigue [n=2], and hypersensitivity). Through data cutoff, MAAEs were reported in 26.2% (n=368) of booster recipients, with only 0.2% (n=3) which were considered related. SAEs and AESIs were reported by 0.4% (n=6) and 0.1% (n=2) of booster recipients, respectively, and are discussed further in Sections 6.3.12.8 and 6.3.12.6.

Table 35. Number and Percentage of Participants Reporting at Least One Safety Event, Participants 12 Through 17 Years, Study P203 Part C, Safety Set and Solicited Safety Set

Event Type	P203 Part C 12-17 Years mRNA-1273 50 µg Booster Dose n (%)
Solicited adverse reactions within 7 days[a]	**N1=1350-1351**
Solicited local adverse reaction	1236 (91.5)
Grade 3 solicited local adverse reaction	62 (4.6)
Solicited systemic adverse reaction	1024 (75.9)
Grade 3 solicited systemic adverse reaction	111 (8.2)
Unsolicited adverse events[b]	N=1405
Unsolicited adverse event up to 28 days after booster injection	209 (14.9)
Non-serious unsolicited adverse event	209 (14.9)
Related non-serious unsolicited AE	59 (4.2)
Severe non-serious unsolicited AE	4 (0.3)
Related severe non-serious unsolicited AE	3 (0.2)
Medically attended adverse events[c]	368 (26.2)
Related MAAE[c]	3 (0.2)
SAE[c]	6 (0.4)
AESI[c]	2 (0.1)
Deaths[c]	0
AE leading to study discontinuation[c]	0

Source: sBLA 125752/68, Study P203 Part C, Tables 14.3.1.1.1.5.1, 14.3.1.7.5.1.1, 14.3.1.7.5.2.1
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BD=booster dose; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants who received a booster dose in Part C; N1=Number of exposed participants who submitted any data for the event;
Notes:
a. Percentages are based on the number of exposed participants who submitted any data for the event (N1)
b. Percentages are based on the number of safety participants in Part C.
c. All numbers reflect AEs reported through the data cut-off of Aug 15, 2022.
The Safety Set (N) consists of all participants who received a booster dose in Part C. The Solicited Safety Set (N1) consists of all participants who received booster dose in Part C, and contributed any solicited AR data, ie, had at least one post-booster solicited safety assessment in Part C. There were no reported Grade 4 adverse reactions or events.

6.3.12.3 Solicited Adverse Reactions

The frequency and severity of solicited local and systemic adverse reactions within 7 days following the booster dose are shown below in Table 36 and Table 37. Assessment of booster dose reactogenicity is limited by the open-label study design for this part of P203. To provide a frame of reference to assess the rates of solicited adverse reactions following a booster dose, the rates of solicited adverse reactions following Dose 1 and Dose 2 (28-day dosing interval) of the primary series (double-blinded Study P203 Part A, reviewed in Section 6.2) are included in these tables.

By order of frequency (>10% of participants), adverse reactions in participants 12 through 17 years of age within 7 days following administration of the booster dose of mRNA-1273 were pain at the injection site (90.6%), fatigue (58.1%), headache (56.3%), myalgia (40.1%), chills (30.2%), axillary swelling or tenderness (27.8%), arthralgia (23.9%), nausea/vomiting (17.9%), and swelling (13.3%).

Solicited Local Reactions

Table 36 presents frequencies and severities of reported solicited local adverse reactions (ARs) within 7 days following booster dose. Overall, the reported rates of solicited local ARs following a booster dose appeared to be similar with that reported following Dose 2 of the primary series (91.5% vs. 93.4%, respectively). Injection site pain was the most frequently reported solicited local AR following booster dose. Most of the solicited local ARs following booster dose were Grade 1 or Grade 2, with Grade 3 solicited local ARs reported by 4.6% of BD recipients, which was lower compared to that reported after Dose 2 of the primary series (9.8%). No Grade 4 solicited local ARs were reported within 7 days following booster dose.

Most (>90%) solicited local ARs reported within 7 days following booster dose occurred within 1 to 2 days post-vaccination, with a median onset of 1-day post-vaccination and resolved after a median of 3 days (range 1 to 33 days). Solicited local ARs persisting beyond 7 days post-booster were reported by 1.3% of participants.

Delayed solicited local reactions (defined as beginning after Day 7) were reported by one (<0.1%) booster dose recipients in the Safety Set (N=1405). The one participant reported ARs of pain and swelling with onset occurring 11 days post-vaccination and had a duration of 1 day.

Table 36. Frequency of Solicited Local Adverse Reactions in Adolescent Participants 12 Through 17 Years Within 7 Days of Primary Series Dose 1 & Dose 2 (Study P203, Part A) and 7 Days of Booster Dose (Study P203 Part C), Solicited Safety Set

Event	Study P203, Part A 12-17 Years Primary Series Dose 1 mRNA-1273 100 µg n (%) N=2482	Study P203, Part A 12-17 Years Primary Series Dose 2[a] mRNA-1273 100 µg n (%) N=2478	Study P203 Part C 12-17 Years Booster Dose[b] mRNA-1273 50 µg n (%) N=1351
Local adverse reaction	N1=2482	N1=2478	N1=1351
Any	2339 (94.2)	2314 (93.4)	1236 (91.5)
Grade 3	171 (6.9)	220 (8.9)	62 (4.6)
Pain	N1=2482	N1= 2478	N1=1351
Any	2310 (93.1)	2290 (92.4)	1224 (90.6%)
Grade 3[c]	133 (5.4)	126 (5.1)	44 (3.3)
Erythema (redness)	N1=2482	N1= 2478	N1= 1350
Any ≥25 mm	329 (13.3)	484 (19.5)	121 (9.0)
Grade 3[d]	22 (0.9)	72 (2.9)	10 (0.7)
Swelling (hardness)	N1=2482	N1= 2478	N1=1350
Any ≥25 mm	401 (16.2)	508 (20.5)	180 (13.3)
Grade 3[d]	27 (1.1)	56 (2.3)	10 (0.7)
Axillary swelling or tenderness	N1=2481	N1= 2477	N1=1350
Any	576 (23.2)	519 (21.0)	375 (27.8)
Grade 3[c]	11 (0.4)	7 (0.3)	5 (0.4)

Source: sBLA 125752/68, Study P203 Part C, Tables 14.3.1.1.1.5.1 for Part C; Table 14.3.1.1.1.1 and Table 14.3.1.1.1.2 for Part A.
Notes:
N=The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post Dose-2, or 1 post-booster solicited safety assessment through 6 days post-vaccination).
N1=Number of exposed participants who submitted any data for the event
No grade 4 solicited local adverse reactions were reported.
Any=Grade 1 or higher.
a. 28-day interval between primary series dose 1 and primary series dose 2
b. Median of 316 days between primary series dose 2 and booster dose
c. Pain and axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity
d. Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm
The primary series phase of Study P203 (Part A) *was not* conducted contemporaneously with the Booster Phase (Part C).

Solicited Systemic Reactions

Table 37 presents frequencies and severities of reported solicited systemic reactions within 7 days following booster dose. Overall, the percentage of participants reporting solicited systemic ARs within 7 days following booster dose was lower relative to those reported following Dose 2 of the primary series (75.9% vs. 86.1%, respectively). Similarly, the percentage of participants reporting Grade 3 or higher solicited systemic ARs within 7 days following booster dose was lower when compared to that reported within 7 days following Dose 2 of the primary series (8.2% vs. 13.8%, respectively). Fatigue and headache were the most frequently reported systemic ARs, reported in 58.1% and 56.3% of booster recipients, respectively. Systemic ARs following booster dose were mostly Grade 1 or Grade 2. There were no Grade 4 systemic ARs reported after the booster dose. Fever was reported by 6.1% of booster recipients compared with 2.3% and 12.0% of mRNA-1283 recipients after Dose 1 and Dose 2 of the primary

series, respectively. Fever ≥39°C post-booster was rare and was reported by 0.6% of booster recipients. Of the 1351 participants in the Solicited Safety Set, 146 (10.8%) took medication to prevent pain or fever, and 476 (35.2%) took medication to treat pain or fever.

Solicited systemic ARs had a median onset of 1 day post-booster and resolved after a median of 2 days (range 1 to 27 days). Solicited systemic ARs persisting beyond 7 days post-booster were reported by 4.7% (64/1351) of participants.

Table 37. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 12 Through 17 Years, Study P203, Solicited Safety Set

Event	Study P203 12-17 Years mRNA-1273 100 µg Primary Series Dose 1 n (%) N=2482	Study P203 12-17 Years mRNA-1273 100 µg Primary Series Dose 2[a] n (%) N=2478	Study P203 12-17 Years Booster Dose[b] mRNA-1273 50 µg n (%) N=1350
Any systemic adverse reaction	N1=2482	N1=2478	N1=1350
Any	1701 (68.5)	2134 (86.1)	1024 (75.9)
Grade 3	108 (4.4)	341 (13.8)	111 (8.2)
Grade 4	0	3 (0.1)	0
Fever	N1=2480	N1=2477	N1=1335
Any: ≥38.0°C	57 (2.3)	298 (12.0)	81 (6.1)
Grade 3: 39°C to 40.0°C	9 (0.4)	48 (1.9)	8 (0.6)
Grade 4: >40.0°C	0	1 (<0.1)	0
Headache[c]	N1=2480	N1=2478	N1=1350
Any	1106 (44.6)	1739 (70.2)	760 (56.3)
Grade 3	56 (2.3)	112 (4.5)	29 (2.1)
Grade 4	0	1 (<0.1)	0
Fatigue[d]	N1=2481	N1=2478	N1=1350
Any	1188 (47.9)	1679 (67.8)	784 (58.1)
Grade 3	33 (1.3)	188 (7.6)	54 (4.0)
Grade 4	0	0	0
Myalgia[d]	N1=2480	N1=2477	N1=1350
Any	670 (27.0)	1155 (46.6)	542 (40.1)
Grade 3	24 (1.0)	129 (5.2)	49 (3.6)
Grade 4	0	0	0
Arthralgia[d]	N1=2480	N1=2477	N1=1350
Any	371 (15.0)	716 (28.9)	322 (23.9)
Grade 3	15 (0.6)	57 (2.3)	18 (1.3)
Grade 4	0	0	0
Nausea/vomiting[e]	N1=2480	N1=2477	N1=1350
Any	281 (11.3)	591 (23.9)	241 (17.9)
Grade 3	2 (<0.1)	2 (<0.1)	2 (0.1)
Grade 4	0	1 (<0.1)	0
Chills[f]	N1=2480	N1=2477	N1=1350
Any	456 (18.4)	1066 (43.0)	408 (30.2)
Grade 3	4 (0.2)	11 (0.4)	7 (0.5)
Grade 4	0	0	0

Event	Study P203 12-17 Years mRNA-1273 100 µg Primary Series Dose 1 n (%) N=2482	Study P203 12-17 Years mRNA-1273 100 µg Primary Series Dose 2[a] n (%) N=2478	Study P203 12-17 Years Booster Dose[b] mRNA-1273 50 µg n (%) N=1350
Use of antipyretic or pain medication	N1=2482	N1=2478	N1=1351
Any	748 (30.1)	1242 (50.1)	526 (38.9)

Source: sBLA 125752/68, Study P203 Part C, Table 14.3.1.1.1.5.1 and Table 14.1.5.3.5 for Part C; Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.1.5.3.1, and Table 14.1.5.3.2 for Part A.
Notes: N=The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post Dose 2, or 1 post-booster solicited safety assessment through 6 days post-vaccination).
N1=Number of exposed participants who submitted any data for the event; Any=grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
The Solicited Safety Set for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post Dose 2, or 1 post-booster solicited safety assessment through 6 days post-vaccination).
Medications were collected on the e-diary.
a. 28-day interval between primary series dose 1 and primary series Dose 2
b. Median of 316 days between primary series dose 2 and booster dose
c. Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
d. Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
e. Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
f. Chills: Grade 3 prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.
The primary series phase of Study P203 (Part A) was not conducted contemporaneously with the Booster Phase (Part C).

Reviewer Comment: Rates of solicited adverse reactions after the booster dose were similar to or less than those observed after Dose 2 of the primary series, except for any axillary swelling, which was reported in 27.8% of participants following the booster dose and 23.2% and 21.0% following primary series Doses 1 and 2, respectively. Despite the approximate 5%-7% increase in rates of any axillary swelling, the rates of Grade 3 or higher axillary swelling were comparable at 0.4%, 0.3%, and 0.4% following Dose 1 and Dose 2 of the primary series, and the booster dose, respectively. Rates of any fever were 6.1% following the booster dose, which was approximately half of the 12.0% observed following Dose 2 of the primary series.

Subgroup Analyses of Solicited Adverse Reactions

Subgroup analyses were performed for solicited adverse reactions to evaluate the reactions post-booster dose by sex, race, and ethnicity. No notable differences were observed among the demographic subgroups, although some race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Subgroup analysis was also performed for solicited local and systemic reactions based on pre-booster SARS-CoV-2 status. SARS-CoV-2 positive participants reported similar rates of local ARs compared to SARS-CoV-2 negative participants (90.5% vs 91.9%, respectively). Systemic reactions were reported at a numerically lower rate overall in SARS-CoV-2 positive participants (68.9%) compared to SARS-CoV-2 negative participants (80.7%). Notably, fever was reported by 2.9% of SARS-CoV-2 positive participants compared to 8.7% of SARS-CoV-2 participants.

6.3.12.4 Unsolicited Adverse Events Through 28 Days Post-Vaccination

Unsolicited AEs within 28 days of booster vaccination were most frequently reported under the SOC *Infections and Infestations* (8.1% of participants), *General disorders and administration site conditions* (2.8%), and *Nervous system disorders* (1.9%). By PTs, the most frequently reported unsolicited AEs within 28 days post-BD were COVID-19 (3.2%), headache (1.9%), and asymptomatic COVID-19 (1.6%).

Unsolicited AEs occurred at similar rates among participants with negative and positive SARS-CoV-2 status pre-booster. Rates of unsolicited AEs were also generally similar across subgroups based on sex, race, and ethnicity, though the low number of participants in several subgroups limited determination of any particular patterns.

> *Reviewer Comment: The open label nature of this study and lack of comparator group limits the interpretability of safety data presented.*

6.3.12.5 Medically Attended Adverse Events

In the 28 days post-BD, 8.5% (n=119) of participants reported MAAEs. Through the data cutoff, MAAEs were reported by 26.2% (n=368) of participants, with 3 events (0.2%) considered by the investigator to be related to study vaccine. These 3 events were: vomiting 5 days post-booster dose in a 13-year-old male, fatigue 7 days post-booster dose in a 15-year-old female, and severe diarrhea 170 days post-booster dose in a 13-year-old female with history of celiac disease and recent COVID-19 diagnosis. The event of diarrhea was re-assessed by the investigator as not related to study vaccine after the data cutoff.

> *Reviewer Comment: This reviewer agrees with the investigator's assessments that the cases of vomiting and fatigue were related to study vaccine due to temporal relationship and as these are solicited adverse reactions after vaccination. The reviewer agrees with the investigator's revised assessment that the event of diarrhea was not related to study vaccine given the concomitant illness and medical history.*

6.3.12.6 Adverse Events of Special Interest

Participants are 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). No AESIs were reported within 28 days after receipt of the BD. As of the data cutoff, AESIs were reported by 2 (0.1%) BD recipients, under the PTs of heart rate irregular and juvenile idiopathic arthritis, which are summarized below.

- A 14-year-old female developed irregular heart rate, graded as mild in severity, with onset 101 days after receipt of BD. The event was associated with concurrent symptomatic COVID-19 and resolved on BD-Day 191 without medical intervention. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigators assessment that this event is not related to the study vaccine. Note: The investigator subsequently removed AESI designation for this event as it did not meet AESI criteria.

- A 12-year-old female developed pain, swelling, and decreased range of motion in her hands and feet bilaterally approximately 7 weeks after BD (BD-Day 54). Several months later (BD-Day 109) she was officially diagnosed with moderate

juvenile idiopathic arthritis (the AESI was reported with an onset day of BD-Day 54, same time as symptom onset). She was treated with adalimumab and methotrexate. The event was not considered resolved at the time of data cutoff. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigators assessment that this event is not related to the study vaccine.

6.3.12.7 FDA Standard MedDRA Queries

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.

SMQ Hypersensitivity

Through the data cutoff, events under the narrow scope SMQ *Hypersensitivity* were reported by 14 participants (1%). Within 28 days of vaccination, hypersensitivity events were reported by 8 (0.6%) participants. All events were assessed as mild to moderate, except for one event under the PT Hypersensitivity which was considered severe: a 12-year-old male who reported allergic reaction with swelling, itching, and hives occurring 15 days post-booster dose. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that this event was unlikely to be related to study vaccine. None of the identified events under the SMQ *Hypersensitivity* were clinically consistent with anaphylaxis.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (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 (Appendix B). Analysis of the data through the data cutoff identified 6 events, described below.

- A 15-year-old male with a history of anxiety, depression, post-traumatic stress disorder, and attention deficit hyperactivity disorder experienced mild dyspnea on the day of the booster dose administration, which resolved the next day without medical intervention. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that this event was likely related to study vaccination, possibly as an immunization anxiety-related reaction.

- A 13-year-old male experienced dyspnea 26 days after receiving booster dose, associated with concurrent AE of symptomatic COVID-19. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that this event was unlikely to be related to study vaccine.

- A 13-year-old male with history of anxiety experienced dyspnea 101 days after receiving booster dose. No other AEs were reported concurrently, and no further

details are available on the event. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was unlikely to be related to study vaccine.

- A 13-year-old male experienced syncope 176 days after BD, which was considered resolved on the same day. No relevant medical history or concurrent AEs were reported. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 14-year-old female experienced cardiac arrythmia 101 days post-booster dose. The participant reported experiencing intermittent palpitations following an episode of symptomatic COVID-19, but did not seek medical attention. Approximately 1 month after the event, a physical examination by the investigator noted irregular heartbeat. The participant was otherwise asymptomatic and no work-up was conducted. At a subsequent follow-up visit, a physical exam by the investigator noted normal sinus rhythm, and the AE was considered resolved. The investigator considered the event not related to the study vaccine. The reviewer agrees with the investigator's assessment that this event was unlikely to be related to study vaccine.

- A 13-year-old male experienced chest pain 201 days after BD. No relevant medical history was reported. The participant had previously been diagnosed with COVID-19 on BD-Day 190, which resolved on BD-Day 201, and the episode of mild chest pain occurred in the setting of vigorous exercise. The participant did not seek medical attention but was referred to a cardiologist. The chest pain was reported resolved after 75 days, with underlying cardiac etiology not identified. The event was considered to be secondary to exercise intolerance due to COVID-19 infection. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

Reviewer Comment: None of these events were considered by the reviewer to be consistent with vaccine-associated myocarditis or pericarditis.

6.3.12.8 Serious Adverse Events (SAEs)

As of the data cutoff (August 15, 2022), SAEs were reported in 6 BD recipients (0.4%), which are summarized below.

- A 17-year-old male experienced acute appendicitis 102 days after receipt of BD. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 16-year-old male experienced cervical vertebral fracture 164 days after receipt of BD. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 14-year-old female with a history of anxiety, depression, occasional suicidal thoughts, PTSD, and self-injurious behavior experienced suicidal ideation 183 days after receipt of BD. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 13-year-old male experienced decreased appetite 222 days after receipt of BD, requiring hospitalization. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 15-year-old female experienced abdominal pain and vomiting 244 days after receipt of BD, requiring hospitalization. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

- A 12-year-old male with a history of ADHD and self-reported anxiety, experienced emotional distress 249 days after receipt of BD, requiring hospitalization. The investigator considered this event not related to the study vaccine. The reviewer agrees with the investigator's assessment that the event was not related to study vaccine.

Reviewer Comment: None of these events were considered by the reviewer to be consistent with vaccine-associated AEs.

6.3.12.9 Deaths

There were no deaths among Study P203 Part C participants through the data cutoff.

6.3.12.10 Dropouts and/or Discontinuations

See Section 6.3.12.8. No participant discontinued the study due to an AE.

6.3.13 Study Conclusions

The primary evidence to support effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in adolescents 12 through 17 years of age was a comparison of the immune responses generated following a single dose (50 µg) of Spikevax (Original monovalent) in adolescents in Study P203 to the immune responses after a 2-dose series (100 µg each) of Spikevax (Original monovalent) in a clinically relevant young adult subgroup (18-25 years) from Study P301, for whom VE had been previously demonstrated. The study met the pre-specified success criteria for the two co-primary endpoints of GMC ratio and difference in SRRs. An analysis of the safety data through the data cutoff of August 15, 2022, with a median duration of follow-up of 204 days post-study dose, revealed no new safety concerns. As of the data cutoff, there were no cases of myocarditis or pericarditis and no vaccine-related SAEs reported. The data generated from this study support the safety and effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in previously COVID-19 vaccinated adolescents 12 through 17 years of age.

6.4 Study P301 (Part C): Adult Moderna COVID-19 Booster Dose (50 µg) Following 2-Dose Primary Series

NCT04470427

Title: A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-COV-2 Vaccine in Adults Aged 18 Years and Older

Study Overview: Study P301 is an ongoing Phase 3 study evaluating the safety, efficacy, and immunogenicity of mRNA-1273 when administered to adult participants 18 years of age and older. Parts A and B of Study P301 evaluated a 2-dose series of mRNA-1273 (100 µg each) and were previously reviewed for the initial BLA for Spikevax (Original monovalent) (see original Spikevax BLA memo). Part C of Study P301 is an open label booster phase to evaluate a single 50 µg booster dose of mRNA-1273 administered at least 6 months following a 2-dose primary series of mRNA-1273 (100 µg each) in Part A or B of the same study. Booster dose data from Part C included 19,609 vaccinated participants. The presented data are from September 23, 2021 (study initiation) through April 5, 2022 (data cut-off), with a database lock date of May 16, 2022.

6.4.1 Objectives and Endpoints

There were no primary study objectives specified for Part C.

Secondary Immunogenicity Objective

To infer effectiveness of the 50 µg mRNA-1273 booster by establishing noninferiority of antibody (Ab) response after the booster dose (BD) compared to the primary series of mRNA-1273 using GMC values of serum Ab and seroresponse rate of post booster in Part C compared with primary series recipients of mRNA-1273

Endpoints:

- GMC of post-booster (Post-booster Day 29, 28 days after the booster dose) Ab levels against D614G strain as compared to post-dose 2 of the mRNA-1273 primary series (Day 57 after start of primary series, 28 days after Dose 2 of the primary series)

  Statistical Criterion for Success:
  - The noninferiority of post-booster GMC at Day 29 in Part C as compared to the primary series at Day 57 was considered to be demonstrated if the LB of the 95% CI of the GMC ratio (ratio of GMC at BD-Day 29 vs. GMC at Day 57 [28 days after Dose 2 of the primary series]) is ≥ 0.67 using a noninferiority margin of 1.5

  - The superiority of post-booster GMC at Day 29 in Part C as compared to the primary series at Day 57 was considered to be demonstrated if the LB of the 95% CI of the GMC ratio (ratio of GMC at BD-Day 29 vs. GMC at Day 57 [28 days after Dose 2 of the primary series]) is > 1

- Seroresponse rate of post-booster/BD-Day 1 from baseline (pre-Dose 1) as compared to post-Dose 2 from baseline (pre-Dose 1) in primary series recipients of mRNA-1273. Seroresponse is defined as a titer change from baseline (pre-

Dose 1 in primary series) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ.

Statistical Criterion for Success:

1) The noninferiority in SRR post-booster at BD-Day 29 in Part C compared with SRR of the primary series at Day 57 (28 days after the second dose of the primary series of mRNA-1273) was considered to be demonstrated if the lower bound of the 95% CI of the SRR (percentage) difference (SRR of the booster at BD-Day 29 – SRR of the primary series at Day 57) is > –10%
2) The superiority in SRR post-booster at BD-Day 29 in Part C compared with SRR of the primary series at Day 57 (28 days after the second dose of the primary series of mRNA-1273) was considered to be demonstrated if the lower bound of the 95% CI of the SRR (percentage) difference (SRR of the booster at BD-Day 29 – SRR of the primary series at Day 57) is > 0%

Exploratory Safety Objective

To evaluate the safety of a booster dose of mRNA-1273 (50 µg dose) following a 2-dose primary series

Endpoints (descriptive analyses only):

a) Unsolicited AEs through 28 days after the booster dose
b) MAAEs throughout the entire study period
c) SAEs throughout the entire study period
d) AESIs throughout the entire study period

Reviewer Comment: A separate study (P201 Part B, see Section 6.6) evaluated the safety, including solicited adverse reactions (ARs), of a 50 µg booster dose of mRNA-1273 in support of the EUA of a mRNA-1273 booster dose. Given these data, solicited ARs were not collected during Part C of P301.

6.4.2 Design Overview

Study P301 is an ongoing 3-part study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 vaccine administered as a 2-dose primary series (Parts A and B) and as a single booster dose at least 6 months after the 2-dose series (Part C).

Following Parts A and B of the study, the protocol was amended to add the open-label Part C in which participants randomized in Part A, and who had received a 2-dose primary series in either Part A or Part B, were offered a single 50 µg booster dose of mRNA-1273 at least 6 months after the last dose of the 2-dose primary series of mRNA-1273. A total of 19,609 participants received a 50 µg dose of mRNA-1273 in Part C. Secondary immunogenicity endpoints evaluated the effectiveness of a 50 µg booster dose of mRNA-1273 as assessed by the serum antibody responses 28 days following the booster dose as compared to the antibody responses 28 days following Dose 2 of the 2-dose primary series. Safety endpoints included unsolicited AEs through 28 days after the 50 µg booster dose, MAAEs, SAEs, and AESIs through study completion. There were no statistically evaluated efficacy endpoints included in Part C; however, participants were monitored for symptomatic COVID-19 and incidence of COVID-19 cases were descriptively evaluated. Participant follow-up is planned for 6 months after the 50 µg booster dose.

6.4.3 Population

Study P301 enrolled adults 18 years of age or older who had no known history of SARS-CoV-2 infection, some of whom were healthy and some of whom had stable pre-existing medical conditions. Enrollment targeted individuals at high risk of SARS-CoV-2 exposure and was stratified to ensure representation of individuals at higher risk of severe COVID-19 (due to age or underlying medical conditions). See original Spikevax BLA memo for further details on eligibility criteria for Study P301.

6.4.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273 (Lot numbers: 7006121001, 7006121003, 7008121001, and 7008921001) is a nucleoside modified mRNA that encodes for the full-length spike protein of SARS-CoV-2 (Original strain) encapsulated in lipid particles.

6.4.5 Directions for Use

Intramuscular injection of mRNA-1273 vaccine containing 50 µg of mRNA-1273 was administered into the deltoid muscle (preferably the nondominant arm) as a single dose at least 6 months after the second dose of the primary series of mRNA-1273 (100 µg).

6.4.6 Sites and Centers

Study P301 enrolled participants at 99 clinical sites in the U.S.

6.4.7 Surveillance/Monitoring

Immunogenicity

Blood samples for immunogenicity assessments were collected from all participants at scheduled time points (pre-study dose, 28 days, and 180 days post-study dose). Immunogenicity assessments included the following:

- Serum nAb levels against SARS-CoV-2 (D614G) as measured by PsVNA. Immunogenicity analyses for Part C were based on nAb concentrations measured using a validated pseudovirus neutralization assay against the actual strain (D614G form of the USA-WA1/2020 Wuhan strain) conducted at PPD Vaccine Laboratories. nAb concentrations were measured for both the post-booster dose and the post-primary series comparison. nAb levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses. This differed from the Duke pseudovirus neutralization assay used previously for other parts of Study P301 which reported results as 50% inhibitory dose (ID50) neutralization titers.

Serum samples were also tested for binding antibodies (bAb) against the SARS-CoV-2 nucleocapsid protein (N-protein) to determine the serostatus of study participants at baseline and to assess for prior seroconversion due to infection during the study.

Safety

Participants were seen in clinic (Days 3, 28, and 180) and received safety follow-up calls (Days 7, 14, and 21) after the booster dose to facilitate collection of: unsolicited AEs through 28 days following vaccination, AEs, MAAEs, and AEs leading to withdrawal from Day 1 through study completion or withdrawal, abnormal vital sign measurements, physical exam findings, pregnancy and accompanying outcomes.

All potential cases of myocarditis and pericarditis, as identified by the investigator or Applicant, were reviewed by an independent Cardiac Event Adjudication Committee (CEAC) to determine whether the case met the CDC criteria (Appendix D) 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.

Efficacy

Participant surveillance for COVID-19 symptoms was conducted during scheduled study clinic visits and safety calls as well as through electronic diary (e-diary) prompts from enrollment through the end of the study. Participants reporting symptoms of COVID-19 outside of scheduled study visits were asked to return within 72 hours to the study site for an unscheduled visit to collect an NP swab sample for RT-PCR testing, a blood sample for antibody testing, and clinical evaluation. If a study site visit was not possible, a home visit was arranged to collect the samples and conduct clinical evaluations. If a home visit was not possible, the participant was asked to submit a saliva sample to the study site by an Applicant approved method.

6.4.8 Endpoints and Criteria for Study Success

See Sections 6.1.1 and 6.1.9.

Part C did not include any efficacy objectives. However, efficacy endpoints were descriptively analyzed, including the incidence of:

1. COVID-19
2. Severe COVID-19
3. COVID-19 or SARS-CoV-2 infection, serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity
4. COVID-19 based on a secondary (less restrictive) definition of COVID-19
5. Death caused by COVID-19

COVID-19 and SARS-CoV-2 case definitions were the same as those used in Part A (see BLA review memo) and also outlined in Appendix C.

6.4.9 Statistical Considerations & Statistical Analysis Plan

For the immunogenicity analyses, comparisons were made either through a paired-comparison in which a participant serves as their own control; or between-group comparison compared to post-primary series in Part A using mRNA-1273 subjects in Per-Protocol Random Subcohort for Immunogenicity (PPRSI) with negative baseline SARS-CoV-2 as historical controls.

The 95% CIs for geometric mean concentrations (GMCs) were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. Geometric fold rises were calculated using either pre-dose 1 or pre-booster dose as a baseline. The 95% CIs were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

Seroresponse was based on the following definitions:

- ≥ 4-fold rise for those with Pre-vaccination /Pre-Dose 1 value ≥LLOQ
- ≥ 4x the LLOQ for those with Pre-vaccination /Pre-Dose 1 value <LLOQ

- If there was no pre-Dose 1 antibody titer information and there was evidence that the participant did not have SARS-CoV-2 infection prior to vaccination, i.e., negative SARS-CoV-2 status at the pre-vaccination/pre-dose 1 of primary series, these participants' pre-vaccination/pre-dose 1 antibody titer were assumed to be <LLOQ at pre-dose 1 of primary series.

Safety analyses were based on the Safety Set, which consisted of all subjects who received a booster dose. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event. Only the maximum severity and strongest assessment of relationship to the study intervention were reported. Subgroup analyses were provided based on age group (<65 and ≥65 years), sex (male, female), pre-booster SARS-Cov-2 serostatus, race, and ethnicity.

Efficacy analyses were based on the Part C PP Set consisting of 50 µg dose recipients who did not have evidence of COVID-19 or SARS-CoV-2 infection prior to receiving a booster dose. Person-time, incidence rate, and 95% CI for incidence rate based on the exact method adjusting for person-time were provided.

6.4.10 Study Population and Disposition

This sBLA submission includes data from the start of enrollment for P301 Part C on September 23, 2021, through the data cutoff date of April 5, 2022. A total of 19609 participants received a dose of mRNA-1273 in Part C: 9647 of whom received their primary series in Part A and 9952 of whom received their primary series during the Part B cross-over phase. There were 10 participants randomized to receive placebo in Part A who received a booster dose in Part C without receiving a primary series in Part B; however, these participants are included in the combined total of 19609 participants used for study analyses (unless otherwise specified).

> *Reviewer Comment: Data from the 10 participants who did not receive a primary series prior to the booster dose are included in study safety analyses. Given the small number of these participants relative to the overall safety population, their inclusion in the safety analyses is unlikely to change the overall study conclusions. A total of 19,599 participants received a booster dose after receiving the primary series in either Part A or Part B.*

Populations Enrolled/Analyzed

The analyses population used for study analyses are defined in Table 38. Immunogenicity analyses were conducted on the Part C Per Protocol Immunogenicity Subset –SARS-CoV-2 Negative (Part C PPIS-Neg). Safety analyses were conducted with the Safety Set. Efficacy analyses were conducted with the Part C Per Protocol Set.

Table 38. Analysis Populations, Study P301 Part C

Population	Description
Safety Set	All participants who were randomized in Part A of the study and received a 50 µg booster dose in study Part C.
Part C Per-Protocol Set (Part C PP set)	All participants who were randomized during Part A of the study, received a mRNA-1273 50 ug booster in Part C, were pre-booster SARS-CoV-2 negative, and had no major protocol deviations that impacted critical data.

Population	Description
Part C Per-Protocol Immunogenicity Subset (Part C PPIS)	The Part C PPIS consists of participants who were in PPRSI in Part A, randomized to mRNA-1273 in Part A, were baseline/pre-Day 1 SARS-CoV-2 negative and received booster in Part C.
Part C Per-Protocol Immunogenicity Subset - Pre-booster SARS-CoV-2 negative (Part C PPIS-Neg)	Participants in the Part C PPIS and were negative for virologic or serologic evidence of SARS-CoV-2 infection on or before receipt of a booster dose of mRNA-1273 (negative RT-PCR from nasal swab and negative bAb specific to SARS-CoV-2 N-protein)

Source: FDA-generated table
Abbreviations: PPRSI=Per-Protocol Random Subcohort for Immunogenicity

Demographics

The PPIS-Negative set was used for analyses of immunogenicity of the mRNA-1273 booster dose and consisted of a total of 682 participants (Table 39). The median age at booster was 59 years (range of 19 to 87 years) with 38.7% of participants ≥65 years of age. Of the participants in the PPIS-Neg, males accounted for 52.9% and 53.7% identified as non-White and/or Hispanic. At least one protocol-defined high-risk condition for severe COVID-19 was present in 40.2% of participants; 48.2% of participants were obese (body mass index ≥30 kg/m^2). The comparator group for the immunogenicity analyses was composed of the same participants in Part C PPIS-Neg set at 28 days following completion of the primary series.

In the Part C PPIS-Neg, the median duration between Dose 2 of the primary series to receipt of the 50 µg booster dose was 12.9 months (range 10.5 months to 16.7 months).

Table 39. Demographics and Other Baseline Characteristics, Adults 18 Years and Older, P301 Part C, Part C PPIS – Neg

Characteristic	P301 Part C ≥18 years mRNA-1273 50 µg Booster Dose N=682 n (%)
Sex	--
Female	321 (47.1)
Male	361 (52.9)
Age (years)	--
Median (min, max) (years)	59 (19, 87)
18-64 years	418 (61.3)
≥65 years	264 (38.7)
Race	--
White	483 (70.8)
Black or African American	134 (19.6)
Asian	17 (2.5)
American Indian or Alaska Native	9 (1.3)
Native Hawaiian or Other Pacific Islander	3 (0.4)
Multiracial	9 (1.3)
Other	21 (3.1)
Not Reported	2 (0.3)
Unknown	4 (0.6)

Characteristic	P301 Part C ≥18 years mRNA-1273 50 µg Booster Dose N=682 n (%)
Ethnicity	--
Hispanic or Latino	207 (30.4)
Not Hispanic or Latino	472 (69.2)
Not Reported	1 (0.1)
Unknown	2 (0.3)
High-risk conditions	--
No high-risk condition	408 (59.8)
With any protocol risk for severe COVID-19	274 (40.2)
Chronic Lung Disease	57 (8.4)
Significant Cardiac Disease	56 (8.2)
Severe Obesity (BMI >40 kg/m^2)	83 (12.2)
Diabetes	121 (17.7)
Liver Disease	14 (2.1)
BMI Subgroup	--
BMI: <30 kg/m^2	349 (51.2)
BMI: ≥30 kg/m^2	329 (48.2)
Missing	4 (0.6)
Age and health risk for severe COVID-19[a]	--
18-64 years and not at risk	229 (33.6)
18-64 years and at risk	189 (27.7)
≥65 years	264 (38.7)
Interval between primary series and booster	--
Median (months*)	12.9
Min, max	(10.5, 16.7)

Source: Adapted from STN 125752/68; P301 add 2 Clinical Study Report, Table 14.1.3.6.3 and Response to IR received 8 May 2023 and 16 Aug 2023
Abbreviations: BMI=body mass index; max=maximum value in range; min=minimum value in range; N=number of participants in the PPIS-Negative set; n=number of participants in the category; PPIS-Neg= Per-protocol immunogenicity set- SARS-CoV-2 negative pre-booster,
*1 month =30.4375 days
a. Based on stratification factor from IRT, participants who are <65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening. Age based on age at booster.

The Safety Set was used for analyses of safety of the booster dose and consisted of a total of 19,609 participants (Table 40). The median age at booster was 55 years (range of 19 to 96 years) with 30.4% of participants ≥65 years of age. Among participants in the Safety Set, 2% had evidence of prior SARS-CoV-2 infection at baseline. Demographic data were similar between the original mRNA-1273 primary series recipients in Part A and the participants who crossed over to receive mRNA-1273 primary series in Part B, except the interval between primary series and booster dose with a median of 13.1 months (range 6.7 months to 19.2 months) in the Part A mRNA-1273 recipients group and a median of 8.3 months (range 5.2 months to 13.6 months) in the crossover group.

Demographics and baseline characteristics were similar between participants in the Part C Safety Set and those in the Part C Per Protocol Set (not shown).

Table 40. Demographics and Other Baseline Characteristics, Adults 18 Years and Older, P301 Part C, Safety Set

Characteristic	P301 Part C ≥18 years mRNA-1273 50 µg Booster Dose n (%) N=19609*
Sex	--
Female	9341 (47.6)
Male	10268 (52.4)
Age (years)	--
Median (Min, max) (years)	55 (19, 96)
18-64 years	13650 (69.6)
≥65 years	5959 (30.4)
Race	--
American Indian or Alaska Native	152 (0.8)
Asian	812 (4.1)
Black or African American	2082 (10.6)
Native Hawaiian or other Pacific Islander	40 (0.2)
White	15481 (78.9)
Multiracial	439 (2.2)
Other	395 (2.0)
Not reported	122 (0.6)
Unknown	86 (0.4)
Ethnicity	--
Hispanic or Latino	3955 (20.2)
Not Hispanic or Latino	15741 (78.9)
Not reported	124 (0.6)
Unknown	59 (0.3)
High-risk conditions	--
No high-risk condition	14845 (75.7)
With any protocol risk for severe COVID-19	4764 (24.3)
Chronic lung disease	1019 (5.2)
Significant cardiac disease	1046 (5.3)
Severe obesity (BMI >40 kg/m^2)	1463 (7.5)
Diabetes	2028 (10.3)
Liver disease	141 (0.7)
HIV infection	138 (0.7)
BMI	--
BMI: <30 kg/m^2	11790 (60.1)
BMI: ≥30 kg/m^2	7685 (39.2)
Missing	134 (0.7)

Characteristic	P301 Part C ≥18 years mRNA-1273 50 µg Booster Dose n (%) N=19609*
Age and health risk for severe COVID-19[a]	--
18-64 years and not at risk	10693 (54.5)
18-64 years and at risk	2957 (15.1)
≥65 years	5959 (30.4)
Baseline SARS-CoV-2 Status[b]	--
Negative	19115 (97.5)
Positive	383 (2.0)
Missing	111 (0.6)
Interval between Dose 2 of primary series and booster dose	--
Median (months**)	10.4
Min, max	5.2, 18.9

Source: Adapted from STN 125752/68, P301 add 2 Clinical Study Report, Tables 14.1.3.6.2, 14.1.6.7, and Response to IR #1 received May
Abbreviations: BMI=body mass index; max=maximum value in range; min=minimum value in range; N=number of participants in the per-protocol set; n=number of participants in the category;
*10 participants received a booster dose in Part C of the study without receiving a primary series. These participants are included in safety analyses. N=19,599 received a booster dose of 50µg mRNA-1273 after a 2 dose primary series of 100µg mRNA-1273
**1 month = 30.4375 days
a. Based on stratification factor from IRT, participants who are <65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening.
b. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 prior to booster dose. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1 prior to booster dose.

Participant Disposition

The dispositions and reasons for exclusion from analysis population of study participants in Part C are shown in Table 41. The Safety Set had a total of 19,609 participants, with 5.7% of participants who discontinued from Part C of the study. The most common reason for discontinuation was withdrawal of participant consent (4.5%), with other causes for exclusion each occurring in fewer than 1% of participants.

The PPIS population had a total of 731 participants. The most common reason for exclusion from the PPIS was Not negative baseline SARS-CoV-2 status (0.8%).

The PPIS-neg population had a total of 682 participants, with all exclusions (0.3%) from this analysis population due to positive pre-booster SARS-CoV-2 status.

Table 41. Disposition, Adults 18 Years and Older, P301 Part C, Study Analysis Populations

Disposition	P301 Part C ≥18 years mRNA-1273 50 µg Booster Dose n (%)[a]
Safety Set	**N=19609***
Discontinued from Study in Part C	1108 (5.7)
Reason for discontinuation	--
Adverse Event	1 (<0.1)
Serious Adverse Event	1 (<0.1)
Death	27 (0.1)
Lost to Follow-Up	49 (0.2)
Physician Decision	10 (<0.1)
Protocol Deviation	42 (0.2)
Study Terminated by Applicant	1 (<0.1)
Withdrawal of Consent by Participant	890 (4.5)
Other	87 (0.4)
Per-protocol Immunogenicity Set (PPIS)	**N=731**
Excluded from PPIS	348 (1.8)
Reason for exclusion[b]	--
Received <2 Primary Doses of mRNA-1273 Prior to Booster	2 (<0.1)
Received Primary Dose 2 of mRNA-1273 Outside of 21 to 42 days after Primary Dose 1	36 (0.2)
Did Not Receive Dose 2 in Part A	33 (0.2)
Received Dose 2 Outside of 21 to 42 Days After Dose 1 in Part A	1 (<0.1)
Human Immunodeficiency Virus Infection	19 (<0.1)
Not Negative Baseline SARS-CoV-2 Status[c]	161 (0.8)
Not Randomized to mRNA-1273	95 (0.5)
Other Major Protocol Deviation Impacting Critical Data	1 (<0.1)
Per-protocol Immunogenicity Set -SARS-CoV-2 Negative[c] (PPIS-Neg)	**N=682**
Excluded from PPIS-Neg (Pre-booster SARS-CoV-2 positive[c])	49 (0.3)

Source: Adapted from STN 125752/68 P301 Addendum 2 Clinical Study Report, Table 14.1.2.6, Response to IR April 27, 2023
Abbreviations: N=number of participants in the analysis set
*10 participants received a booster dose without receiving a primary series as discussed in Section 6.1.10. These participants are included in safety analyses.
a. Percentages are based on the number of participants in the Safety Set.
b. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.
c. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 prior to booster dose. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1 prior to booster dose.

6.4.11 Analysis of Vaccine Effectiveness

6.4.11.1 Immunogenicity Analyses

In Study P301 Part C, immunogenicity endpoints evaluated nAb concentrations against the D614G strain 28 days post-booster dose (post-BD) compared to 28 days post-Dose 2 of the primary series (post-PS) in the same group of participants (Table 42). The GMC ratio (post-BD/post-PS) of nAb responses was 7.0 (95% CI 6.5, 7.5), which met the pre-specified superiority criteria of a lower bound of the 95% CI >1.

Table 42. Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against D614G at 28 Days Post-Booster Dose Compared to at 28 Days Post-Primary Series, Adults 18 Years of Age and Older, Study P301 Part C, PPIS-Neg

P301 Part C PPIS-Neg ≥18 years mRNA-1273 50 µg BD GMC (95% CI[a]) N=636	P301 Part C PPIS-Neg ≥18 years mRNA-1273 100 µg PS GMC (95%CI) N=680	GMC Ratio Post-BD/Post-PS (95% CI)[b]
7759.3 (7258.7, 8294.4)	1111.3 (1041.7, 1185.5)	7.0 (6.5, 7.5)

Source: Adapted from 125752/68, P301 Addendum 2 Clinical Study Report, Table 14.2.4.2.4.5.2
Abbreviations: BD=booster dose, CI=confidence interval; GMC=geometric mean concentration, LLOQ=lower limit of quantification, ULOQ=upper limit of quantification; nAb=neutralizing antibodies, PS=primary series; N=number of participants with available GMC data at relevant timepoints
LLOQ: 10; ULOQ: 281600
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
a. 95% CI is calculated based on the t-distr bution of the log-transformed values or the difference in the log-transformed values for GMC, then back transformed to the original scale for presentation.
b. The log-transformed ant body levels are analyzed using paired t-test method with the group variable and 95% CI is calculated based on the t-distribution of the mean of paired difference in the log-transformed values, then back transformed to the original scale for presentation.

Analyses of SRRs against D614G found an SRR (percentage) difference of 0.9% (95% CI of 0.1 to 1.8) and met the pre-specified superiority criterion of a lower bound of the 95% CI >0%. SRRs for these analyses were evaluated using a baseline of GMC pre-dose 1 of the primary series.

Table 43. Seroresponse Rates (SRRs) as Measured by Pseudovirus nAb Assay Against D614G at 28 Days Post-Booster Dose Compared to at 28 Days Post-Primary Series, Adults 18 Years of Age and Older, Study P301 Part C, PPIS-Neg

P301 Part C PPIS-Neg ≥18 years mRNA-1273 50 µg BD SRR % (95% CI[a]) N=636	P301 Part C PPIS-Neg ≥18 years mRNA-1273 100 µg PS SRR % (95%CI[a]) N=680	SRR Difference (%) Post-BD - Post-PS (95% CI)[b]
100 (99.4, 100)	98.8 (97.7, 99.5)	0.9 (0.1, 1.8)

Source: Adapted from STN 125752/68, P301 Addendum 2 Clinical Study Report, Table 14.2.4.2.4.5.2
Abbreviations: BD=booster dose CI=confidence interval
Seroresponse at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline (Pre Dose 1) is equal to or above the LLOQ.
a. 95% CI is calculated using the Clopper-Pearson method.
b. Difference in seroresponse rate and 95% CI were calculated using adjusted Wald method for the paired binary data. The number of subjects included in the comparison could be different from N1

The SRR (percentage) from pre-booster dose to post-booster dose was 98.4% (95% CI 97.1, 99.2). In response to a CBER information request (IR) (STN125752/68.26, dated August 22, 2023), the Applicant provided additional analyses of the difference in percentages of SRRs using the pre-booster to post-booster SRR. The difference in

percentage of SRRs [(post-booster – pre-booster) minus (post- Dose 2 primary series – pre-Dose 1 primary series)] was -0.8% (95% CI -2.1, 0.5).

> *Reviewer Comment: Overall, nAb responses described above demonstrate that a single dose (50 µg) of mRNA-1273 administered 6 months after a 2-dose 100 µg series elicits nAb levels that are greater than those achieved following the 2-dose 100 µg series.*

6.4.11.2 Subpopulation Analyses

Most of the study participants in Study P301 were White, Non-Hispanic, and non-obese; therefore, subgroup analyses of co-primary endpoints by race, ethnicity, and obesity status were not conducted, as the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results.

Subgroup analyses by age resulted in similar nAb GMCs against D614G at 28 days post-booster dose among participants 65 years of age and older (GMC of 7802.4 with 95% CI 6901.0, 8821.5) compared to participants 18-64 years (GMC of 7734.3 with 95% CI 7153.5, 8362.1).

Percentages of seroresponse rates against D614G (based on a pre-booster dose baseline) were also similar irrespective of age subgroup (18-64 years: 98.7% [95% CI 97.1, 99.6]; ≥65 years: 97.9% [95% CI 95.1, 99.3]).

Subgroup analyses of nAb GMCs based on SARS-CoV-2 infection status before booster dose vaccination demonstrated higher nAb GMCs among participants who had evidence of prior SARS-CoV-2 infection pre-booster as compared to those who had no evidence of prior SARS-CoV-2 infection pre-booster.

> *Reviewer Comment: The immunogenicity analyses by subgroup based on demographic and baseline characteristics do not suggest substantial differences in the immune responses to mRNA-1273 when compared to the overall analyses, other than the expected higher post-booster nAb GMC among participants who were SARS-CoV-2 positive at baseline as compared to this who were SARS-CoV-2 negative at baseline. The higher post-booster nAb GMCs among participants who were SARS-CoV-2 positive at baseline are expected due to prior SARS-CoV-2 exposure (i.e., hybrid immunity).*

6.4.11.3 COVID-19 Cases

Participants were monitored throughout the study for symptoms of COVID-19 (see Section 6.4.7). Additional clinical efficacy analyses evaluated the endpoints described in Section 6.4.8 among the Part C PP Set participants considered at risk of COVID-19 (i.e., participants that did not have evidence of prior COVID-19 or SARS-CoV-2 infection) beginning 14 days after booster dose through data cut-off (N=15,981). The median duration of follow-up for effectiveness among booster recipients was approximately 5.3 months. Overall, 9.1% (N=1462) of participants in the Part C PP Set reported an adjudicated case of protocol-defined COVID-19, with an incidence rate of 20.4 per 1,000 persons-months (95% CI 19.4, 21.5). All cases, except 10, had occurred during the period when the Omicron variant and its sublineages were the predominant circulating SARS-CoV-2 strain (December 2021 through data cutoff).

Incidence rates of COVID-19 based on demographic subgroup were consistent across the subgroups, except for a lower incidence rate observed among participants ≥65 years (11.2 per 1,000 persons-months [95% CI 9.8, 12.7]) as compared to that among participants 18-64 years (24.6 per 1,000 person-months [95% CI 23.2, 26.0]).

Participants in the Part C PP Set who contributed to the analyses above were pre-booster SARS-CoV-2 negative. Incidence of COVID-19 post-booster by pre-booster SARS-CoV-2 status was analyzed based on the Part C Safety Set, which included all participants who received a booster dose in Part C. The incidence of adjudicated protocol-defined COVID-19 was greater among participants who were pre-booster SARS-CoV-2 negative (20.4 per 1,000 person-months) compared to participants who were pre-booster SARS-CoV-2 positive (13.7 per 1,000 person-months). However, this analysis was limited by the small number of at-risk participants who were pre-booster SARS-CoV-2 positive (N=238) compared to those who were pre-booster SARS-CoV-2 negative (N=16,463).

Severe COVID-19 cases and Deaths Associated with COVID-19
Among participants in the Part C PP Set, there were 75 (0.5%) adjudicated cases of severe COVID-19 reported starting 14 days post-booster dose through the data cut-off, with an incidence rate of 1.0 per 1,000 person-months (95% CI 0.8, 1.3). All but one of the 75 cases occurred during the Omicron variant predominant period (December 2021 through data cutoff). Of the severe COVID-19 cases reported, 73.3% were in participants who were not considered at high risk for severe COVID-19 and 72% were in participants 18 to <65 years of age.

There were 3 COVID-19 related deaths which occurred during Part C of the study, which are summarized below:

1) A 66-year-old male with a history of mitral and aortic valve replacements, cardiac pacemaker, type 2 diabetes, hypertension, and hypothyroidism developed symptomatic COVID-19 and then respiratory failure 90 days after the booster dose. He died on Day 97 after the booster dose.
2) A 63-year-old male with a history of chest pain developed symptomatic COVID-19 134 days after the booster dose. He died 141 days after the booster dose due to a probable myocardial infarction.
3) An 82-year-old male developed severe COVID-19 disease on the day of his booster dose. He was hospitalized and died 39 days later from severe COVID-19 and related complications.

Reviewer Comment: Interpretation of the incidence rates of COVID-19 cases, including severe disease, is limited by the open-label design of the booster phase, the lack of a comparator group, and the changing SARS-CoV-2 epidemiology during the study. Given the similar immune responses observed post-booster across age groups, the lower incidence rate of COVID-19 among participants ≥65 years as compared to participants 18-64 years may be a reflection of the continued observance of social distancing and masking that was more likely to be practiced in the elderly age cohort during this time period as compared to in younger adults.

6.4.12 Safety Analyses

The Study P301 Part C Safety Set included 19,609 mRNA-1273 booster dose recipients. The median duration of follow-up after the booster dose through a data cut-off date of

April 5, 2022, was 161 days (5.4 months). As of data cut-off, 98.2% of participants had at least 2 months of follow-up after the booster dose. Approximately 15% of participants (N=3361) had at least 6 months of follow-up after the booster dose.

6.4.12.1 Methods

Please see Section 6.1.7.

6.4.12.2 Overview of Adverse Events

Table 44 provides an overview of the safety data collected during Part C of Study 301 for the overall Safety Set. Solicited adverse reactions were not collected as part of Part C. Among booster recipients, 31.7% reported unsolicited AEs occurring within 28 days following booster administration, while severe unsolicited AEs were less common, reported in 0.7% of participants. Through data cutoff, MAAEs were reported in 33.0% of booster recipients, with 1.1% which were considered related. SAEs and AESIs were reported by 2.3% and 3.3% of booster recipients, respectively, and are discussed further in Sections 6.4.12.9 and 6.4.12.6.

Table 44. Number and Percentage of Participants Reporting at Least One Safety Event after mRNA-1273 Booster Dose, Adults 18 Years and Older, P301 Part C, Safety Set

Unsolicited AE Type	P301 Part C >18 years mRNA-1273 50 µg Booster Dose Safety Set N=19,609 n (%[a])
Unsolicited AE up to 28 days post-booster	6209 (31.7)
Non-serious unsolicited AE	6115 (31.2)
Related non-serious unsolicited AE	4456 (22.7)
Severe non-serious unsolicited AE	133 (0.7)
Related severe non-serious unsolicited AE	60 (0.3)
MAAE [c]	6466 (33.0)
Related MAAE	208 (1.1)
SAEs [c]	442 (2.3)
Related SAEs	5 (<0.1)[b]
AESI[c]	646 (3.3)
Deaths [c]	25 (0.1)
AE leading to discontinuation [c]	26 (0.1)

Source: Adapted from STN 125752/68; P301 Clinical Study Report Addendum 2, Table 14.3.1.7.17.1, Table 14.3.1.7.18.1, Table 14.3.1.38.1.2
Abbreviations: AE=adverse event; AESI=adverse event of special interest; MAAE=medically attended adverse events; SAE=serious adverse event
a. Percentages are based on number of exposed participants in the Safety Set
b. At time of data cut-off 6 SAEs were initially assessed as related to the booster dose. Additional information discovered after the database lock led to investigator re-assessment of 1 SAE as unrelated making the final number of related SAEs N=5
c. All numbers reflect AEs reported through the data cutoff of April 5, 2022

Reviewer Comment: The rates and severities of reported AEs were similar to those reported following the 2-dose series and do not suggest new safety concerns associated with a single 50 µg dose of mRNA-1273.

Subgroup analyses
The overall rates of unsolicited AEs were generally similar between the two age subgroups (18-64 years, 65 years and older). Subgroup analyses of AEs by baseline (pre-booster) SARS-CoV-2 status did not show substantial differences between groups in the frequencies or severities of the reported AEs. Subgroup analyses by sex, race, and ethnicity were also similar across subgroups, although interpretation is limited by the small number of participants in some of the subgroups.

6.4.12.3 Immediate AEs

Immediate AEs were defined as events occurring within 30 minutes after vaccination. Of all participants in the Safety Set, 0.6% (n=121) reported immediate AEs after the booster dose. The most frequently reported immediate AE was injection site pain, reported by 0.3% (n=65) of participants. There were no anaphylactic reactions reported within 30 minutes after the booster dose.

6.4.12.4 Unsolicited Adverse Events Within 28 Days Post-Booster Dose

Unsolicited AEs within 28 days of booster dose in Part C were most frequently reported under the SOC *General disorders and administration site conditions* (21.4%), *Nervous system disorders* (5.9%), and *Musculoskeletal and connective tissue disorders* (5.4%). The most frequently reported unsolicited AEs by PTs were injection-site pain (13.6%), fatigue (6.9%), and headache (4.9%).

During the 28 days following vaccination, unsolicited AEs considered to be related to study vaccination by the investigator were reported by 22.7% of vaccine recipients, the majority of which were conditions representative of vaccine reactogenicity.

Subgroup analyses showed no substantial differences in the frequency or severity of reported AEs within 28 days by age group (18-64 years and ≥65 years) or pre-vaccination SARS-CoV-2 status.

> *Reviewer Comment:* *The reported unsolicited AEs were consistent with commonly reported medical conditions in the general population. The most frequently reported unsolicited AEs were synonymous with expected adverse reactions following vaccination.*

6.4.12.5 Medically Attended Adverse Events

Through 28 days post-booster, MAAEs were reported by 9.3% (n=1826) of booster recipients in Part C. Through the data cutoff, MAAEs were reported by 33.0% (n=6466) of booster recipients, of which 1.1% (n=208) were considered related by the investigator. The events considered related were generally events which are reflective of vaccine reactogenicity, with the most common being injection site pain (0.2%; n=42) and headache (0.1%; n=26).

6.4.12.6 Adverse Events of Special Interest

Participants were monitored in Part C for AESIs based on terms listed in Appendix A. Through the data cutoff, AESIs were reported by 646 booster recipients (3.3%) in the Safety Set, with 88 participants (0.4%) reporting an AESI within 28 days of receipt of the booster dose. Participants (N=19, <0.1%) reporting AESIs assessed by the investigators as related to the booster dose through 42 days post-booster dose vaccination are listed in Table 45.

Table 45. AESIs[a] Assessed by the Investigator as Related to Booster Dose Through 42 Days Following the Booster Dose, Adults 18 Years and Older, Study P301 Part C, Safety Set

Age/Sex	Start Day Relative to Booster Dose	AESIs	Assessments of Relatedness Investigator/Applicant
43/F	1	Atrial fibrillation	Related/Not Related
25/F	1	Tachycardia	Related/Related
64/M	1	Fatigue, Myalgia	Related/Related
35/M	1	Bradycardia	Related/Related
40/M	1	Myocarditis*	Related/Related
38/F	1	Chest discomfort	Related/Unlisted
20/M	2	Tachycardia	Related/Related
65/F	2	Heart rate irregular	Related/Related
62/M	2	Palpitations	Related/Related
19/M	3	Suspected myocarditis*	Related/Unlisted
53/F	3	Ageusia	Related/Not Related
49/F	4	Hypogeusia	Related/Not Related
52/M	6	Ageusia, Anosmia	Related/Not Related
71/F	11	Arteriospasm coronary**	Related/Not Related
39/M	12	Cardiac flutter**	Related/Not Related
64/F	29	Ventricular extrasystoles	Related/Not Related
28/F	42	Facial paralysis	Related/Not Related

Source: Adapted from STN 125752.68 Am Response to IR received August 18. 2023
* Discussed in myocarditis section below. An additional case of myocarditis was reported at day 134 following the booster dose and is discussed in the myocarditis section below.
**Discussed in Section 6.1.12.4
a. Participants may have reported more than 1 AESI

Reviewer Comment: The clinical reviewer's assessment of AESIs listed in the table above include the following:

1. *For the events of ageusia, hypogeusia, and anosmia, this reviewer agrees with the Applicant's assessments as concurrent respiratory tract infections provide plausible alternative explanations. Similarly, this reviewer agrees with the Applicant's assessment for the event of atrial fibrillation due to the confounding medical conditions of hypothyroidism, receipt of chemotherapy, and prior history of arrhythmia.*
2. *For the event of rheumatoid arthritis, this reviewer agrees with the Applicant's assessment as there was insufficient information available to make a definitive diagnosis of rheumatoid arthritis and there were confounding medical conditions (osteoarthritis) and recent influenza vaccination.*
3. *For the event of ventricular extrasystoles (verbatim: premature ventricular contractions, PVCs), this reviewer agrees with the Applicant's assessment based on the temporal association with vaccination and the baseline prevalence of PVCs given the participant's age.*

It is this reviewer's opinion that the event of facial paralysis may be related to the study booster dose; however, confounding medical conditions (recent viral illness, thyroid disease, and recent influenza vaccination) provide alternative etiologies.

Myocarditis and Pericarditis

Of the AESIs reported through the data cut, there were 3 reported cases of myocarditis and 1 case of pericarditis.

1. A 42-year-old male developed an SAE of myocarditis on the day of the booster dose. The participant reported fever, myalgia, and chest pain the night of booster dose administration. His symptoms worsened and he presented to the emergency department 2 days later. Laboratory tests were significant for an elevated troponin level (159.4 pg/mL with a normal range of 0.0-19.8 pg/mL). An initial electrocardiogram (ECG) was normal; however, a repeat ECG the following day had non-specific T-wave abnormalities. Cardiac catheterization showed no coronary artery abnormalities and an echocardiogram was normal. The participant was admitted to the hospital for treatment with diagnosis of myocarditis and discharged on hospital Day 4 after symptom improvement. Cardiac MRI performed 6 weeks after the event was read as normal. The participant's myocarditis resolved on 71 days following receipt of the booster dose. Of note, the participant had a viral upper respiratory infection 1 month prior to vaccination. The investigator assessed this case as related to the vaccine. The Cardiac Event Adjudication Committee (CEAC) adjudicated the case as probable acute myocarditis, as defined in the charter.

2. A 66-year-old female, at the time of the event, with a history of hypertension, hypercholesterolemia, and gastroesophageal reflux disease developed an SAE of myocarditis after the data cutoff but prior to the database lock, one day after receipt of a non-study dose of mRNA-1273. The participant reported nausea, malaise, fatigue, myalgia, poor appetite, headache, dizziness, palpitations, and chest pain the day after receiving the Moderna COVID-19 Vaccine (mRNA-1273) booster dose (50 µg) outside of the study protocol (133 days after receipt of the study booster dose). Three days after receipt of the non-study vaccine, she reported worsening chest pain, hypertension, and tachycardia. She was seen by her primary care physician and diagnosed with a urinary tract infection (UTI), but antibiotics were not started until 9 days later. A cardiologist evaluated the participant the following day and diagnosed nonspecific worsening of her ECG. The participant had a cardiac stress test and PET myocardial perfusion imaging scan two weeks after onset of symptoms, both of which were read as normal. The event was not resolved at the time of database lock. The investigator assessed this case as not related to the study investigational product but related to the non-study vaccine based on the temporal association. The CEAC adjudicated the case as "not a charter-defined event".

3. A 20-year-old male with a history of low body weight, depression, and nonspecific T wave abnormality developed myocarditis 2 days after receipt of the booster dose. The participant reported chest pain, chest pressure, and heart pounding 2 days after receiving the booster dose. He did not seek medical care and had resolution of his symptoms 3 days after onset. The participant was evaluated in clinic 7 days after onset of symptoms (9 after receipt of the booster dose) and found to have normal vital signs, normal cardiac enzymes, and an ECG that was consistent with the participant's baseline. The event was assessed by the investigator as related to the study vaccine. The event was

adjudicated by the CEAC as "not a charter-defined event" and did not meet CDC criteria for myocarditis.

4. A 68-year-old male developed pericarditis with onset 63 days following receipt of a booster dose. The participant reported a viral infection with onset 54 days post-booster dose and sinusitis 59 days post-booster dose. He was treated with ibuprofen and colchicine for pericarditis and the event resolved 7 days after onset. The event was adjudicated by the CEAC as a case of acute pericarditis, as defined in the charter. The event was assessed as unrelated to study vaccine by the investigator.

Reviewer Comment:

1) Based on the submitted information, the clinical reviewer assessment includes the following:

a. The event described in the 42-year-old male participant was adjudicated by the CEAC as probable myocarditis and was assessed by the investigator as related to the study dose due to the close temporal relationship with vaccination, lack of underlying cardiac disease or other risk factors, and positive diagnostic findings (elevated troponin and abnormal ECG). Although viral myocarditis is a possible alternative etiology given the participant's recent history of an upper respiratory viral infection, this reviewer agrees with the investigator's assessment and the CEAC adjudication and recommends inclusion of this event in product labeling (USPI, Section 6).

b. The event reported in a 66-year-old female participant was adjudicated by the CEAC as inconsistent with a defined case of myocarditis. The investigator assessed the event as unrelated to the study dose. This reviewer agrees with the CEAC adjudication and the investigator assessment. The determination of relatedness to non-study vaccine is confounded by lack of specific findings on cardiac evaluations and the potential alternate etiology for the patient's symptoms (UTI). Therefore, this event is not recommended for inclusion in the product labeling.

c. The event reported in the 20-year-old male participant was adjudicated by the CEAC as inconsistent with a defined case of myocarditis. The symptoms were assessed by the investigator as related to the study dose due to close temporal relationship with vaccination. However, the participant's duration of symptoms was short, and he had normal findings on cardiac evaluation which was not conducted when he was symptomatic. This reviewer agrees with the CEAC adjudication that the event was not consistent with CDC's case definition for myocarditis and therefore it is not recommended for inclusion in the product labeling.

d. The pericarditis event in a 68-year-old male participant was likely not related to the study vaccine given the confounding illness (viral infection) and the latency of onset of the event after the study dose and therefore is not recommended for inclusion in the product labeling.

6.4.12.7 FDA Standard MedDRA Queries

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). There were no additional events identified concerning for myocarditis or pericarditis that were not described in the AESIs section above.

SMQs Hypersensitivity

Through 28 days following the booster dose, a total of 77 events were identified under the SMQs *Hypersensitivity* with urticaria, injection site urticaria, and rash as the most reported PTs. Of these events, 54 were assessed as related to the study dose. The most common PTs among these events were injection site urticaria, urticaria, and rash. There were no events of anaphylaxis assessed as related to the study dose.

SMQs Embolic and Thrombotic Events and Central Nervous System Vascular Disorders

Through the data cutoff, events were reported by 83 participants (0.4%) under the SMQ *Embolic and Thrombotic Events* and by 37 participants (0.2%) under the SMQ *Central Nervous System Vascular Disorders* in the Safety Set. Acute Myocardial Infarction (<0.1%) and Cerebrovascular Accident (<0.1%) were the most frequently reported PT in each respective SMQ. Of the events in these SMQs, 4 (<0.1%) were considered related to the study dose (N=3 for *Embolic and Thrombotic Events;* N=1 for *Central Nervous System Vascular Disorders*) and included cerebral ischemia and related sequelae as the most frequently reported terms.

1. Cerebral ischemia (verbatim: chronic cerebral microvascular ischemia) was reported in a 74-year-old White female on Day 24 after booster dose vaccination and was ongoing at time of data cutoff. The event was considered by the investigator to be mild, non-serious, and related to the study vaccine and was not medically attended. The participant had previously reported dizziness on BD-Day 14 and hypertension on BD-Day 16 that were not resolved as of data cutoff. The participant was also diagnosed with a meningioma on Day 24 after the booster dose that was considered by the investigator to be unrelated to study vaccine.

2. Hemiparesis (specified in verbatim term as leg, arm, face) was reported in an 80-year-old White female with a medical history of atrial fibrillation and a cardiac pacemaker. The event started on Day 2 after the booster dose and was assessed as related to the study vaccine by the investigator. The event resolved

on BD-Day 10. The participant's concomitant medications included apixaban and atorvastatin.

3. Aphasia was reported on day 2 following booster in a 48-year-old White and Asian female with a medical history of anxiety and bipolar disorder. The event was considered by the investigator to be related to the study vaccine. The event resolved on booster Day 4 without treatment.

4. Monoplegia of the left arm (arm of booster dose administration) was reported in a 65-year-old White male on BD-Day 2 and was assessed as related to the study vaccine by the investigator. The event resolved on BD-Day 4. The event was not medically attended.

Reviewer Comment: Although events #1 - #3 were assessed by the investigator as related to the study dose and, In this reviewer's assessment, although events #1 - #3 may have been related to the study dose based on temporal association, the medical conditions reported for participants #1 - #3 provide alternative causes for the reported events and confound the assessment of causality of the study dose. For event #4, the event also may have been related to the study dose based on temporal association; however, there was insufficient information to allow for a definitive assessment of causality as the participant did not have medical evaluation during the event.

6.4.12.8 Deaths

Overall, there were 27 deaths reported among mRNA-1273 booster dose recipients in Part C, through the database lock of May 16, 2022. Most deaths were reported among participants ≥60 years of age (n=20). Most of the deaths reported (n=19) occurred ≥2 months after receipt of the booster dose, and there were no deaths occurring within 14 days of the study vaccine. The causes of deaths were representative of the common causes of death in the general population. None of the reported deaths were considered related to vaccination by the study investigators. There was one death, assessed by the study investigator as unrelated to the study dose, which this reviewer considers clinically significant (discussed below).

1. A 56-year-old male participant with a history of hypertension, morbid obesity (BMI 52 kg/m^2), insulin resistance, and sleep apnea died due to cardiac arrest (b) (6) days after receipt of the study dose. The participant reported non-serious AEs of fatigue, dyspnea, and angina pectoris the day after receiving the study dose. These symptoms resolved 4 days later without intervention. (b) (6) days following the study dose, the participant experienced cardiac arrest at home and was transported to the hospital where he was ultimately declared dead after unsuccessful resuscitation attempts. The official cause of death was listed as unknown. The participant's wife reported, post-mortem, that the participant had experienced shortness of breath prior to the cardiac arrest event and was awaiting a medical appointment to evaluate this symptom. The investigator assessed the event as unrelated to the study dose due to the participant's underlying medical conditions.

Reviewer Comment: The participant's medical co-morbidities were significant risk factors for cardiac arrest. Although additional information preceding the event were not available (response to IR, STN 127752/68.25), it is unlikely that vaccination with

the study dose contributed to the participant's cardiac arrest. Therefore, the clinical reviewer agrees with the investigator's assessment.

6.4.12.9 Serious Adverse Events (SAEs)

In P301 Part C, through the data cut-off, SAEs were reported by 2.3% (n=442) booster dose recipients. SAEs within 28 days of vaccination were reported by 0.5% (n=94) booster dose recipients.

At the time of data cut-off, a total of 6 SAEs were assessed as related to the booster dose by the investigator. The first SAE was myocarditis in a 42-year-old male participant, that was previously described in Section 6.4.12.6. The next two cases were myocarditis in a 66-year-old female participant, and a fatal event of cardiac arrest in a 56-year-old male participant (described above), which were initially assessed by the investigator as related to the booster dose. The investigators later changed their assessments to not related following review of additional information made available after data cut-off but before the database lock. The remaining 3 SAEs assessed as related to booster dose vaccination by the investigator are described below.

1. A 71-year-old female participant with history of hyperlipidemia, hypertension, COPD, and bradycardia, developed coronary arterio-spasm with onset 10 days after vaccination with the study dose. The participant reported chest pain 10 days following vaccination and was admitted to the hospital for evaluation. An exercise stress test was positive and she was found to have elevated troponin levels. The participant underwent cardiac catheterization (results not available) and received symptomatic treatment. The event resolved 71 days after symptom onset. This event was also reported as an AESI.

2. A 40-year-old male with a history of anxiety and gastroesophageal reflux disease developed cardiac flutter with onset 11 days after receipt of the study dose. The participant reported episodes of "heart fluttering" starting 11 days following vaccination. He denied chest pain, pressure, or shortness of breath. The participant reported similar episodes of heart fluttering in the past associated with anxiety. He did not seek medical care and the fluttering sensation resolved the following day without intervention. This event was also reported as an AESI.

3. A 73-year-old female with a history of botulinum toxin and dermal filler injections, hypertension, arthritis, and seasonal allergies developed an SAE of erythema nodosum with onset 8 days after receipt of the study dose. The participant reported erythematous, nodular, tender rash on both lower extremities with pain, swelling and redness, and a diagnosis of erythema nodosum was confirmed by punch biopsy. The erythema nodosum resolved 21 days after symptom onset.

Reviewer Comment:
The clinical reviewer's assessment of each of SAE include the following:
1) Coronary arterio-spasm: unlikely to be related to the study vaccine due to participant's underlying medical history of cardiac disease and other risk factors which likely were significant contributing factors.
2) Cardiac fluttering: unlikely to be related to study vaccination due to the participant's prior history of anxiety and episodes of heart palpitations.
3) Erythema nodosum: likely related to study vaccine due to the temporal association with the study dose and the lack of alternative causative etiology.

Following review of the clinical narratives of the other SAEs reported in this study, the reviewer agrees with the investigator assessments that there were no other SAEs reported in Part C which were likely to be related to the study vaccine.

Pregnancies
A total of 25 pregnancies occurred during Part C of Study 301. Of the reported pregnancies, 6 had known outcomes (1 live birth, 4 spontaneous abortion/miscarriage, and 1 elective termination). The majority reported pregnancies (N=19) had an unknown outcome and/or were lost to follow-up.

Table 46. Pregnancies Reported in Study P301 Part C, Safety Set

Parameter	P205 Part H ≥18 years mRNA-1273 n N=19609
Total number of pregnancies	25
Timing of dose relative to LMP	
Prior to LMP	19
Within 30 days after LMP	2
>30 days after LMP	1
LMP unknown	3
Lost to follow-up	19
Known outcomes	6
Spontaneous abortion/miscarriage	4
Elective termination	1
Live born	1

Source: Adapted from mRNA-1273-P301 Addendum 2 Clinical Study Report Table 26
Abbreviations: LMP=last menstrual period

6.4.12.10 Dropouts and/or Discontinuations

See Section 6.4.10. Through the data cutoff, AEs leading to study withdrawal were reported in 26 participants. Of these, 25 were due to deaths (see Section 6.4.12.8). The non-fatal AE leading to study discontinuation was an SAE of upper limb fracture.

6.4.13 Study Conclusions

The open-label trial P301 Part C evaluated the effectiveness and safety of a 50 µg dose of Spikevax (Original monovalent) in participants 18 years of age and older at least 6 months following completion of a 2-dose series (100 µg each) of Spikevax (Original monovalent). The study met the pre-specified superiority criterion for nAb GMTs and seroresponse rates elicited by a 50 µg dose of Spikevax (Original monovalent) against the D614G strain as compared to after Dose 2 of the 2-dose series in the same group of study participants. The safety profile following the 50 µg dose was comparable to that reported after the 2-dose series. The reported SAEs that were assessed as related to the 50 µg dose, including the cases of myocarditis, were consistent with known risks after mRNA COVID-19 vaccines. Overall, the submitted clinical data support the safety and effectiveness of a 50 µg dose of SPIKEVAX including Spikevax (2023-2024 Formula) in previously COVID-19 vaccinated adults 18 years of age and older.

6.5 Study P205 (Part H): Adult 2nd Booster Dose with Moderna COVID-19, Bivalent (Original and Omicron BA.4/BA.5)

NCT04927065

Title: A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants

Study Overview: Study P205 is an ongoing, open-label, multi-part Phase 2/Phase 3 study that evaluated a single booster dose of original monovalent prototype mRNA-1273 (50 µg dose) and a single booster dose of modified bivalent mRNA-1273.222 (50 µg dose) that targeted SARS-CoV-2 variants BA.4/BA.5. Each of these vaccinations were administered as 2nd booster doses in adult participants 18 years of age and older who had previously completed at least a two-dose primary series of mRNA-1273 (each 100 µg dose) *and* a 1st booster dose vaccination with mRNA-1273 (50 µg). Table 47 below provides an overview of Part H and Part F in Study P205, which were not conducted concurrently.

Table 47. Relevant Study P205 Study Parts

P205 Part	Study Design	Vaccine Regimen/Dose	Study Dates	Vaccinated Participants*
H	Open label-2ndbooster-bivalent vaccine	Single mRNA-1273.222 25 µg Original + 25 µg Omicron BA.4/BA.5) dose following a 2-dose primary series of mRNA-1273 (100 µg) and a 1st booster dose of mRNA-1273 (50 µg)	Sep 23, 2022, ongoing	511 adults
F	Open label-2nd booster-monovalent prototype vaccine	Single mRNA-1273 (50 µg) dose following a 2-dose primary series of mRNA-1273 (100 µg) and a 1st booster dose of mRNA-1273 (50 µg)	Feb 18, 2022, ongoing	376 adults

Source: FDA-generated table
Notes: *Part H and Part F were not conducted concurrently; therefore, mRNA-1273.222 and mRNA-1273 booster dose groups were not contemporaneously evaluated

6.5.1 Objectives and Endpoints

Reviewer Comment: The following study objectives listed below are presented from Study P205 Part H evaluating the safety and effectiveness of mRNA-1273.222. However, data from both mRNA-1273.222 (Part H) and mRNA-1273 (Part F) are reviewed to support use of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals previously vaccinated with mRNA-1273. These two study parts were not conducted concurrently in Study P205 (see table above).

Primary Objectives/Endpoints

1. To evaluate the safety and reactogenicity of mRNA-1273.222 50 µg

   Endpoints:

a. Solicited local and systemic reactogenicity (adverse reactions, ARs) during a 7-day follow-up period after injection.
b. Unsolicited AEs during the 28-day follow-up period after injection
c. MAAEs from Day 1 through the end of study
d. SAEs from Day 1 through the end of study

2. To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second booster dose against Omicron BA.4/BA.5 based on GMT ratio and SRR difference at Day 29 following vaccination.

   Endpoints:
   a. Ratio of geometric mean titer (GMT) of Omicron BA.4/BA.5 neutralizing antibodies (nAb) at Day 29 following mRNA-1273.222 (Part H) over the Omicron BA.4/BA.5 nAb GMT following mRNA-1273 50 µg (Part F, Cohort 2) at Day 29 following vaccination.

      Success criterion: The noninferiority of mRNA-1273.222 at Day 29 following vaccination, as compared to mRNA-1273, was demonstrated if the lower bound of the 95% CI for the ratio of the GMTs was >0.667

   b. Seroresponse rate (SRR, percentage) difference between nAb against Omicron BA.4/BA.5 following mRNA-1273.222 (Part H) compared to following mRNA-1273 (Part F, Cohort 2) at Day 29 following vaccination. SRR is defined as the proportion of participants in each study group with a post-vaccination nAb titer 4-times the LLOQ for those participants with baseline (pre-dose 1 of the 2-dose series) and 4-times the baseline titer for those participants with a baseline titer ≥LLOQ.

      Success criterion: The noninferiority of mRNA-1273.222 at Day 29 following vaccination, as compared to mRNA-1273, was demonstrated if the lower bound of the 95% CI of the SRR (percentage) difference (SRR of 50 µg mRNA-1273.222 against Omicron BA.4/BA.5 at Day 29 minus SRR of 50 µg mRNA-1273 against Omicron BA.4/BA.5 at Day 29) was > -5%

3. To demonstrate superiority of the antibody response of mRNA 1273.222 administered as a second booster dose compared to mRNA-1273 50 µg administered as a second booster dose against the Omicron BA.4/BA.5 variant based on GMT ratio at Day 29 following vaccination

   Endpoint
   a. Ratio of GMT of Omicron BA.4/BA.5 nAbs following mRNA-1273.222 (Part H) over the Omicron BA.4/BA.5 GMT following mRNA-1273 50 µg (Part F, Cohort 2) at Day 29 following vaccination.

      Success criterion: The superiority of mRNA-1273.222 at Day 29 following vaccination, as compared to mRNA-1273, was demonstrated if the lower bound of the 95% CI for the ratio of the GMTs was >1

4. To demonstrate non-inferiority of the antibody response dose against D614G elicited by mRNA-1273.222 50 µg when administered as a second booster dose compared to mRNA-1273 50 µg when administered as a second booster based on GMT ratio and SRR (percentage) difference at Day 29 following vaccination.

   Endpoint
   a. Ratio of SARS-CoV-2 D614G GMT at Day 29 following mRNA-1273.222 over the SARS-CoV-2 D614G GMT at Day 29 following mRNA-1273

      Success criterion: The noninferiority of mRNA-1273.222 at Day 29 following vaccination, as compared to mRNA-1273, was demonstrated if the lower bound of the 95% CI for the ratio of the GMTs was >0.667

   b. Seroresponse rate (SRR) percentage difference between nAb against D614G (Part H) compared to following mRNA-1273 (Part F, Cohort 2) at Day 29 following vaccination. SRR is defined as the proportion of participants in each study group with a post-vaccination nAb titer 4-times the LLOQ for those participants with baseline (pre-dose 1 of the 2-dose series) and 4-times the baseline titer for those participants with a baseline titer ≥LLOQ.

      Success criterion: The noninferiority of mRNA-1273.222 at Day 29 following vaccination, as compared to mRNA-1273, was demonstrated if the lower bound of the 95% CI of the SRR (percentage) difference (SRR of 50 µg mRNA-1273.222 against D614G at Day 29 minus SRR of 50 µg mRNA-1273 against D614G at Day 29) was >-5%

Exploratory Objectives/Endpoints
1. To assess for symptomatic and asymptomatic SARS-CoV-2 infection

   Endpoints (descriptive analyses only)
   a. Laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection based on:
      i. Primary case definition per Study P301
      ii. Secondary case definition per CDC criteria
      iii. Asymptomatic SARS-CoV-2 infection defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test at time of enrollment

6.5.2 Design Overview

Part H of P205 was an open-label study evaluating the safety and immunogenicity of a 50 µg dose of mRNA1273.222 administered as a 2nd booster dose to 511 adults ≥18 years of age at least 3 months after vaccination with a 1st booster dose of mRNA-1273 50 µg which was received at least 6 months after completion of the 2-dose primary series. The comparator groups for the safety and immunogenicity endpoints were adults ≥18 years of age in Cohort 2 of Part F of Study P205 who received a 2nd booster dose of mRNA-1273 50 µg at least 3 months after vaccination with a 1st booster dose of mRNA-1273 50 µg which was received at least 6 months after completion of the 2-dose primary series.

Participants in Part H had safety follow-up through 6 months following vaccination, which was the end of the study (EOS). Primary safety endpoints included solicited adverse reactions (ARs) through 7 days following vaccination, unsolicited AEs through 28 days following vaccination, and SAEs, MAAEs, AEs leading to withdrawal, and AESIs through the EOS. Primary immunogenicity endpoints evaluated the nAb titers against the Omicron BA.4/BA.5 variant of SARS-CoV-2 elicited at Day 29 following the study dose

6.5.3 Population

The study enrolled adults 18 years of age and older with and without a history of prior SARS-CoV-2 infection and with and without risk factors for severe COVID-19. Participants completed their 2-dose mRNA-1273 series at least 6 months prior to enrollment and a 50 µg dose of mRNA-1273 at least 3 months prior to enrollment. Prior vaccination may have been received either as a part of the mRNA-1273-P301 study or under EUA.

6.5.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273.222 (Lot # 8524100101) contains 25 µg of CX-024414, mRNA encoding for the prefusion stabilized spike glycoprotein (S-2P) of the Wuhan-Hu-1 isolate of SARS-CoV-2 and 25 µg of CX-034476, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 subvariants BA.4/BA.5 encapsulated in lipid particles.

6.5.5 Directions for Use

Intramuscular injection of the 50 µg mRNA-1273.222 vaccine was administered into the deltoid muscle (preferably the nondominant arm) as a single dose at least 6 months after the 2nd primary series dose of mRNA-1273 (100 µg) and 3 months after receiving a first booster dose of mRNA-1273 (50 µg).

6.5.6 Sites and Centers

This study was conducted at 23 study sites in the U.S.

6.5.7 Surveillance/Monitoring

Immunogenicity
All participants provided pre- and postvaccination blood specimens for immunogenicity through 6 months after the study vaccine with primary study endpoints evaluated at Day 29 following vaccination. The following immunogenicity assessments were performed:

- Serum nAb titers against Omicron (BA.4/BA.5) and against SARS-CoV-2 (D614G) as measured by a PsVNA 50% inhibitory dose (ID50) performed at Duke University Medical Center.

Serum samples were also tested for bAb titers against the SARS-CoV-2 nucleocapsid protein (N-protein) to determine the immunologic status of study participants at baseline and to assess for seroconversion due to infection during the study.

Safety

Following the study dose, participants were seen in clinic (Days 0, 28, 90, and 180) and received safety follow-up calls (Day 8 and biweekly from Day 43-Day 169) to facilitate

collection of solicited ARs through 7 days; unsolicited AEs observed or reported during the 28 days following vaccination (i.e., the day of vaccination and 27 subsequent days); SAEs, MAAEs, and AEs leading to withdrawal from Day 1 through study completion or withdrawal; abnormal vital sign measurements; physical exam findings; pregnancy and accompanying outcomes.

All potential cases of myocarditis and pericarditis, as identified by the investigator or Applicant, were reviewed by an independent Cardiac Event Adjudication Committee (CEAC) to determine whether the case met the CDC criteria (Appendix D) 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.

6.5.8 Endpoints and Criteria for Study Success

See Section 6.2.1 and 6.2.9.

6.5.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity Analyses

The Per-Protocol Immunogenicity Set (PPIS-Neg) set was used to assess immunogenicity endpoints and consisted of all participants who received a booster dose, had no major protocol deviations that impacted key or critical data, and who had no serologic or virologic evidence of SARS-CoV-2 infection at baseline (defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid prior to the study dose). The comparator group for immunogenicity analyses was participants in Cohort 2 of Study Part F who met the same criteria as those set for the PPIS-Neg set. An analysis of covariance (ANCOVA) model was performed to assess the difference in immune response between mRNA-1273.222 and mRNA-1273 as a second booster dose following a first booster dose of mRNA-1273.

For immune responses against the BA.4/BA.5 strain, in the ANCOVA model, antibody titers at Day 29 post-booster against the BA.4/BA.5 strain was a dependent variable, and a group variable (mRNA-1273.222 and mRNA-1273) was the fixed effect, adjusting for age groups (<65, ≥65 years) and pre-booster antibody titer level, if applicable.

The GMT was estimated by the geometric least squared mean (GLSM) from the model and its corresponding 95% was provided for each group. The GMT Ratio for mRNA-1273.222 with respect to mRNA-1273 was estimated by the ratio of GLSM from the model and the corresponding 95% CIs was provided. The 95% CI for GMR was used to assess the between group difference in immune response against the B.1.1.222 strain for mRNA-1273.529 at Day 29 compared to the mRNA-1273.

The number and percentage (rate) of participants achieving SRR at Day 29 was summarized with 95% CI calculated using the Clopper-Pearson method for each group. The difference in SRR percentages between mRNA-1273.529 and mRNA-1273 was calculated with 95% CI based on Miettinen-Nurminen method.

Safety Analyses

Safety endpoints were assessed descriptive without formal hypothesis testing.

6.5.10 Study Population and Disposition

This sBLA submission includes data from the start of enrollment for P205 Part H on August 10, 2022, through the data cutoff date of September 23, 2022. A total of 511 participants received a dose of mRNA-1273.222 in Part H.

6.5.10.1 Populations Enrolled/Analyzed

The analyses population used for study analyses are defined in Table 48. Immunogenicity analyses were conducted on the Per Protocol Immunogenicity Subset – SARS-CoV-2 Negative (PPIS-Neg). Safety analyses were conducted on the Safety Set except for summaries of solicited adverse reactions, which were based on the Solicited Safety Set.

Table 48. Analysis Populations, Study P205 Part H

Population	Description
Safety Set	All participants who received the study vaccine
Solicited Safety Set	All participants who received study vaccine and contributed any solicited AR data
Full Analysis Set (FAS)	All participants who received the study vaccine
Per-Protocol Immunogenicity Set (PPIS)	The PPIS included all participants in the FAS who: received the planned dose of study vaccination per the schedule, had pre-booster and Day 29 a neutralizing antibody (nAb) data against the Omicron BA.1 variant for Part F (Cohort 2) or against the BA.4/BA.5 variant for Part H, had no major protocol deviations that impacted key or critical data, had no previous HIV infection
PPIS-SARS-CoV-2 Negative (PPIS-Neg)	Participants in the PPIS who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline, i.e., who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid

Source: FDA-generated table
Abbreviations: AR=adverse reaction; bAb=binding antibody; HIV=human immunodeficiency virus; FAS=full analysis set; PPIS=per protocol immunogenicity set; RT-PCR=real-time polymerase cycle reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

6.5.10.1.1 Demographics

The Part H PPIS-Neg population was used for analyses of the primary immunogenicity endpoints and consisted of a total of 209 participants who received 50 µg of mRNA-12732.222 (Table 49). The median age at screening was 51 years (range of 21 to 84 years) with 25.4% of participants ≥65 years of age. There was a higher percentage of female participants (64.6%) compared to male participants (35.4%). Most study participants in the PPIS-Neg identified as White (89%) and non-Hispanic or Latino (89.5%). The comparator group used for the analyses of the immunogenicity endpoints was the Part F Cohort 2 PPIS-Neg population, which consisted of a total of 259 participants who received 50 µg of mRNA-1273. The median age at screening was 63 years (range of 21 to 96 years). Compared to Part H, a higher percentage (46.3%) of Part F participants were 65 years of age and older. The Part F PPIS-Neg population included a more balanced proportion of female (51.7%) and male (48.3%) participants as compared to Part H which included a higher percentage of female participants (64.6%) as compared to male participants (35.4%). Demographics based on race and ethnicity were similar between the Part H and Part F.

In the PPIS-Neg population for both Part H and Part F Cohort 2, the median interval between Dose 2 of the primary series and receipt of the first booster dose was approximately 8 months. There was a longer median interval between the first booster and the second booster (dose evaluated in this study) among Part H participants (approximately 9-10 months) as compared to Part F participants (approximately 4-5 months).

Table 49. Demographics and Other Baseline Characteristics, Adults 18 Years and Older, PPIS – Neg, Study P205 Part H and P205 Part F*

Characteristic	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose n (%[a]) N=209	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose n (%[a]) N=259
Sex	--	--
Female	135 (64.6)	134 (51.7)
Male	74 (35.4)	125 (48.3)
Age	--	--
Median (min, max) (years)	51 (21,84)	63 (21, 96)
18-64 years	156 (74.6)	139 (53.7)
≥65 years	53 (25.4)	120 (46.3)
Race	--	--
White	186 (89.0)	233 (90.0)
Black or African American	11 (5.3)	11 (4.2)
Asian	7 (3.3)	11 (4.2)
American Indian or Alaska Native	1 (0.5)	0
Multiracial	2 (1.0)	0
Other	1 (0.5)	1 (0.4)
Not Reported	1 (0.5)	2 (0.8)
Unknown	0	1 (0.4)
Ethnicity	--	--
Hispanic or Latino	20 (9.6)	22 (8.5)
Not Hispanic or Latino	187 (89.5)	237 (91.5)
Not reported	2 (1.0)	0
BMI: <30 kg/m^2	115 (55%)	140 (54%)
BMI: ≥30 kg/m^2	94 (45%)	119 (46%)
Interval between Dose 2 of primary series and 1st booster	--	--
Median (days)	250	242
Min, max (days)	67, 440	172, 435
Interval between 1st booster and 2nd booster (study dose)	--	--
Median (days)	288	133
Min, max (days)	138, 334	90, 310

Source: STN 125752.68, P205 Part H, Table 14.1.3.3.9, Response to IR request received 16 August 2023
Abbreviations: max=maximum; min=minimum; PPIS-Neg=Per protocol immunogenicity subset-SARS-CoV-2 negative; N=number of participants in the PPIS-Neg; n=number of participants in the category
Notes:
*Part F Cohort 2
a. %=n/N

The Part H Safety Set was used for safety analyses of the booster dose and consisted of a total of 511 participants (Table 50). The comparator group was Cohort 2 of Study

Part F, which consisted of 376 participants. The demographics and baseline characteristics of the Safety Set for each of the studies were similar to those of the PPIS-Neg for the respective study. Compared to Part F, Part H included a higher proportion of female participants (61.8% vs 50.5%) and a lower proportion of participants who were ≥65 years of age (20.5% vs 39.9%).

A greater proportion of Part H participants had evidence of prior SARS-CoV-2 infection pre-booster dose (56.0%) as compared to Part F participants (26.9%). There was a longer median interval between the first booster and the second booster among Part H participants (approximately 9-10 months) as compared to Part F participants (approximately 4-5 months).

Table 50. Demographics and Other Baseline Characteristics, Adults 18 Years and Older, Study P205 Part H and P205 Part F*, Safety Set

Characteristic	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose n (%a) N=511	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose n (%[a]) N=376
Sex	--	--
Female	316 (61.8)	190 (50.5)
Male	195 (38.2)	186 (49.5)
Age (years)	--	--
Median (min, max) (years)	50 (19, 89)	60.5 (20, 96)
18-64 years	406 (79.5)	226 (60.1)
≥65 years	105 (20.5)	150 (39.9)
Race	--	--
White	426 (83.4)	322 (85.6)
Black or African American	56 (11.0)	28 (7.4)
Asian	11 (2.2)	16 (4.3)
American Indian or Alaska Native	1 (0.2)	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)
Multiracial	8 (1.6)	2 (0.5)
Other	6 (1.2)	2 (0.5)
Not Reported	2 (0.4)	3 (0.8)
Unknown	1 (0.2)	1 (0.3)
Ethnicity	--	--
Hispanic or Latino	58 (11.4)	37 (9.8)
Not Hispanic or Latino	448 (87.7)	339 (90.2)
Not reported	4 (0.8)	0
Unknown	1 (0.2)	0
BMI: <30 kg/m^2	257 (50.3)	201 (53.5)
BMI: ≥30 kg/m^2	254 (49.7)	175 (46.5)
Pre-study dose SARS-CoV-2 status[b]	--	--
Negative	216 (42.3)	267 (71.0)
Positive	286 (56.0)	101 (26.9)
Missing	9 (1.8)	8 (2.1)
Interval between primary series and 1st booster	--	--
Median (m)	251	242
Min, max	67, 533	170, 438

Characteristic	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose n (%a) N=511	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose n (%[a]) N=376
Interval between 1st booster dose and 2nd booster dose	--	--
Median (m)	289	134
Min, max*	103, 371	90, 310

Source: Adapted from STN 125752.68, P205 Part H Clinical Study Report, Tables 14.1.3.1.9, Response to IR request received August 2, 2023
Abbreviations: BMI=body mass index; max=maximum; min=minimum; m=months; N=number of participants in the Safety Set; n=number of participants in the category
Notes:
*Part F Cohort 2
a. %=n/N
b. Pre-study dose SARS-CoV-2 status was evaluated with RT-PCR test for SARS-CoV-2 and serology test based on bAb specific to SARS-CoV-2 nucleocapsid prior to receipt of the study dose. SARS-CoV-2 negative was defined has having a negative result on both tests. SARS-CoV-2 positive was defined as a positive result with one or more of the tests.

Reviewer Comment: As a result of the later start date of Part H as compared to Cohort 2 of Part F, participants in Study Part H had a longer interval between the 1st 50 µg dose and the study dose. This longer interval may impact the interpretation of the relative immune responses following the study dose as well as the observed rates of COVID-19 given epidemiologic differences of COVID-19 during the different study periods.

6.5.10.1.2 Participant Disposition

The dispositions and reasons for exclusion from analysis populations for Part H and Part F Cohort 2 participants are shown in Table 51. Discontinuations from the study were rare in both groups, with a higher proportion of participants who discontinued from Part F (1.6%) compared to Part H (0.8%), most of which were due to lost to follow-up. One participant in each part of the study discontinued due to death (discussed in Section 6.5.12.7), neither event was considered related to study vaccine.

The most common reason for exclusion from the PPIS-Neg for both Part H and Part F Cohort 2 participants was SARS-CoV-2 PCR and/or serology positive or missing at baseline (Part H: 55%; Part F Cohort 2: 28.5%).

Table 51. Disposition, Adults 18 Years and Older, Study P205 Part H and Part F*, Study Analysis Populations

Disposition	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose n (%)	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose n (%)
Full Analysis Set	N=511	N=376
Discontinued from study[a]	4 (0.8)	6 (1.6)
Reason for discontinuation	--	--
Death	1 (0.2)	1 (0.3)
Lost to follow-up	1 (0.2)	4 (1.1)
Withdrawal of consent by participant	2 (0.4)	1 (0.3)
Safety Set	N=511	N=376

Disposition	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose n (%)	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose n (%)
Solicited Safety Set[b]	508 (99.4)	350 (93.1)
Per-protocol Immunogenicity Set	N=490	N=366
Per-protocol Immunogenicity Set, SARS CoV-2 Negative (PPIS-Neg)	N=209	N=259
Excluded from PPIS-Neg[a]	302 (59.1)	117 (31.1)
Reason for exclusion[a]	--	--
Received incorrect vaccination	0	0
Had no baseline immunogenicity data	3 (0.6)	0
Had no Day 29 immunogenicity data	16 (3.1)	6 (1.6)
Had Day 29 immunogenicity data out of window	0	2 (0.5)
Had major protocol deviation(s)	1 (0.2)	1 (0.3)
History of HIV infection	1 (0.2)	1 (0.3)
SARS-CoV-2 PCR and/or serology positive or missing at baseline	281 (55.0)	107 (28.5)

Source: Adapted from STN 125752.68, P205 Part H Clinical Study Report Tables 14.1.1.1.9, 14.1.2.9, 14.1.2.2.9, 14.1.2.2.1.9, P205 Part G Clinical Study Report Tables 14.1.1.1.8, Response to IR received August 2, 2023
Abbreviations: HIV- human immunodeficiency virus; PPIS- Per protocol immunogenicity set; PCR- polymerase cycle reaction; SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
*Part F Cohort 2
a. Percentages are based on the number of participants in the Full Analysis Set.
b. Percentages are based on the number of participants in the Safety Set.
A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.

6.5.11 Analyses of Vaccine Effectiveness

6.5.11.1 Analyses of Primary Endpoints

Vaccine effectiveness of a booster dose of mRNA-1273.222 was inferred based on the evaluation of the nAb GMT and the SRR against Omicron (BA.4/BA.5) and D614G strains elicited by mRNA-1273.222 as compared to mRNA-1273, 28 days following a second booster. Co-primary endpoints, described in Section 6.2.1, were evaluated in participants without evidence of prior SARS-CoV-2 infection prior to the study dose (PPIS-Neg Set).

Results of the analyses of the primary endpoints are shown in Table 52 and Table 53. The GMT ratio of mRNA-1273.222 compared to mRNA-1273 against Omicron BA.4/BA.5 was 6.3 (95% CI 5.3, 7.5), which met the pre-specified success criterion for superiority (lower bound [LB] of the 95% CI of the GMT ratio >1). The GMT ratio of mRNA-1273.222 compared to mRNA-1273 against D614G was 2.0 (95% CI 1.7, 2.3), which met the pre-specified success criterion for non-inferiority (LB of the 95% CI of the GMT ratio >0.667).

Table 52. Geometric Mean Titers (GMTs) as Measured by Pseudovirus nAb Assay Against the Omicron BA.4/BA.5 and D614G at 28 Days Following the Study Dose , Adults 18 Years and Older, Study P205 Part H and Part F*, PPIS-Neg

Strain	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose N=209 GMT (95% CI)[a]	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose N=259 GMT (95% CI)[a]	GMT Ratio (Part H/Part F*) (95% CI)[a]
Omicron BA.4/BA.5	2747.3 (2399.2, 3145.9)	436.7 (389.1, 490.0)	6.3 (5.3, 7.5)
D614G	9555.8 (8593.6, 10625.7)	4882.2 (4457.7, 5347.1)	2.0 (1.7, 2.3)

Source: Adapted from STN 125752.68, P205 Part H Clinical Study Report, Table 14.2.2.1.1.9
Abbreviations: CI=confidence interval; GMT=Geometric mean titer; N=number of participants with non-missing data at the corresponding timepoint; nAb=neutralizing antibodies; PPIS-Neg=Per protocol immunogenicity subset-SARS-CoV-2 negative
Notes: *Part F Cohort 2
For Omicron BA.4/BA.5: LLOQ=36.7; ULOQ=13705; For D614G: LLOQ=18.5; ULOQ=45118
a. 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 were not available. The log-transformed antibody levels were analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, >=65 years) and pre-study dose antibody titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose. The resulted least square (LS) means, difference of LS means, and 95%CI were back transformed to the original scale for presentation.

As described in Section 6.2.1, the primary analyses of seroresponse following the study dose were based on nAb titer levels prior to the 1st dose of the 2-dose series. Using this primary definition of SRR, the difference in SRR (percentage) of mRNA-1273.222 compared to mRNA-1273 against Omicron BA.4/BA.5 was 12.1% (95% CI 6.9, 17.3), which met the pre-specified success criterion for non-inferiority (LB of the of the 95% CI of the difference in seroresponse rates > -5%).

The difference in SRR (percentage) of mRNA-1273.222 compared to mRNA-1273 against D614G was 0% (95% CI non-evaluable; both groups had 100% SRR), which also met the pre-specified success criterion for non-inferiority for this endpoint (LB of the of the 95% CI of the percentage difference in SRR rates > -10%).

However, the nAb titer levels after the second booster dose may be influenced by the prior three mRNA-1273 doses (two primary series doses and the first booster dose) and a SRR using the primary study definition cannot solely be attributed to vaccination with the second booster dose. Consequently, the Applicant evaluated the SRRs using a revised SRR definition assessing the increase in nAb titer levels using a baseline of the pre-second booster dose nAb titers as follows:

- Seroresponse for participants with pre-2nd booster <LLOQ is defined as ≥4 x LLOQ
- Seroresponse for participants with pre-2nd booster ≥LLOQ is defined as ≥4-fold increase in titers compared to pre-2nd booster titer

Analyses of SRR rates using a baseline measure prior to the second booster dose resulted in SRR (percentage) difference of 53.9% (95% CI 46.7, 61.2) for Omicron BA.4/BA.5 and 37.3% (95% CI 29.0, 45.6) for D614G. Analyses of SRR using this definition would also have met the pre-specified success criteria for non-inferiority for the two endpoints (Table 53).

Table 53. Seroresponse Rates (SRRs) as Measured by Pseudovirus nAb Assay Against the Omicron BA.4/BA.5 and D614G at 28 Days Following the Study Dose (From Pre-Second Booster Dose), Adults 18 Years and Older, Study P205 Part H and Part F*, Study P205, PPIS-Neg

Strain	P205 Part H ≥18 years mRNA-1273.222 50 µg Booster Dose N1=209 SRR % (95% CI)	P205 Part F* ≥18 years mRNA-1273 50 µg Booster Dose N1=259 SRR % (95% CI)	Difference in SRR (Part H-Part F*) % (95% CI)[a]
Omicron BA.4/BA.5	90.9 (86.2, 94.4)	37.8 (31.9, 44.0)	53.9 (46.7, 61.2)
D614G	80.4 (74.3,85.5)	42.9 (36.7, 49.1)	37.3 (29.0, 45.6)

Source: Adapted from STN 125752.68, P205 Part H Clinical Study Report, Table 14.2.2.1.2.1.9
*Part F Cohort 2. For Omicron BA.4/BA.5: LLOQ=36.7 ; ULOQ=13705
For D614G: LLOQ= 18.5; ULOQ=45118
95% CI was calculated using the Clopper-Pearson method.
Abbreviations: CI=confidence interval; N1=number of participants with non-missing data at baseline and the corresponding timepoint; PPIS-Neg=Per protocol immunogenicity subset-SARS-CoV-2 negative; SRR=Seroresponse rate
Seroresponse from pre-second booster dose baseline at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on N1.
a. Common risk difference and 95% CI is calculated using the stratified Miettinen-Nurminen method to adjust for age group (<65, >=65 years).

Reviewer Comment: The reported GMTs and SRRs suggest that the dose of bivalent mRNA-1273.222 elicits substantially higher immune responses against the Omicron BA.4/BA.5 strain and the D614G strain as compared to a dose of mRNA-1273. All tested immunogenicity endpoints, including those for which superiority criteria were not pre-specified, met the superiority criteria in the FDA guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19 (updated March 2022)." The interpretation of these data is somewhat limited by the longer interval between the 1st 50 µg dose and the study dose in the Part H group which may have contributed to higher nAb responses in this group although the Part H group did have generally lower pre-study dose nAb titers (Part H nAb GMT of 796.9 vs Part F Cohort 2 nAb GMT of 1515.4). Overall, the immunogenicity data suggest the effectiveness of mRNA-1273.222 against SARS-CoV-2, including variant Omicron BA.4/BA.5.

6.5.11.2 Subpopulation Analyses

Most of the study participants in Study P205 were White, Non-Hispanic, and non-obese; therefore, subgroup analyses of co-primary endpoints by race, ethnicity, and obesity status were not conducted, as the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results.

Subgroup analyses of serum GMTs based on the age at booster dose (18-64 years and ≥65 years) in the PPIS-Neg set showed higher nAb GMTs against the actual strain among participants ≥65 years in both study parts (Part F and Part H). Responses against the BA.4/BA.5 variant were comparable between age groups within each study cohort (Table 54).

Table 54. Antibody GMTs as Measured by Pseudovirus nAb Assay Against the Omicron BA.4/BA.5 and D614G by Age at 28 Days Following the Study Dose, Adults 18 Years and Older, Part H and Part F*, Study P205, PPIS-Neg

Strain	P205 Part H mRNA-1273.222 50 µg BD 18-64 years N=156 GMT (95% CI)	P205 Part H mRNA-1273.222 50 µg BD ≥65 years N=53 GMT (95% CI)	P205 Part F* mRNA-1273 50 µg BD 18-64 years N1=139 GMT (95% CI)	P205 Part F* mRNA-1273 50 µg BD ≥65 years N=120 GMT (95% CI)
Omicron BA.4/BA.5	2526.7 (2181.6, 2926.3)	2941.0 (2266.5, 3816.2)	374.7 (320.7, 437.8)	537.3 (452.2, 638.4)
D614G	7522.8 (6712.6, 8430.7)	12862.4 (10429.4, 15862.9)	3836.6 (3399.4, 4330.0)	6663.3 (5804.8, 7648.8)

Source: Adapted from Study P205 Part H Clinical Study Report Table 14.2.2.1.7.9
Abbreviations: BD=booster dose; CI=confidence interval; GMT= Geometric mean titer; N=number of participants with non-missing data at the corresponding timepoint; nAb=neutralizing antibodies; PPIS-Neg=Per protocol immunogenicity subset-SARS-CoV-2 negative
Notes: *Part F Cohort 2
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
Subjects' immune response data is censored at the last date of study participation (study discontinuation, study completion, or death), non-study COVID-19 vaccination date, or data cutoff/extraction date, whichever is the earliest.
The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for pre-booster ant body titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Analyses of the SRRs against Omicron BA.4/BA.5 (based on a pre-study dose baseline) showed similar SRRs among Part H PPIS-Neg participants irrespective of age group (18-64 years: 91.7% [86.2, 95.5]; ≥65 years: 88.7% [77.0, 95.7]). The SRRs against D614G among Part H participants were also similar (18-64 years: 82.7% [75.8, 88.3]; ≥65 years: 73.6% [59.7, 84.7]).

Subgroup analyses of nAb GMTs based on SARS-CoV-2 status prior to the study dose (PPIS-All and PPIS-positive) found similar patterns of nAb responses following the study dose as for the PPIS-negative set. nAb responses were higher among participants who were SARS-CoV-2 positive at baseline.

Table 55. Antibody GMTs as Measured by Pseudovirus nAb Assay Against the Omicron BA.4/BA.5 and D614G at 28 Days Following the Study Dose By Baseline SARS-CoV-2 Status[a], Adults 18 Years and Older, Part H and Part F*, Study P205, PPIS

Strain	P205 Part H ≥18 years mRNA-1273 50 µg BD Any SARS-CoV-2 N=490 GMT (95% CI)	P205 Part H ≥18 years mRNA-1273 50 µg BD SARS-CoV-2 Positive N=274 GMT (95% CI)	P205 Part F* ≥18 years mRNA-1273 50 µg BD Any SARS-CoV-2 N1=366 GMT (95% CI)	P205 Part F* ≥18 years mRNA-1273 50 µg BD SARS-CoV-2 Positive N=99 GMT (95% CI)
Omicron BA.4/BA.5	4289.4 (3789.0, 4855.9)	7607.7 (6607.4, 8759.5)	642.5 (567.1, 727.9)	1490.2 (1217.3, 1824.4)
D614G	9318.9 (8541.0, 10167.7)	12659.4 (11361.6, 14105.4)	6050.2 (5466.3, 6696.4)	6872.8 (5877.7, 8036.2)

Source: Adapted from Study P205 Part H Clinical Study Report Table 14.2.2.1.3.9, 14.2.2.1.9.9
Abbreviations: BD=booster dose; CI=confidence interval; GMT= Geometric mean titer; N=number of participants with non-missing data at the corresponding timepoint; nAb=neutralizing antibodies; PPIS =Per protocol immunogenicity subset
Notes: *Part F Cohort 2
a. Pre-booster study dose SARS-CoV-2 status was evaluated with RT-PCR test for SARS-CoV-2 and serology test based on bAb specific to SARS-CoV-2 nucleocapsid prior to receipt of the study dose. SARS-CoV-2 negative was defined has having a negative result on both tests. SARS-CoV-2 positive was defined as a positive result with one or more of the tests. Any SARS-CoV-2 included those with negative, positive, or missing SARS-CoV-2 test results
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the treatment variable as fixed effect, adjusting for age group (<65, >=65 years), pre-booster SARS-CoV-2 status (negative, positive), and pre-booster antibody titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale.

Reviewer Comment: The immunogenicity analyses of the subgroups do not suggest substantial differences in the immune responses to mRNA-1273.222 based on age or SARS-CoV-2 status. The higher post-booster nAb GMTs among participants who were SARS-CoV-2 positive at baseline are expected due to prior SARS-CoV-2 exposure (i.e., hybrid immunity).

6.5.11.3 Exploratory Endpoints

COVID-19 Incidence Rates

The occurrence of COVID-19 cases beginning 14 days after vaccination through the cut-off date of September 23, 2022, was evaluated as an exploratory endpoint. The median duration of follow-up for Part H participants at the time of the data cutoff was 37 days. A total of 5 participants (2.3%) met the primary case definition of COVID-19 using the criteria defined in the P301 study (Appendix C) and 7 participants (3.2%) met the CDC case definition of COVID-19.

Reviewer Comment: Part H was not designed to assess the efficacy of mRNA-1273.222 in preventing COVID-19. As the Part H and Part F study groups were not contemporaneous, the relative occurrence of SARS-CoV-2 infection and COVID-19 between the study groups was not evaluated. The reported rates of COVID-19 among mRNA-1273.222 recipients cannot be meaningfully interpreted due to the lack of a comparator group.

6.5.12 Safety Analyses

P205 Part H was an open-label study and did not include a contemporaneous comparator group for safety. Safety analyses for Part H included data from 511 mRNA-1273.222 booster dose recipients through the cutoff date of September 23, 2022. The median duration of follow-up after booster was 37 days. As of the data cutoff, 99.6% of participants had at least 28 days of follow-up post-booster dose.

6.5.12.1 Methods

See Section 6.1.7.

6.5.12.2 Overview of Adverse Events

Table 56 provides an overview of AEs among mRNA-1273.222 booster recipients in Part H of Study P205. Solicited local and systemic adverse reactions were reported by 82.8% and 73.2% of study participants within 7 days post-booster, respectively.

Within 28 days of the booster dose, unsolicited AEs were reported by 22.7% of study participants; severe unsolicited AEs were rare, reported by 0.4% of participants. Through the data cutoff, MAAEs were reported by 16.2% of study participants. SAEs and deaths through the data cutoff were reported by 0.6% and 0.2% of study participants, respectively, and are further discussed in Sections 6.5.12.8 and 6.5.12.7. There was 1 additional death that was reported soon after the data cut-off and is discussed in Section 6.5.12.7 for completeness. There were no AEs leading to discontinuation from the study.

Solicited ARs and unsolicited AEs are shown in comparison to those reported by participants in P205 Part F Cohort 2 (Table 56). The rates of solicited ARs and unsolicited AEs were generally comparable between the 2 groups.

Table 56. Number and Percentage of Participants Reporting at Least One Safety Event Following the Study Dose, Adults 18 Years and Older, P205 Part H, Safety Set and Solicited Safety Set

Event Type	P205 Part H ≥18 years mRNA-1273.222 50 µg BD N=511	P205 Part F* ≥18 years mRNA-1273 50 µg BD N=376
Solicited Adverse Reactions (ARs)	**N1=507-508 n(%N1[a])**	**N1=349-350 n(%N1[a])**
Any ARs	443 (87.2)	300 (85.7)
Local ARs	420 (82.8)	278 (79.4)
Systemic ARs	372 (73.2)	231 (66.0)
Unsolicited Adverse Events (AEs)**	**N=511 n(%N[b])**	**N=376 n (%N[c])**
Unsolicited AEs up to 28 days after booster	116 (22.7)	80 (21.3)
Non-serious unsolicited AEs*	113 (22.1)	79 (21.0)
Related non-serious unsolicited AEs	40 (7.8)	21 (5.6)
Severe non-serious unsolicited AEs*	2 (0.4)	2 (0.5)
Related severe non-serious unsolicited AEs	2 (0.4)	2 (0.5)
MAAEs[d]	83 (16.2)	180 (47.9)
Related MAAE	0	2 (0.5)
SAEs[d]	3 (0.6)	10 (2.7)
Deaths[d]	1 (0.2)	1 (0.3)
AEs leading to study discontinuation[d]	0	0

Source: Adapted from STN 125752.68, P205 Part H Clinical Study Report, Table 14.3.1.7.1.9, 14.3.1.7.2.9 and P205 Part G Clinical Study Report, Table 14.3.1.7.2.8, Table 14.3.1.6.1.8
Abbreviations: BD=booster dose; AE=adverse event; AR=adverse reaction; MAAE=medically attended adverse events; n=number of participants reporting an event; N=partipants in the Safety Set; N1=participants in the Solicited Safety Set; SAE=serious adverse event
Notes: Part H and Part F were not conducted concurrently; therefore, mRNA-1273.222 and mRNA-1273 booster dose groups were not contemporaneously evaluated.
*Part F Cohort 2
**An adverse event (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.
a.Percentages are based on number of exposed participants who submitted any data for the event (N1)
b.Percentages are based on the number of safety participants in Part H
c. Percentages are based on the number of safety participants in Part F Cohort 2
d. All numbers reflect AEs reported through the data cutoff of September 23, 2022

In the Safety Set, approximately 42% of participants had no evidence of prior SARS-CoV-2 infection pre-study dose. The rates of safety events were similar between SARS-

CoV-2 positive and SARS-CoV-2 negative participants with 20 to 26% of participants reporting any unsolicited AE within 28 days after the booster dose. SAEs were reported by 2 participants in the SARS-CoV-2 negative group and 1 participant in the SARS-CoV-2 positive group.

> *Reviewer Comment: Overall, the rates and severities of AEs were generally similar when analyzed according to baseline SARS-CoV-2 status.*

Solicited Adverse Reactions (ARs) up to 7 Days After Booster Dose
Local and systemic ARs were solicited from study participants through 7 days following the study dose, by age subgroup, are shown in Table 57 and Table 58 below. Given the open-label design of this study, to provide a frame of reference to assess the rates of solicited ARs following a booster dose of mRNA-1273.222, the rates of solicited local and systemic ARs following a booster dose of mRNA-1273 from Study P205 Part F Cohort 2 are included in these tables.

By order of frequency (>10%), the frequently reported solicited ARs in adults 18 years of age and older within 7 days following receipt of mRNA-1273.222 in Part H were pain at injection site (82.4%), fatigue (59.8%), headache (49.1%), myalgia (46.4%), arthralgia (34.9%), and axillary swelling or tenderness (20.9%).

Solicited Local Adverse Events
Overall, frequencies of solicited local ARs following a booster dose of mRNA-1273.222 were similar to those observed in Part F after a booster dose of mRNA-1273. Most reported local ARs were Grade 1 or 2. There were no Grade 4 local ARs. Pain and axillary swelling/ tenderness were more commonly reported among participants 18-64 years of age and were generally of a higher grade among these participants.

In Part H, solicited local ARs had a median onset of 1-day post-booster and resolved after a median of 3 days. Solicited local ARs persisting beyond 7 days following the study dose were reported by 1.6% of participants in Part H.

Delayed solicited local reactions (defined as beginning after Day 7) were reported by 0.2% of booster dose recipients in the Safety Set (N=511).

Table 57. Solicited Local ARs up to 7 Days Following the Study Dose by Age, Study P205 Part H as Compared to Study 205 Part F*, Solicited Safety Set

Event	P205 Part H 18-64 Years mRNA-1273.222 50 µg BD n(%) N1=402-403	P205 Part H ≥65 Years mRNA-1273.222 50 µg BD n(%) N1=105	205 Part F* 18-64 Years mRNA-1273 50 µg BD n(%) N=210	205 Part F* ≥65 Years mRNA-1273 50 µg BD n(%) N=140
Local ARs	--	--	--	--
Any	347 (86.3)	73 (69.5)	179 (85.2)	99 (70.7)
Grade 3	49 (12.2)	5 (4.8)	9 (4.3)	3 (2.1)
Pain	--	--	--	--
Any	347 (86.3)	71 (67.6)	174 (82.9)	94 (67.1)
Grade 3	19 (4.7)	1 (1.0)	4 (1.9)	0
Axillary swelling or tenderness	--	--	--	--

Event	P205 Part H 18-64 Years mRNA-1273.222 50 µg BD n(%) N1=402-403	P205 Part H ≥65 Years mRNA-1273.222 50 µg BD n(%) N1=105	205 Part F* 18-64 Years mRNA-1273 50 µg BD n(%) N=210	205 Part F* ≥65 Years mRNA-1273 50 µg BD n(%) N=140
Any	91 (22.6)	15 (14.3)	38 (18.1)	15 (10.7)
Grade 3	1 (0.2)	0	4 (1.9)	0
Swelling				
Any	32 (8.0)	8 (7.6)	14 (6.7)	8 (5.7)
Grade 3	2 (0.5)	3 (2.9)	2 (1.0)	3 (2.1)
Erythema	--	--	--	--
Any	17 (4.2)	6 (5.7)	10 (4.8)	3 (2.1)
Grade 3	3 (0.7)	2 (1.9)	1 (0.5)	2 (1.9)

Source: Adapted from Study P205 Part H CSR Table 14.3.1.1.2.9 and Study P205 Part G CSR Table 14.3.1.1.2.8
Abbreviations: AR=adverse reaction; BD=booster dose
Notes: * Part F Cohort 2
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
95% CI is calculated using the Clopper-Pearson method
Part H and Part F were not conducted concurrently; therefore, mRNA-1273.222 and mRNA-1273 booster dose groups were not contemporaneously evaluated.
Toxicity grades for Swelling and Erythema (Redness) defined as: Grade 1=25-50 mm; Grade 2=51-100 mm; Grade 3=>100 mm.
Toxicity grades for Pain and Axillary Swelling or tenderness defined as Grade 1: No interference with activity; Grade 2: Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity; Grade 3: Any use of prescription (narcotic) pain reliever or prevents daily activity

Solicited Systemic Adverse Events

Most reported systemic ARs were Grade 1 or 2. There were no Grade 4 systemic ARs. The younger age cohort (i.e., 18-64 years) reported headache, myalgia, and nausea/vomiting more frequently than the older age cohort (≥65 years) in the Part H group. This was similar to the solicited ARs in the Part F Cohort 2 group. The severities of ARs were generally comparable between age groups. The frequency and severity of reported systemic ARs were generally comparable between Part H and Part F Cohort 2 participants.

In Part H, solicited systemic ARs had a median onset of 1 day post-booster and resolved after a median of 3 days. Solicited systemic ARs persisting beyond 7 days post-booster were reported by 7.7% of participants in Part H.

Table 58. Solicited Systemic ARs up to 7 Days Following the Study Dose by Age, Study P205 Part H as Compared to Study 205 Part F*, Solicited Safety Set

Event	P205 Part H 18-64 Years mRNA-1273.222 50 µg BD n (%) N1=402-403	P205 Part H ≥65 Years mRNA-1273.222 50 µg BD n (%) N1=105	205 Part F* 18-64 Years mRNA-1273 50 µg BD n (%) N=210	205 Part F* ≥65 Years mRNA-1273 50 µg BD n (%) N=139-140
Systemic ARs	--	--	--	--
Any	307 (76.2)	65 (61.9)	148 (70.5)	83 (59.3)
Grade 3	30 (7.4)	5 (4.8)	9 (4.3)	7 (5.0)
Headache	--	--	--	--
Any	210 (52.2)	39 (37.1)	99 (47.1)	44 (31.7)
Grade 3	11 (2.7)	1 (1.0)	1(0.5)	1(0.7)

Event	P205 Part H 18-64 Years mRNA-1273.222 50 µg BD n (%) N1=402-403	P205 Part H ≥65 Years mRNA-1273.222 50 µg BD n (%) N1=105	205 Part F* 18-64 Years mRNA-1273 50 µg BD n (%) N=210	205 Part F* ≥65 Years mRNA-1273 50 µg BD n (%) N=139-140
Fatigue	--	--	--	--
Any	243 (60.3)	61 (58.1)	114 (54.3)	65 (46.8)
Grade 3	14 (3.5)	3(2.9)	7 (3.3)	4 (2.9)
Myalgia	--	--	--	--
Any	197 (49.0)	38 (36.2)	89 (42.4)	45 (32.4)
Grade 3	17 (4.2)	3 (2.9)	8 (3.8)	5 (3.6)
Fever	--	--	--	--
Any	16 (4.0)	4 (3.8)	9 (4.3)	2 (1.4)
Grade 3	1 (0.2)	0	0	0
Arthralgia	--	--	--	--
Any	145 (36.1)	32 (30.5)	68 (32.4)	42 (30.2)
Grade 3	9 (2.2)	0	2 (1.0)	1 (0.7)
Nausea/vomiting	--	--	--	--
Any	67 (16.7)	4 (3.8)	27 (12.9)	8 (5.8)
Grade 3	1 (0.2)	0	0	0
Chills	--	--	--	--
Any	96 (23.9)	16 (15.2)	54 (25.7)	20 (14.4)
Grade 3	3 (0.7)	1 (1.0)	0	1 (0.7)

Source: Adapted from Study P205 Part H CSR Table 14.3.1.1.2.9 and Study P205 Part G CSR Table 14.3.1.1.2.8
Abbreviations: AR=adverse reaction; BD=booster dose
Notes: *Part F Cohort 2
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
95% CI is calculated using the Clopper-Pearson method
Part H and Part F were not conducted concurrently; therefore, mRNA-1273.222 and mRNA-1273 booster dose groups were not contemporaneously evaluated.
Toxicity grades for ARs (other than fever) defined as Grade 1: No interference with activity; Grade 2: Repeated use of over-the-counter (non-narcotic) pain reliever >24 hours or some interference with activity; Grade 3: Any use of prescription (narcotic) pain reliever or prevents daily activity
Toxicity grade for Fever is defined as: Grade 1=38-38.4 C; Grade 2=38.5-38.9 C; Grade 3=39-40 C; Grade 4=>40 C.

Additional subgroup analyses of ARs according to baseline (pre-booster) SARS-CoV-2 status did not show substantial differences between groups in the frequencies or severities of the reported ARs. Subgroup analyses by race/ethnicity were not performed as the subgroups were too small to draw meaningful conclusions.

Reviewer Comment: The rates of solicited ARs reported in this study were similar to those reported following a single dose of mRNA-1273 (50 µg) and do not suggest new safety concerns regarding the reactogenicity of a single dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

6.5.12.3 Unsolicited AEs Through 28 Days After Any Dose

Unsolicited AEs within 28 days of the study dose in Part H were most frequently reported under the SOC *Infections and infestations* (11.0%) and *General disorders and administration site conditions* (6.1%). The most frequently reported unsolicited AEs (by PTs) were fatigue (4.3%) and headache (2.9%).

During the 28 days following vaccination, unsolicited AEs considered to be related to study vaccination by the investigator were reported by 7.8% (n=40) of vaccine recipients, the majority of which were conditions representative of vaccine reactogenicity. None of the related AEs were serious.

Subgroup analyses showed no substantial differences in the frequency or severity of reported AEs by age group (18-64 years and ≥65 years) or pre-vaccination SARS-CoV-2 status.

> *Reviewer Comment: The reported unsolicited AEs were consistent with commonly reported medical conditions in the general population. The most frequently reported unsolicited AEs were synonymous with expected adverse reactions following vaccination.*

6.5.12.4 Medically Attended Adverse Events

Through 28 days post-booster, MAAEs were reported by 13.7% (n=70) of participants in Part H. Through the data cutoff, MAAEs were reported by 16.2% (n=83) of study participants. None of these events were assessed by the investigator as related to study vaccination.

6.5.12.5 Adverse Events of Special Interest

The Applicant monitored participants for unsolicited AESIs associated with COVID-19 vaccines (see Appendix A). There were no investigator-identified AESIs through the date of data cutoff.

6.5.12.6 FDA Standard MedDRA Queries

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.

SMQs Hypersensitivity

Through 28 days post-booster dose, events under the narrow scope SMQ *Hypersensitivity* were reported by one participant (0.2%), an event of urticaria (described as urticaria of face) with onset 12 days following the study dose. This event was assessed by the investigator as being unrelated to the booster dose. There were no other events reported under this SMQ through the data cutoff.

> *Reviewer Comment: This reviewer agrees with the investigators' assessments that the identified hypersensitivity event was unrelated to the study vaccine based on the temporal relationship of the event and vaccination.*

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, several cardiac-related SMQs were conducted, including the following: *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).

There were 4 events reported by 2 participants under these SMQs. Both were assessed by the investigator as being unrelated to the study vaccine. There were no reported cases of myocarditis or pericarditis.

1. A 69-year-old male with a history of hypertension, hypercholesterolemia, type 2 diabetes mellitus, coronary artery disease with prior coronary angioplasty, smoking, and ongoing chest pain for 1 month prior to vaccination developed abdominal pain on Day 3 following the study dose. On Day 4 he developed anginal equivalent and diarrhea. The participant developed syncope and dyspnea on Day 10 and was hospitalized for evaluation. Although an EKG had ST-segment depressions and a stress echocardiogram noted reversible ischemia, the participant's cardiac enzymes were normal and cardiac catheterization identified no abnormalities. The participant was treated symptomatically and discharged on Day 12 following resolution of his chest pain, dyspnea, and diarrhea. His abdominal pain had not resolved by the date of data cut-off. The investigator and Applicant assessed the events as unrelated to the study vaccine due to the participant's co-morbid conditions and concomitant illness.

2. A 64-year-old-female irritable bowel syndrome, diverticulosis, hypercholesterolemia, and osteopenia who took hydrochlorothiazide (unknown indication) and chondroitin sulfate at baseline developed transient bradycardia and premature ventricular complexes (PVCs) on Day 1 after the study dose. The bradycardia resolved on Day 1 and the PVCs resolved on Day 2. Both events resolved without treatment. The investigator assessed both events as unrelated to the booster dose.

Reviewer Comment: This reviewer agrees with the investigators' assessments that the identified events were unrelated to the study dose and do not suggest new safety concerns regarding a single dose of mRNA-1273.222

6.5.12.7 Deaths

There were 2 deaths reported in this study, summarized below:

1. An event of death due to subarachnoid hemorrhage in a 70-year-old man with pertinent medical history of type 2 diabetes, hyperlipidemia, transient ischemic attack, atrial fibrillation, and hypertension. Starting 3 days after the study dose, the participant developed nausea, vomiting, and headache. He was hospitalized the next day, became unresponsive, and a head CT showed subarachnoid hemorrhage. A CT angiogram showed normal head/neck vessel anatomy without evidence of thrombosis. The participant died (b) (6) days after receipt of the study dose. Based on the confounding conditions and medications, the investigator assessed this event as unrelated to the study vaccine.

2. An event of death of unknown cause in a 68-year-old woman with a pertinent medical history of bipolar disorder, alcohol and drug addiction, and depression. The patient was found dead (b) (6) days post-booster dose vaccination due to an unknown cause, but suspected drug overdose pending final autopsy results. The investigator assessed the death as unrelated to the study dose.

Reviewer Comment: Based on review of the clinical narratives and the presence of confounding factors (e.g., predisposing conditions), the reviewer assessed the deaths in this study as unrelated to mRNA-1273.222 vaccine.

6.5.12.8 Serious Adverse Events (SAEs)

SAEs were reported by 0.6% of participants (N=3) in Study P205 Part H through data cut-off. There was 1 additional SAE reported soon after data cut-off. None of the events were assessed by the study investigators as related to the booster dose. See Sections 6.2.12.3 and 6.2.12.6 for discussion of SAEs not listed below.

1. A 62-year-old male with a history of hepatitis C, liver cirrhosis, cholelithiasis, gastro-esophageal reflux, and anemia requiring blood transfusions was diagnosed with anemia (hemoglobin of 5.6 g/dL) on day 9 following the booster dose. He was hospitalized and received a blood transfusion. He was started on iron supplementation and was discharged from the hospital on day 10 post-booster when his anemia resolved.

Reviewer Comment: This reviewer agrees with the investigators' assessments of the unrelatedness of reported SAEs due to the presence of confounding medical conditions.

6.5.12.9 Dropouts and/or Discontinuations

In Part H of Study P205, a total of 4 participants (0.8%) were discontinued from the study. Two withdrew due to non-AE related withdrawal of consent, 1 withdrew due to death, and 1 withdrew due to lost to follow-up. There were no withdrawals due to AEs assessed as related to the study vaccine.

6.5.13 Study Conclusions

The open-label trial P205 Part H evaluated the effectiveness and safety of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in 511 participants 18 years of age and older. The study met the pre-specified superiority criterion for nAb GMTs elicited by Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) against Omicron BA.4/BA.5, the noninferiority criterion for nAb GMTs against the D614G strain, and the non-inferiority criteria for the seroresponse rates against Omicron BA.4/BA.5 and the D614G strains. Reactogenicity and safety profiles for Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) recipients were similar to those reported by Spikevax (Original monovalent) recipients. There were no reported deaths or SAEs that were considered related to Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and no reported cases of myocarditis. Overall, the submitted clinical data support the safety and effectiveness of SPIKEVAX including Spikevax (2023-2024 Formula) in previously COVID-19 vaccinated adults 18 years of age and older.

6.6 Study P201 (Part B-Booster): Phase 2 Adult Booster

NCT04405076

Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 COVID-19 Vaccine in Adults Aged 18 Years and Older

Overview:
Study mRNA-1273-P201 was a study with multiple parts conducted at 8 U.S. study sites in adult participants (≥18 years of age). Part A was the blinded and placebo controlled portion of the study that evaluated a 2-dose primary series of either 50 µg dose or 100 µg dose of mRNA-1273 vaccine, the result of which were previously reviewed in the original Spikevax BLA memo. Following the EUA of Moderna COVID-19 Vaccine (Original monovalent) in December 2020, Study P201 transitioned to the open label Part B portion. Part B was designed to offer participants who received placebo in Part A of this study the option to receive the 2-dose series of mRNA-1273 (Part B-Crossover) and participants who received 1 or 2 doses of mRNA-1273 (50 µg or 100 µg) in Part A of this study the option to receive a single booster dose of mRNA-1273 (50 µg, Part B-Booster). Only results from the Part B-Booster portion of Study P201 will be discussed in this sBLA review as this was the only portion of the study relevant to the current proposed indication and usage.

6.6.1 Objectives and Endpoints

Primary safety objective: to evaluate the safety and reactogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose

Endpoints:

- Solicited local and systemic ARs within 7 days post-vaccination
- Unsolicited AEs during the 28 days post-vaccination
- AEs leading to discontinuation from study participation through the study period
- MAAEs, SAEs, vital sign measurements, and physical examination findings through the study period
- Additional safety analyses for AEs of interest performed by using Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) and Custom MedDRA Queries (CMQs) (not prespecified in the protocol)
- Assessments for SARS-CoV-2 infection

Primary immunogenicity objective: to evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose as assessed by bAb (primary) and nAb (secondary)

Endpoints:

- *Primary* - Serum bAb level against SARS-CoV-2 assessment measured by an ELISA specific to the SARS-CoV-2 S2P
- *Secondary* - Pseudovirus nAb assay for measuring nAb against SARS-CoV-2 pseudotyped viruses against the D614G strain as well as Beta (B.1.351), Delta (B.1.617.2), and Omicron (B.1.1.529) variants

All analyses were descriptive without formal hypothesis testing.

6.6.2 Study Treatments or Agents Mandated by the Protocol

50 µg of mRNA-1273 (Lot Numbers: 8520100103 and 8520100104)

6.6.3 Study Population and Disposition

A total of 344 participants received a 50 µg mRNA-1273 booster dose in Part B-Booster (173 who had received the 50 µg 2-dose primary series and 171 who had received the 100 µg 2-dose primary series in Part A). The median time between Dose 2 of the 50 µg primary series and the booster dose was 216 days and median time between Dose 2 of the 100 µg primary series and the booster dose was 219 days. Participants included in the population used for the analyses of safety were 66% female, 95% White, and 94% non-Hispanic/Latino. Demographic characteristics were similar between the Safety Set and the population used for analyses of immunogenicity.

6.6.4 Effectiveness Analyses

Immunogenicity

At 28 days after study booster dose administration, neutralizing antibody titers were higher relative to the nAb titers 28 days after dose 2 of the primary series [GMTs after booster (following 50 µg or 100 µg primary series): 1834.3 and 1951.7, respectively vs GMTs after 2-dose primary series (50 µg or 100 µg) 629.2 and 1271.5, respectively]. In addition, the nAb titers following the 50 µg booster dose in the 50 µg primary series group were comparable to those elicited after the 50 µg booster dose in the 100 µg primary series [GMT: 1834.3 vs 1951.7, respectively]. Though the nAb titers decreased over time, GMTs remained 5-fold higher at 6 months post-booster relative to pre-booster levels. Analyses of nAb responses at 28 days post-booster by age cohort (18-64 years, ≥65 years) showed comparable nAb titers between the age cohorts.

6.6.5 Safety Analyses

Solicited Adverse Reactions

Solicited local and systemic adverse reactions in participants 18 years through 64 years of age starting within 7 days after administration of a booster dose included pain at the injection site (86.0%), fatigue (62.0%), headache (58.9%), myalgia (49.6%), arthralgia (41.9%), chills (40.3%), axillary swelling/tenderness (24.8%), nausea/vomiting (12.4%), fever (7.0%), swelling at the injection site (6.2%), erythema at the injection site (5.4%), and rash (2.3%).

Solicited local and systemic adverse reactions in participants 65 years of age and older starting within 7 days after administration of a booster dose included pain at the injection site (76.3%), fatigue (47.4%), myalgia (47.4%), headache (42.1%), arthralgia (39.5%), chills (18.4%), nausea/vomiting (7.9%), fever (5.4%), axillary swelling/tenderness (5.3%), erythema at the injection site (2.6%), and swelling at the injection site (2.6%).

No Grade 4 adverse reactions were reported. The median duration of solicited local and systemic adverse reactions was 2 to 3 days.

Unsolicited Adverse Events

Overall, the 171 participants who received a booster dose had a median follow-up time of 176 days after the booster dose to the database lock date (November 23, 2021). Through 28 days after the booster dose, unsolicited AEs were reported by 14.6% of participants (n=25) after the booster dose. There were no new unsolicited AEs not

otherwise reported as solicited local and systemic reactions, that were considered causally related to mRNA-1273.

Serious Adverse Events

There were no SAEs reported from the booster dose through 28 days after the booster dose. Through the database lock date (November 23, 2021), there were no SAEs following the booster dose considered causally related to mRNA-1273.

> *Clinical Reviewer Comment: Solicited and unsolicited safety analyses reviewed for Study P201 Part B-Booster were for participants who received a single dose (50 µg) of mRNA-1273 following a 2-dose (100 µg each) series of mRNA-1273. A total of 344 participants contributed to the P201 Part B Safety Set, and 171 participants primed with the 2-dose (100 µg each) series contributed to the P201 Part B solicited safety set. Based on this reviewer's assessment of safety data, no new concerns were identified following the administration of a single dose (50 µg) in those previously vaccinated with a 2-dose mRNA-1273 series (100 µg or 50 µg). Though data are not presented above, the safety findings from this study were comparable to those described in other adult studies described in this memo and included in the Spikevax (Original monovalent) labeling.*

6.6.6 Study Conclusions

The single 50 µg dose of Spikevax (Original monovalent) elicited a robust immune response as measured by neutralizing antibodies, at 28 days following the study dose, with higher GMTs relative to 28 days post-Dose 2 of the 2-dose series (100 µg each) of Spikevax (Original monovalent). No new safety concerns were identified.

7. Integrated Overview of Efficacy

This sBLA included clinical studies which evaluated different dosing regimens (primary series, single dose, or booster dose) and formulations (monovalent or bivalent) of Moderna COVID-19 vaccines across different age groups (adolescents or adults); therefore, an integrated overview of efficacy is not applicable. The totality of data on effectiveness support the use of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status.

8. Integrated Overview of Safety

As noted in Section 7 above, an integrated overview of safety would not be informative due to the differences in the dosing regimens and study populations in the clinical studies. Therefore, an integrated overview of safety is not applicable to this review. The totality of data on safety support the use of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Study participants of childbearing potential were screened for pregnancy prior to vaccination and at any time during the study at the discretion of the investigators. Individuals with a positive screening test were not enrolled. Participants were followed for outcomes for all reported pregnancies that occurred after vaccination. A total of 25 pregnancies were reported in Study P301 (Part C), discussed in Section 6.4.12.9. There were no pregnancies reported in Study P205 (Part H) or Study P203 (Parts A, B, C, or 3).

The data on pregnancy and pregnancy outcomes from this study are limited. There have been no post-authorization safety signals associated with receipt of mRNA-1273 vaccine in pregnant individuals. As part of the postmarketing surveillance, the Applicant is conducting a prospective, observational pregnancy exposure registry study in the U.S., Canada, and European Union to evaluate pregnancy and birth outcomes in individuals exposed to mRNA-1273 vaccine during pregnancy (NCT04958304).

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 Applicant has proposed the following to address requirements under PREA to assess a single dose of SPIKEVAX in pediatric individuals <18 years of age:

Partial Waiver

Pediatric age group to be waived: 0 to <2 years of age

- Statutory reason for waiving pediatric assessment requirements:
  There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group [Section 505B(a)(5)(B)(ii) of the Food, Drug, and Cosmetics Act (FD&C Act)].

- Justification for Waiver:
  Seroprevalence (due to vaccination and infection) estimates in individuals younger than 2 years of age are lower than among older age groups (75%, 85%, 92%, 97%, and 99% among children 6-11 months, 12-23 months, 2-4 years, 5-11 years, and 12-17 years, respectively). Furthermore, a significant proportion of children <2 years of age have no evidence of prior infection (63% and 82% for the age groups 6-11 months and 12-23 months, respectively) (CDC, 2023a). Evidence from clinical studies in individuals 6 months through 23

months of age strongly suggests that a single dose of SPIKEVAX would be ineffective in individuals younger than 2 years of age.

Deferral of Assessment

Pediatric age group to be deferred: 2 years through 11 years 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

Safety and effectiveness data from Study P203 submitted to this sBLA (reviewed in Section 6) fulfill the pediatric study requirement for assessment of a single dose of SPIKEVAX individuals 12 through 17 years of age. This submission also fulfills the PREA postmarketing requirement #1 identified in the approval letter for Spikevax (Original monovalent) (125752/0 approval letter dated January 31, 2022). SPIKEVAX will be indicated for use in individuals 12 years of age and older.

The Applicant's request for partial waiver in individuals <2 years, deferral of pediatric assessment in individuals 2 through 11 years, and fulfillment of pediatric assessment in individuals 12 through 17 years were reviewed and agreed to by FDA's Pediatric Review Committee on August 15, 2023.

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.

Limited data are available for individuals with HIV infection (total of 185 participants in Study P301) on stable antiretroviral therapy; all the participants had stable viral load <50 copies/mL and CD4 count >350 cells/mm^3 within 1 year before enrollment. Please see the for additional details.

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

Please refer to Section 8.6 of U.S. Package Insert.

9.1.5 Geriatric Use

The safety and effectiveness of Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Spikevax (2023-2024 Formula) because these vaccines are manufactured using a similar process.

Clinical studies of Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) included approximately 7,800 participants 65 years of age and older and 1,400 participants 75 years of age and older.

Some local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older compared to participants 18 through 64 years of age (Section 6.5.12.2).

Vaccine effectiveness was similar between participants 65 years of age and older and participants 18 through 64 years of age (Section 6.4.11 and Section 6.5.11).

10. CONCLUSIONS

The data submitted to this sBLA provide evidence to support the safety and effectiveness of SPIKEVAX including Spikevax (2023-2024 Formula) for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, when administered as a single dose (50 µg), irrespective of prior COVID-19 vaccination status.

Data supporting effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, include:

- Immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve participants 12-17 years of age with evidence of prior SARS-CoV-2 infection in Study P203 (Part 3) [reviewed in Section 6.1], and
- Immunogenicity of a 50 µg booster dose of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older in Study P203 (Part A, B, and C) [reviewed in Section 6.2 and 6.3], P301 (Part C) [reviewed in Section 6.4], and P205 (Part H) [reviewed in Section 6.5]

Data from Study P203 Part 3 serve as the basis for FDA's determination that a single dose vaccination can achieve protective immunity at a dosage level lower than what was included as part of the two previous doses that was used to demonstrate clinical efficacy. These data provide substantial evidence that single dose immunization with a 50 µg (25 µg Original Wuhan + 25 µg Omicron BA.4/BA.5) bivalent vaccine in individuals previously infected can achieve immune responses similar to those achieved following two 100 µg doses of an Original monovalent vaccine. Data on effectiveness of a single dose (50 µg) in COVID-19 vaccine-naïve adolescents can be extrapolated to support the effectiveness of a single dose (50 µg) in COVID-19 vaccine-naïve adults given the comparable efficacy and immunogenicity results observed after completing two previous doses of Spikevax (Original monovalent) between adolescent participants and adult participants in the clinical studies.

Spikevax (2023-2024 Formula) contains 50 µg mRNA encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5, which is better matched to currently circulating SARS-CoV-2 lineages in the U.S. than the lineages in the current FDA-authorized bivalent COVID-19 vaccines (CDC, 2023b). Therefore, Spikevax (2023-2024 Formula) is anticipated to be clinically effective against the predominant circulating strain.

Data supporting the safety of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, include:

- Data on safety of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve individuals 12-17 years from Study P203 (Part 3) [reviewed in Section 6.1]

- Data on safety of a 2-dose series (100 µg each, 1 month apart) of Spikevax (Original monovalent) in COVID-19 vaccine naïve individuals in Study P203 (Part A and B) [reviewed in Section 6.2], and
- Data on safety of a single dose (50 µg) of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older from Study P203 (Part C) [see Section 6.3], P301 (Part C) [reviewed in Section 6.4], and P205 (Part H) [reviewed in Section 6.5]

In the clinical studies, across all age groups (12-17 years, 18-64 years, ≥65 years) local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration. There were no safety concerns identified in study data reviewed in this application which are not already captured in the Spikevax (Original monovalent) prescribing information. Based on FDA review of available data, the clinical safety profile of mRNA-1273 platform was not adversely impacted by strain changes to the encoded mRNA Spike protein.

The safety and effectiveness of Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to SPIKEVAX including Spikevax (2023-2024 Formula) because these vaccines are manufactured using a similar process.

Postmarketing data with authorized or approved mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following vaccination. For Spikevax (Original monovalent), the observed risk is highest in males 18 years through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. The risk of myocarditis is appropriately described in the prescribing information (Section 5 Warnings and Precautions, Section 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience).

Based on the totality of data and the risk-benefit considerations as described in Section 11 below, the clinical reviewers conclude that the clinical trial data submitted in this application, and complemented by available postmarketing data, support approval of Spikevax (2023-2024 Formula), administered as a single dose (50 µg) for the indication of active immunization to prevent symptomatic COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 59. STN125752/68: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 is associated with significant morbidity, mortality (6.95 million deaths worldwide to date) and long-term sequelae among survivors. In the U.S., COVID-19 has been responsible for 6.2 million hospitalizations and 1.1 million deaths to date. • There has been a succession of variants (Delta, Omicron BA.1, BA.5. and more recently XBB.1.5, among others) that are associated with a reduction in vaccine effectiveness. • Although the available COVID-19 vaccines based on the bivalent strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased.	• COVID-19 is a serious disease associated with significant acute morbidity and mortality and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals. • mRNA-based COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals, but decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups.
Unmet Medical Need	• Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity. • There are two authorized mRNA bivalent COVID-19 vaccines for use as a two or three dose series in 6 months through 5 years of age and as a single dose in most individuals 5 or 6 years of age and older. • An adjuvanted, protein subunit COVID-19 vaccine is authorized for use as a primary series in individuals 12 years of age and older and as a single booster dose for certain individuals 18 years of age and older.	• 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) • Vaccines play an important role in pandemic control and provide important protection.

Clinical Benefit	• Effectiveness of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) is inferred from the following:
	  • Immunogenicity of a single dose (50 µg) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in COVID-19 vaccine naïve participants 12-17 years of age with evidence of prior SARS-CoV-2 infection, as evaluated in Study P203 Part 3
	  • Immunogenicity of a single dose (50 µg) dose of Spikevax (Original monovalent) and/or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated individuals 12 years of age and older, as evaluated in Study P203 Part A, B, and C, P301 Part C, and P205 Part H
		• The evidence for clinical benefit of a single dose (50 µg) of SPIKEVAX including Spikevax (2023-2024 Formula) meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 12 years of age and older.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• All studies met their pre-specified success criteria	
Risk	• The most frequently reported adverse reactions were solicited injection site reactions of injection site pain and localized axillary swelling or tenderness and systemic adverse reactions of fatigue, headache, muscle pain, chills, and joint pain, which were generally less frequent in older (≥65 years) vs younger (18-65 years) participants.	• In the clinical studies, across all age groups (12-17 years, 18-64 years, >65 years) local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration. There were no safety concerns found in these studies which are not already captured in the Spikevax (Original monovalent) prescribing information. • The safety profile of mRNA-1273 platform was not adversely impacted with strain changes to the encoded mRNA Spike protein.
Risk Management	• Labeling for Spikevax (2023-2024 Formula) describes the common and uncommon (but potentially serious) risks associated with the vaccine, which are unchanged from the Spikevax (Original monovalent) prescribing information. The labeling includes warning statements for severe allergic reactions and myocarditis/pericarditis.	• Risk mitigation strategies for SPIKEVAX including Spikevax (2023-2024 Formula) for use in individuals 12 years of age and older are unchanged from the Spikevax (Original monovalent) approval 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

COVID-19 caused by SARS-CoV-2 is associated with a wide spectrum of manifestations, including mild illness in some individuals and severe morbidity (in some cases with long-term sequelae) and/or mortality in others. Over 6.95 million deaths attributable to COVID-19 have been reported worldwide since the beginning of the pandemic in late 2019, and the virus has been responsible for over 104 million cases of COVID-19 and over 1.1 million deaths in the U.S. Since the start of the pandemic, there has been a succession of SARS-CoV-2 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and other Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. These interventions are generally most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2, they are generally not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA-approved and authorized vaccines may provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech, and an adjuvanted, protein subunit vaccine from Novavax (in individuals 12 years of age and older only).

The original monovalent vaccines were based on the Original strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has gradually reduced vaccine effectiveness. Vaccine effectiveness against symptomatic disease declined more rapidly than that against serious disease, as illustrated by studies conducted in the United States (Dorabawila et al., 2022; Lauring et al., 2022), Israel (Bar-On et al., 2022), Qatar (Chemaitelly et al., 2022), Portugal (Kislaya et al, 2022), and England (Andrews et al., 2022). In the setting of emerging viral variants, booster doses updated to more closely represent these variants were able to restore some degree of protection against serious and symptomatic disease.

The immunogenicity and safety of mRNA vaccines developed against the Beta, Delta, and Omicron BA.1 variants have been evaluated previously by both Moderna and Pfizer-BioNTech. However, these vaccines were not deployed in the U.S. due to the rapid evolution of the SARS-CoV-2 variants. Following emergence of the Omicron variant and its sublineages (BA.4/BA.5 and related sublineages) in November 2021, and based on data suggesting improved protection against Omicron sublineages conferred by the bivalent vaccines compared to the Original monovalent vaccines, FDA, on August 31, 2022, authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 12 or 18 years of age and older, respectively. In April 2023, the FDA authorized the use of the bivalent COVID-19 vaccines for all doses in individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65

years of age and older; and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of the Moderna COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing the mRNA encoding spike protein of original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of approved COVID-19 vaccines in the U.S.

Data from published observational studies of real-world use of the Bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines, although not independently reviewed and confirmed by FDA, suggest improved protection provided by the updated vaccines against COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage (Tenforde et al., 2023; Surie et al., 2022; Lin et al., 2023).

Safety and effectiveness data accrued with Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/ BA.5) are relevant to SPIKEVAX including Spikevax (2023-2024 Formula) because these vaccines are manufactured using a similar process. The scientific evidence available to support this sBLA application for licensure of SPIKEVAX including Spikevax (2023-2024 Formula) for use as a single dose in individuals 12 years of age and older irrespective of prior COVID-19 vaccination status include:

- Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the Spikevax (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (see Section 6).
- Preclinical data demonstrating that Spikevax (2023-2024 Formula) when administered to vaccine naive and vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) against XBB-related sublineages (see CMC review memorandum).
- Chemistry, Manufacturing and Control Information related to single dose vial presentation of Spikevax (2023-2024 Formula) including the manufacturing facilities (see CMC review memorandum).
- Postmarketing safety surveillance data of Spikevax (Original monovalent) and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (see Pharmacovigilance review memorandum).
- Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies (see Section 5.1).

There were no new safety signals identified in the submitted safety data that are not already addressed in the Spikevax (Original monovalent) U.S. prescribing information.

11.3 Discussion of Regulatory Options

The data submitted with the BLA efficacy supplement indicate the safety and efficacy of single dose vaccination with SPIKEVAX including Spikevax (2023-2024 Formula) meet the statutory requirements to support its use in individuals 12 years of age and older 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 12 years of age and older, the clinical reviewers recommend approval of Spikevax (2023-2024 Formula) when administered as a single dose, and 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 pharmacovigilance with adverse event reporting under 21 CFR 600.80. The initial approval of Spikevax (Original monovalent) (125752/0 approval letter dated January 31, 2022) includes postmarketing requirement studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis following administration of SPIKEVAX.

The current pharmacovigilance plan, version 7.2 dated June 28, 2023, is adequate to monitor postmarketing safety for SPIKEVAX including Spikevax (2023-2024 Formula) in accordance with 21 CFR 600.800.

As summarized in Section 9.1.3, the Applicant is required to conduct following licensure the PREA deferred study listed below:

1. Deferred pediatric study under PREA (Study mRNA-1273-P204) to evaluate the safety of a single dose of SPIKEVAX in children 2 years through 11 years of age.
   Final Protocol Submission: February 28, 2022 (submitted)
   Study Completion Date: December 31, 2023
   Final Report Submission: March 31, 2024

12 APPENDIX A. ADVERSE EVENTS OF SPECIAL INTEREST

Table 60. 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

13 APPENDIX B. LIST OF PREFERRED TERMS USED IN THE ENHANCED ANALYSIS FOR POTENTIAL CASES OF MYOCARDITIS OR PERICARDITIS, BASED ON CDC CASE DEFINITION

The following PTs were used in the enhanced analysis to identify potential cases of myocarditis or pericarditis based on the CDC case definition (for adults).

- acute chest syndrome
- angina pectoris
- autoimmune myocarditis
- autoimmune pericarditis
- cardiac dysfunction
- cardiac function test abnormal
- cardiomyopathy
- cardiovascular function test abnormal

- chest discomfort
- chest pain
- conduction disorder
- defect conduction intraventricular
- dyspnea
- dyspnea at rest
- dyspnea exertional
- ECG electrically inactive area
- ECG P wave inverted
- ECG signs of myocardial infarction
- ECG signs of myocardial ischemia
- ECG signs of ventricular hypertrophy
- electrocardiogram abnormal
- electrocardiogram ST segment
- electrocardiogram ST segment abnormal
- electrocardiogram ST segment depression
- electrocardiogram ST segment elevation
- electrocardiogram ST-T segment depression
- electrocardiogram ST-T segment abnormal
- electrocardiogram ST-T segment elevation
- eosinophilic myocarditis

14 APPENDIX C: COVID-19 CASE DEFINITIONS

Table 61. COVID-19 Case Definitions

Endpoint	Definition
COVID-19 “P301 case definition”	A confirmed COVID-19 case was defined as NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR along with: At least 2 systemic symptoms: Fever (≥38°C/≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
COVID-19 “CDC case definition”	At least one symptom from a pre-specified list of COVID-19 symptoms derived from the CDC case definition Systemic symptoms: fever (temperature >38°C/≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea, AND At least one positive RT-PCR for SARS-CoV-2.

Endpoint	Definition
SARS-CoV-2 Infection (regardless of symptoms)	Combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: • Binding antibody (bAb) levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR • Positive RT-PCR test.
Asymptomatic SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection was identified by absence of symptoms and infections as detected by RT-PCR or serology tests: Antibody sent of COVID-19 symptoms AND at least one from below: • Binding antibody (bAb) levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR • Positive RT-PCR test at scheduled or unscheduled/illness visits.

Source: mRNA-1273-P203 Protocol Amendment 4
Abbreviations: bAb=binding antibody; CDC=Centers for Disease Control and Prevention; COVID-19=coronavirus disease 2019; RT-PCR=reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2.

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

Acute Myocarditis

A. Confirmed case
Presence of ≥1 new or worsening of clinical symptoms (persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis [probable or confirmed]):

- ≥12 years of age: Chest pain/pressure/discomfort; Dyspnea/shortness of breath/pain with breathing; Palpitations; Syncope
- <12 years of age (must have ≥2 symptoms): Irritability, Vomiting, Poor feeding, Tachypnea, Lethargy

AND presence of ≥1 new finding of:

- Histopathologic confirmation of myocarditis (using the Dallas criteria [Aretz et al., 1987]) or,
- Cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis in the presence of troponin level above upper limit of normal (ULN) (any type of troponin)

AND no other identifiable cause of the symptoms and findings

B. Probable case
Presence of ≥1 new or worsening of clinical symptoms (persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis [probable or confirmed]):

- ≥12 years of age: Chest pain/pressure/discomfort; Dyspnea/shortness of breath/pain with breathing; Palpitations; Syncope
- <12 years of age (must have ≥2 symptoms): Irritability, Vomiting, Poor feeding, Tachypnea, Lethargy

AND presence of ≥1 new finding of:

- Troponin level above upper limit of normal (ULN) (any type of troponin) or,
- Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis
- Abnormal cardiac function or wall motion abnormalities on echocardiogram
- Cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis (Ferreira et al., 2018)

AND no other identifiable cause of the symptoms and findings

Acute Pericarditis
Presence of ≥2 new or worsening of the following clinical features (Adler et al., 2015):

- Acute chest pain (typically described as pain made worse by lying down, deep inspiration, or cough; and, relieved by sitting up or leaning forward, although other types of chest pain may occur)
- Pericardial rub on examination
- New ST-elevation or PR-depression on EKG
- New or worsening pericardial effusion on echocardiogram or magnetic resonance imaging (MRI)