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Application Type	BLA Supplement
STN	125752/68
CBER Received Date	March 28, 2023
PDUFA Goal Date	January 26, 2024
Division / Office	DVRPA/OVRR
Committee Chair	Joseph Kulinski
Clinical Reviewers	Timothy Brennan, Mark Connelly, Gregory Raczniak
Project Manager	Katherine Berkhousen
Priority Review	No
Reviewer Names	Ross Peterson Mathematical Statistician, VEB, DB, OBPV
Review Completion Date/Stamped Date	
Concurrence	Ye Yang Lead Mathematical Statistician, VEB, DB, OBPV
Supervisory Concurrence	Tsai-Lien Lin Branch Chief, VEB, DB, OBPV
Applicant	ModernaTX, Inc.
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	SPIKEVAX
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	For COVID-19 vaccine-naïve individuals: - For individuals 12 to 64 years of age, single dose, 0.5 mL. - For individuals 65 years of age or older, single dose, 0.5 mL. One additional dose, 0.5 mL, may be administered ≥4 months after a dose of a currently approved COVID-19 vaccine For individuals who previously received at least one dose of any COVID-19 vaccine, same regimen as for COVID-19 vaccine-naïve individuals but dose of SPIKEVAX must be delivered ≥2 months after most recent dose of COVID-19 vaccine.
Indication(s) and Intended Population(s)	SPIKEVAX is a vaccine indicated for 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.

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Glossary

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
bAb	Binding Antibody
BD	Booster Dose
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
D.R.	Dominican Republic
EoS	End-of-Study
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLSM	Geometric Least Squares Mean
GMR	Geometric Mean Titer Ratio
GMT	Geometric Mean Titer
IP	Investigational Product
IR	Incidence Rate
IS	Immunogenicity Subset
LLOQ	Lower Limit of Quantitation
LTSS	Long-Term Safety Set
MAAE	Medically Attended Adverse Events
MIS-C	Multisystem Inflammatory Syndrome in Children
mITT	Modified Intent-to-Treat Set
mITT1	Modified Intent-to-Treat-1 Set
nAb	Neutralizing Antibody
NE	Not Estimated
PPE	Per-Protocol Set for Efficacy
PPIS	Per-Protocol Immunogenicity Subset
PPIS-NEG	Per-Protocol Immunogenicity Subset – Pre-booster SARS-CoV-2
PPIS-POS	Per-Protocol Immunogenicity Subset-Positive
RS	Randomization Set
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBLA	supplemental Biologics License Application

SD	Standard Deviation
SRR	Seroresponse Rate
SS	Safety Set
SSS	Solicited Safety Set
STN	Submission Tracking Number
ULOQ	Upper Limit of Quantitation
U.S.	United States
VE	Vaccine Efficacy
YOA	Years of Age

1. Executive Summary

SPIKEVAX (i.e., mRNA-1273 encoding for the ancestral strain) is licensed for active immunization to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as a two-dose, 100 µg mRNA-1273 series for individuals 18 years of age (YOA) and older.

Under Emergency Use Authorization (EUA), for individuals 12 YOA and older and children 6 to 11 YOA regardless of previous vaccination status, the vaccine is authorized for active immunization to prevent COVID-19 caused by SARS-CoV-2 as a single bivalent (i.e., Original and Omicron BA.4/BA.5) dose of 50 and 25 µg mRNA-1273.222, respectively. For COVID-19 vaccine-naïve children 6 months to 5 YOA, the vaccine is authorized as a two-dose, 25 µg mRNA-1273.222 primary series. For children 6 months to 5 YOA who previously received at least one dose of mRNA-1273, the vaccine is authorized as a single dose of 10 µg mRNA-1273.222.

Originally, the Applicant submitted two supplemental Biologics License Applications (sBLAs) to request licensure of SPIKEVAX as 1) (b) (4) (i.e., Submission Tracking Number [STN] 125752/(b) (4)); and 2) a single bivalent booster dose of 50 µg mRNA-1273.222 for individuals 12 YOA and older who previously received primary series (i.e., STN 125752/68). During the review cycle, two changes were made to the requested indication.

First, the vaccination schedule for individuals 12 YOA and older was simplified to a single bivalent dose of 50 µg mRNA-1273.222 regardless of previous vaccination status to align with the EUA. In communication with the Applicant, the sBLA for STN 125752/(b) (4) was withdrawn and its contents were resubmitted under STN 125752/68.

Second, there was a strain change for the vaccine formulation. Specifically, recommendations from the June 25, 2023 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting led to the Food and Drug Administration's (FDA) recommendation for the development of a monovalent COVID-19 vaccine encoded for Omicron XBB.1.5, which is currently in circulation.

Effectiveness of a single dose of the monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older regardless of previous vaccination status was inferred based on the 1) immunogenicity and efficacy of mRNA-1273 administered as a two-dose, 100 µg mRNA-1273 primary series in adolescents 12 to 17 YOA; 2) immunogenicity of mRNA-1273 administered as a single booster dose (BD) of 50 µg mRNA-1273 in adolescents 12 to 17 YOA; 3) immunogenicity of mRNA-1273.222 administered as a second BD of 50 µg mRNA-1273.222 in adults 18 YOA or older; and 4) immunogenicity of mRNA-1273.222 administered as a single dose of 50 µg mRNA-1273.222 in previously unvaccinated adolescents 12 to 17 YOA with evidence of prior SARS-CoV-2 infection.

Since its emergence in January 2020 in the United States (U.S.), it is assumed that almost everyone 12 YOA and older in the U.S. has been exposed to some strain of SARS-CoV-2 and

therefore has developed some natural immunity to the disease. The studies supporting the requested indication thus cover subjects with or without evidence of prior SARS-CoV-2 infection, and who may or may not have been previously vaccinated with some formulation of mRNA-1273.

This review memo focuses on the immunogenicity, efficacy, and safety data obtained from the following seven studies to support licensure of this vaccine:

1. mRNA-1273-P301 (hereafter referred to as P301): A phase 3, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 YOA and older. P301 is the pivotal efficacy study for SPIKEVAX primary series. Participants were randomized 1:1 to receive either 100 μg mRNA-1273 or placebo at Day 1 and Day 29, stratified by age category (18 to 64 years, ≥65 years) and health risk. Immunogenicity data from a random subset of young adults 18 to 25 YOA randomized to mRNA-1273 were provided to support immunobridging for Studies mRNA-1273-P203 – Part 1A (hereafter referred to as P203 – Part 1A), mRNA-1273-P203 – Part 1C-1 (hereafter referred to as P203 – Part 1C), and mRNA-1273-P203 – Part 3 (hereafter referred to as P203 – Part 3).

2. P203 – Part 1A: A phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273 administered in 2 doses 28 days apart in adolescents 12 to 17 YOA. Subjects were randomized in a 2:1 ratio to receive either 100 μg mRNA-1273 or placebo at Day 1 and Day 29. Vaccine effectiveness was inferred from bridging the immune responses of adolescents in P203 – Part 1A to those of young adults 18 to 25 YOA from P301. The co-primary immunogenicity objectives were demonstrating non-inferiority of Day 57 pseudovirus neutralizing antibody (nAb) ID50 titer in terms of the geometric mean titer (GMT) and seroresponse rate (SRR), where seroresponse was defined as change in nAb titer from either below the lower limit of quantitation (LLOQ) at baseline (i.e., Day 1) to ≥4 * LLOQ at Day 57, or at least a 4-fold rise from baseline when the baseline titer is ≥ LLOQ. The success criterion was that the lower bounds of the two-sided 95% CIs for both geometric mean ratio (GMR) (adolescents divided by young adults) and SRR difference (adolescents minus young adults) were > 0.67 and > -10%, respectively. The success criterion was met. In addition, there was a secondary efficacy objective to describe the incidence of COVID-19 between treatment groups after vaccination as measured by reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed COVID-19 based on the Centers for Disease Control and Prevention (CDC) and P301 protocol case definitions starting at 14 days after Dose 2. For both the CDC and P301 case definitions, the estimated Vaccine Efficacies (VEs) were ≥90%.

3. mRNA-1273-P203 – Part 1B (hereafter referred to as P203 – Part 1B): A phase 2/3, open-label study to evaluate long-term safety of two-dose, 100 μg mRNA-1273 primary series prompted by the authorization of a non-study COVID-19 vaccine for adolescents in the U.S. All participants who received placebo in P203 – Part 1A were offered the opportunity to receive mRNA-1273 in P203 – Part 1B. Therefore, there were two treatment groups: mRNA-1273 and placebo-mRNA-1273. There was no success criterion for the trial, and all

safety endpoints were analyzed descriptively.

4. P203 – Part 1C: A phase 2/3, open-label study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273 administered as a single BD of 50 µg mRNA-1273 in adolescents 12 to 17 YOA who previously received 2 doses of 100 µg mRNA-1273 as a primary series in either P203 – Part 1A or 1B. Vaccine effectiveness was inferred from bridging the immune responses of adolescents in P203 – Part 1C to those of young adults 18 to 25 YOA from P301. The co-primary immunogenicity objectives were demonstrating non-inferiority of Day 29 (for P203 – Part 1C) to Day 57 (for P301) pseudovirus nAb titer in terms of the GMT and SRR, where seroresponse was defined as change in nAb titer from either below the LLOQ at baseline (i.e., Day 1) to ≥4 * LLOQ at Day 29 (for P203 – Part 1C) or Day 57 (for P301), or at least a 4-fold rise from baseline when the baseline titer is ≥ LLOQ. The success criterion was that the lower bounds of the two-sided 95% CIs for both the GMR (adolescents divided by young adults) and SRR difference (adolescents minus young adults) were > 0.67 and > -10%, respectively. The success criterion was met.

5. mRNA-1273-P205 – Part F – Cohort 2 (hereafter referred to as P205 – Part F): A phase 2/3, open-label study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273 administered as a second BD of 50 µg mRNA-1273 in individuals 18 YOA or older who previously received 2 doses of 100 µg mRNA-1273 as a primary series and one BD of 50 µg mRNA-1273. Immunogenicity data from P205 – Part F were provided to support immunobridging for Study mRNA-1273-P205 – Part H (hereafter referred to as P205 – Part H).

6. P205 – Part H: A phase 2/3, open-label study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273.222 administered as a second BD of 50 µg mRNA-1273.222 in individuals 18 YOA or older who previously received 2 doses of 100 µg mRNA-1273 as a primary series and one BD of 50 µg mRNA-1273. Vaccine effectiveness was inferred from bridging the immune responses of adults in P205 – Part H to those of adults from P205 – Part F. The co-primary immunogenicity objectives were demonstrating non-inferiority of Day 29 pseudovirus nAb ID50 titer in terms of GMT and SRR for both Omicron BA.4/BA.5 and the ancestral strain, where seroresponse was defined as change in nAb titer from either below the LLOQ at baseline (i.e., Day 1) to ≥4 * LLOQ at Day 29, or at least a 4-fold rise from baseline when the baseline titer is ≥ LLOQ. The success criterion was that the lower bounds of the two-sided 95% CIs for both the GMR (Part H divided by Part F) and SRR difference (Part H minus Part F) were > 0.67 and > -10%, respectively, for both Omicron BA.4/BA.5 and the ancestral strain. The success criterion was met.

7. P203 – Part 3: A phase 2/3, open-label study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273.222 administered as a single dose of 50 µg mRNA-1273.222 in previously unvaccinated adolescents 12 to 17 YOA with evidence of prior SARS-CoV-2 infection. Vaccine effectiveness was inferred from bridging the immune responses of adolescents in P203 – Part 3 to those of young adults 18 to 25 YOA from P301. The co-primary immunogenicity objectives were demonstrating superiority and non-inferiority of Day 29 (for P203 – Part 1C) to Day 57 (for P301) pseudovirus nAb titer in

terms of GMT for Omicron BA.4/BA.5 and the ancestral strain, respectively. The success criterion was that the lower bounds of the two-sided 95% CIs for the GMRs (adolescents divided by young adults) were > 1.0 and > 0.67 for Omicron BA.4/BA.5 and the ancestral strain, respectively. The success criterion was met.

For all studies but P203 – Part 3, all subjects evaluated in the immunogenicity analyses had no evidence of prior SARS-CoV-2 infection at baseline. For P203 – Part 3, all subjects evaluated in the immunogenicity analyses had evidence of prior SARS-CoV-2 infection.

Overall, SPIKEVAX when administered as a 1) two-dose, 100 µg mRNA-1273 primary series in adolescents 12 to 17 YOA; 2) single BD of 50 µg mRNA-1273 in adolescents 12 to 17 YOA; 3) second BD of 50 µg mRNA-1273.222 in adults 18 YOA or older; and 4) single dose of 50 µg mRNA-1273.222 in previously unvaccinated adolescents 12 to 17 YOA with evidence of prior SARS-CoV-2 infection met the pre-specified immunogenicity objectives evaluated in the respective Phase 2/3 studies. No major statistical issues have been identified.

Solicited adverse reactions (ARs) and unsolicited Adverse Events (AEs) were collected through 7 and 28 days, respectively, after each dose administration. Unsolicited AEs included Medically Attended Adverse Events (MAAEs), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESIs). Unsolicited AEs were also collected up the respective data cutoffs.

In adolescents 12 to 17 YOA, comparing the two-dose, 100 µg mRNA-1273 primary series to placebo in P203 – Part 1A, rates of both local and systemic ARs were generally higher in the mRNA-1273 group than the placebo group for both doses. Comparing a single dose of 50 µg mRNA-1273.222 in COVID-19 vaccine-naïve subjects with evidence of prior SARS-CoV-2 infection from P203 – Part 3 to the second dose of a two-dose, 100 µg mRNA-1273 primary series in subjects without evidence of prior infection at baseline from P203 – Part 1A, subjects from P203 – Part 3 had generally fewer local and systemic ARs. Across studies for individuals 12 YOA and older who received some formulation of mRNA-1273, injection site pain was the most frequently reported solicited local AR. Fatigue and headache tended to be the most frequently reported solicited systemic ARs.

In adolescents 12 to 17 YOA, for unsolicited AEs that occurred within 28 days after each dose administration regardless of relationship to study vaccination, comparing a two-dose, 100 µg mRNA-1273 primary series to placebo in P203 – Part 1A, there were similar or slightly higher percentages of unsolicited AEs, MAAEs, and SAEs. In the mRNA-1273 group, there was 1 participant who had an AESI of appendicitis that was not considered related to study vaccination by the investigator. No events of myocarditis, pericarditis, or Multisystem Inflammatory Syndrome in Children (MIS-C) were reported. For unsolicited AEs that occurred within 28 days after each dose administration and were considered related to study vaccination by the investigator, comparing the mRNA-1273 group to the placebo group, there were higher percentages of both related unsolicited AEs and related MAAEs. No related SAEs or related AESIs as determined by the investigator were reported.

Across all studies in individuals 12 YOA and older who received some formulation of mRNA-1273, the percentages of unsolicited AEs, MAAEs, SAEs, and AESIs were generally consistent

within 28 days after each dose administration regardless of relationship to study vaccination as well as those considered related to study vaccination by the investigator. No events of myocarditis, pericarditis, or MIS-C were reported. One death was reported in P205 – Part H that was not considered related to study vaccination by the investigator.

Across all studies in individuals 12 YOA and older, up to the data cutoff (with median follow-up ranging from 35 to 131 days), no events of myocarditis, pericarditis, or MIS-C were reported. One additional death was reported in P205 – Part F that was not considered related to study vaccination by the investigator. No related SAEs or related AESIs as determined by the investigator were reported.

In P203 – Part 1B, adolescents 12 to 17 YOA who originally received a two-dose, 100 µg mRNA-1273 primary series in Part 1A were followed for unsolicited AEs over a substantially longer follow-up period (with median follow-up of 312 days) than the other studies. Compared to the other studies for unsolicited AEs regardless of relationship to study vaccination, subjects in P203 – Part 1B had elevated rates of both unsolicited AEs and MAAEs. According to the Applicant, this was primarily due to a higher case rate of COVID-19, which likely reflected the Omicron BA.1 surge that was observed during the months of December 2021 and January 2022 which overlapped with the follow-up period for P203 – Part 1B. The rates of both SAEs and AESIs were generally similar to the other studies. No deaths, events of myocarditis, pericarditis, or MIS-C were reported. For unsolicited AEs considered related to study vaccination by the investigator, the rates of unsolicited AEs, MAAEs, SAEs, and AESIs were similar to the other studies.

Overall, the available immunogenicity, exploratory efficacy, and safety data support the licensure of the monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older.

2. Clinical and Regulatory Background

SPIKEVAX is licensed for active immunization to prevent COVID-19 caused by SARS-CoV-2 as a two-dose, 100 µg mRNA-1273 series for individuals 18 YOA and older.

Under EUA, for individuals 12 YOA and older and children 6 to 11 YOA regardless of previous vaccination status, the vaccine is authorized for active immunization to prevent COVID-19 caused by SARS-CoV-2 as a single bivalent dose of 50 and 25 µg mRNA-1273.222, respectively. For COVID-19 vaccine-naïve children 6 months to 5 YOA, the vaccine is authorized as a two-dose, 25 µg mRNA-1273.222 primary series. For children 6 months to 5 YOA who previously received at least one dose of mRNA-1273, the vaccine is authorized as a single dose of 10 µg mRNA-1273.222.

Originally, the Applicant submitted two sBLAs to request licensure of SPIKEVAX as 1) (b) (4) (i.e., STN 125752/(b) (4)); and 2) a single bivalent booster dose of 50 µg mRNA-1273.222 for individuals 12 YOA and older who previously received primary series (i.e., STN 125752/68). During the review cycle, two changes were made to the requested indication.

First, the vaccination schedule for individuals 12 YOA and older was simplified to a single bivalent dose of 50 µg mRNA-1273.222 regardless of previous vaccination status to align with the EUA. In communication with the Applicant, the sBLA for STN 125752/[redacted] was withdrawn and its contents were resubmitted under STN 125752/68.

Second, there was a strain change for the vaccine formulation. Specifically, recommendations from the June 25, 2023 VRBPAC meeting led to the FDA's recommendation for the development of a monovalent COVID-19 vaccine encoded for Omicron XBB.1.5, which is currently in circulation.

Effectiveness of a single dose of the monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older regardless of previous vaccination status was inferred based on the 1) immunogenicity and efficacy of mRNA-1273 administered as a two-dose, 100 µg mRNA-1273 primary series in adolescents 12 to 17 YOA; 2) immunogenicity of mRNA-1273 administered as a single BD of 50 µg mRNA-1273 in adolescents 12 to 17 YOA; 3) immunogenicity of mRNA-1273.222 administered as a second BD of 50 µg mRNA-1273.222 in adults 18 YOA or older; and 4) immunogenicity of mRNA-1273.222 administered as a single dose of 50 µg mRNA-1273.222 in previously unvaccinated adolescents 12 to 17 YOA with evidence of prior SARS-CoV-2 infection.

Since its emergence in January 2020 in the U.S., it is assumed that almost everyone 12 YOA and older in the U.S. has been exposed to some strain of SARS-CoV-2 and therefore has developed some natural immunity to the disease. The studies supporting the requested indication thus cover subjects with or without evidence of prior SARS-CoV-2 infection, and who may or may not have been previously vaccinated with some formulation of mRNA-1273.

This review memo focuses on both the immunogenicity and safety data obtained from the following seven studies to support licensure of this vaccine: one Phase 3 clinical study, P301; and six Phase 2/3 clinical studies, P203 – Parts 1A, 1B, and 1C; P205 – Parts F and H; and P203 – Part 3.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

No data integrity issues were identified during the review.

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

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered

5.1 Review Strategy

This review focuses on one Phase 3 clinical study, P301, and six Phase 2/3 clinical studies, P203 – Parts 1A, 1B, and 1C, P205 – Parts F and H; and P203 – Part 3, supporting licensure of the single dose monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older regardless of previous vaccination status.

P203 – Parts 1C-2 and 2 are not included in this review memo. P205 – Parts A (i.e., Parts A.1 and A.2), B, C, D, E, F – Cohort 1, and G are also not included in this review memo.

5.2 sBLA Documents That Serve as the Basis for the Statistical Review

The following documents submitted to the sBLA are reviewed:

125752/68.0 (submitted on 3/28/2023)
1. Module 2. Clinical Summaries
   - Summary of Clinical Safety
2. Module 5. Interim Clinical Study Reports
   - P203 – Part 1C Interim Clinical Study Report
   - P205 – Part H Interim Clinical Study Report

125752/68.17 (submitted on 8/4/2023)
1. Module 2. Clinical Summaries
   - Clinical Overview of P203 – Part 3

125752/68.33 (submitted on 8/30/2023)
1. Module 5. Clinical Study Reports
   - P203 Clinical Study Report – Parts 1A and 1B

5.3 Table of Studies/Clinical Trials

One Phase 3 clinical study, P301, and six Phase 2/3 clinical studies, P203 – Parts 1A, 1B, and 1C, P205 – Parts F and H, and P203 – Part 3 were conducted to support licensure of the single dose monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older regardless of previous vaccination status. The studies are summarized in Table 1.

Table 1: Clinical Studies Supporting the sBLA

Study	N	Age	Description
P301	1779	18 to 25 years	Phase 3, randomized, placebo-controlled study to evaluate safety and efficacy of mRNA-1273 administered as a two-dose, 100 µg mRNA-1273 primary series
P203 – Part 1A	3733	12 to 17 years	Phase 2/3, randomized, placebo-controlled study to evaluate safety and effectiveness of mRNA-1273 administered as a two-dose, 100 µg mRNA-1273 primary series
P203 – Part 1B	2577	12 to 17 years	Phase 2/3 open-label study to evaluate long-term safety of mRNA-1273 administered as a two-dose, 100 µg mRNA-1273 primary series prompted by the authorization of a non-study COVID-19 vaccine for adolescents in the U.S.
P203 – Part 1C	1405	12 to 17 years	Phase 2/3, open-label study to evaluate safety and effectiveness of mRNA-1273 administered as a single BD of 50 µg mRNA-1273
P205 – Part F	376	≥ 18 years	Phase 2/3, open-label study to evaluate safety and effectiveness of mRNA-1273 administered as a second BD of 50 µg mRNA-1273
P205 – Part H	511	≥ 18 years	Phase 2/3, open-label study to evaluate safety and effectiveness of mRNA-1273.222 administered as a second BD of 50 µg mRNA-1273.222
P203 – Part 3	379	12 to 17 years	Phase 2/3, open-label study to evaluate safety and effectiveness of mRNA-1273.222 administered as a single dose of 50 µg mRNA-1273.222 in previously unvaccinated individuals

N = number of enrolled subjects.
Source: Adapted from P203 Clinical Study Report – Parts 1A and 1B, P203 – Part 1C, P205 – Part H Interim Clinical Study Reports, and P203 – Part 3 Clinical Overview.

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Study P301

Title of Study: 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

As data from P301 were only submitted to support immunobridging for adolescents 12 to 17 YOA from P203 – Parts 1A, 1C, and 3, a full review of P301 is not provided in this review memo. Instead, a summary of the design of P301 is provided.

P301 is an ongoing, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 YOA and older. Participants were randomized 1:1 to receive either 100 µg mRNA-1273 vaccine or placebo at Day 1 and Day 29, stratified by age category (18 to 64 years, ≥65 years) and health risk. Baseline and Day 57 immunogenicity data from a random subset of young adults 18 to 25 YOA randomized to mRNA-1273 were provided to support immunobridging for P203 – Parts 1A, 1C, and 3.

6.2 Clinical Study P203 – Parts 1A and 1B

Title of Study: 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 17 YOA – mRNA-1273 Primary Series Phase

Dates:
1. Study initiation date (First Subject First Visit): 09 December 2020
2. Data cutoff date for efficacy analyses: 31 May 2021
3. Data cutoff date for safety analyses: 31 January 2022

6.2.1 Objectives

Part 1A

Primary Immunogenicity Objective:
1. To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart) by comparing serum antibody responses obtained 28 days after Dose 2 of mRNA-1273 (Day 57) between P203 – Part 1A vaccine recipients (12 to 17 YOA) and P301 vaccine recipients (18 to 25 YOA).

Secondary Efficacy Objective:
1. To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo.

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

Part 1B

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

6.2.2 Design Overview

P203 consisted of three parts, where Part 1 consisted of multiple parts (i.e., Parts 1A, 1B, 1C-1 (referred to as 1C), and 1C-2) and Parts 2 and 3 consisted of single parts.

As only Parts 1A, 1B, 1C, and 3 were submitted to support the sBLA, this review memo focuses on Parts 1A, 1B, 1C, and 3. Parts 1A and 1B are reviewed in this Section, Part 1C is reviewed in Section 6.3, and Part 3 is reviewed in Section 6.5.

Part 1A

Part 1A was a randomized, observer-blind, placebo-controlled study to evaluate the safety and reactogenicity and to infer the effectiveness of mRNA-1273 administered in 2 doses 28 days apart in an adolescent population 12 to 17 YOA. Subjects were randomized in a 2:1 ratio to receive either 100 µg mRNA-1273 or placebo at Day 1 and Day 29. For immunogenicity, blood samples were collected from a subset of participants selected for immunogenicity testing at Day 1 (i.e., baseline) and Day 57 (i.e., 28 days after Dose 2). Vaccine effectiveness was inferred from bridging the immune responses of adolescents in P203 – Part 1A to those of young adults 18 to 25 YOA from P301. The endpoint selected for immunobridging was the pseudovirus nAb ID50

titer. For efficacy, participants were surveilled for cases of COVID-19 defined according to both the CDC and P301 protocol case definitions. In addition, cases of asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection (regardless of symptoms) were collected. For safety, solicited ARs and unsolicited AEs were collected through 7 and 28 days, respectively, after each dose. Unsolicited AEs included MAAEs, SAEs, and AESIs. Unsolicited AEs that occurred after 28 days post-Dose 2 were reported in Part 1B.

Part 1B

Part 1B was an open-label study to evaluate long-term safety of two-dose, 100 µg mRNA-1273 primary series prompted by the authorization of a non-study COVID-19 vaccine for adolescents in the U.S. on 10 May 2021. All participants who received placebo in Part 1A were offered the opportunity to receive mRNA-1273 in Part 1B. According to the Applicant, administration of mRNA-1273 to placebo recipients was delayed until 06 Oct 2021 because of both ongoing US regulatory review of the adolescent EUA (submitted June 2021) and the emergence of the Delta variant wave. There were two treatment groups: mRNA-1273 and placebo-mRNA-1273. For safety, unsolicited AEs, including SAEs, MAAEs, and AESIs were collected up to End-of-Study (EoS; i.e., 31 January 2022).

6.2.3 Population

Subjects 12 to 17 YOA were enrolled.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Part 1A

100 µg mRNA-1273 or saline placebo administered in 2 doses 28 days apart.

Part 1B

For participants who rolled over from the mRNA-1273 group in Part 1A, no additional vaccination was administered. For participants who rolled over from the placebo group in Part 1A, 100 µg mRNA-1273 was administered in 2 doses 28 days apart.

6.2.6 Sites and Centers

The study was conducted at 25 sites in the U.S.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Study Success Criteria

Part 1A

Co-Primary Immunogenicity Endpoints:

1. GMR and SRR[a] difference between P203 – Part 1A vaccine recipients (12 to 17 YOA) and P301 vaccine recipients (18 to 25 YOA) at Day 57.
    - The lower bound of the two-sided 95% CI of the GMR (adolescents to young adults) is > 0.67 AND the GMR point estimate is > 0.8.
    - The lower bound of the two-sided 95% CI for the difference in SRR (adolescents minus young adults) is > -10% AND the SRR point estimate is > -5%.

[a]Seroresponse was defined as a change from below the LLOQ at baseline to ≥ 4 * LLOQ at Day 57, or at least a 4-fold rise in participants with a baseline titer ≥ LLOQ.

Secondary Efficacy Endpoints:

1. Starting 14 days after the second dose of investigational product (IP), the incidence of the first occurrence of: COVID-19 defined according to the CDC definition, COVID-19 defined according to the P301 protocol definition, asymptomatic SARS-CoV-2 infection, and SARS-CoV-2 infection.

Safety Endpoints:

1. In all participants:
    - Solicited local and systemic ARs through 7 days after each injection.
    - Unsolicited AEs, MAAEs, SAEs, and AESIs through 28 days after each injection.

Part 1B

Safety Endpoints:

1. In all participants:
    - Unsolicited AEs, MAAEs, SAEs, and AESIs up to EoS.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Part 1A

Analysis of Immunogenicity:

GMRs were estimated via Analysis of Covariance (ANCOVA) using Day 57 log-titers as the dependent variable and group (adolescents vs. young adults) as the only independent variable. The 95% CI for the SRR difference was estimated via the Miettinen-Nurminen method.

For both studies P203 – Part 1A and P301, the immunogenicity analyses were conducted on the PPIS, which was a subset of the Immunogenicity Subset (IS), which was a subset of the Full Analysis Set (FAS), which was a subset of the Randomization Set (RS). All four analysis sets are defined below:

- RS: All participants who were randomized, regardless of the participants' treatment status in the study.

- FAS: All randomized participants who received at least 1 injection of IP.
  - IS: A subset of participants in the FAS selected for immunogenicity testing.
    - PPIS: Participants in the IS who were seronegative at baseline, received planned doses of IP per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that impacted key or critical data.

Subgroup analyses were performed by age category (12 to 16 YOA or 16 to 17 YOA), sex (male or female), race (African American, Caucasian, or Other), ethnicity (Hispanic/Latino or not Hispanic/ Latino), and race and ethnicity (non-Hispanic Caucasian or Communities of Color).

Analysis of Efficacy:

Adolescents were followed to assess vaccine efficacy (VE) against Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)-confirmed COVID-19. Case definitions are displayed in Table 2. VE was defined as 1 - incidence rate ratio (mRNA-1273 vs. placebo). The 95% CI of the VE was calculated using the exact method conditional on the total number of cases adjusted by the total person-years. VEs and associated 95% CIs were provided descriptively based on both cases and person-years.

Due to unblinding and attrition of placebo recipients after the non-study vaccine authorization in early May 2021, 31 May 2021 was selected as the data cutoff date for the efficacy analyses.

For the efficacy analyses, both cases and person-years were counted within the time points specified by the analysis set. Cases and person-years were counted until the event date, data cutoff date, last date of study participation, date of unblinding, date of non-study COVID-19 vaccination, date of crossover dose, or date of BD, whichever was earliest.

The efficacy analyses were conducted on the Per-Protocol Set for Efficacy (PPE), which was a subset of the FAS. Sensitivity efficacy analyses were performed on the Modified Intent-to-Treat-1 Set (mITT1), which was a subset of the Modified Intent-to-Treat Set (mITT), which was a subset of the FAS. All three analysis sets are defined below:

- PPE: Participants in the FAS who received planned doses of IP, had no immunologic or virologic evidence of prior SARS-CoV-2 infection before Dose 1 of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on binding antibody [bAb] specific to SARS-CoV-2 nucleocapsid), and had no major protocol deviations that impact key or critical efficacy data.
- mITT: Participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection before Dose 1 of IP.
  - mITT1: Participants in the mITT excluding those who received the wrong treatment (i.e., at least 1 dose received was not as randomized).

For the PPE, both cases and person-years were counted starting from 14 days post Dose 2; for the mITT1, both cases and person-years were counted starting from 14 days post Dose 1.

Table 2: Case Definitions

Endpoint	Definition
CDC	At least 1 symptom from a pre-specified list of COVID-19 symptoms derived from the US CDC case definition: Systemic symptoms: fever (temperature > 38°C/≥ 100.4°F) or chills (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding, **OR** respiratory signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours) **AND** At least 1 positive RT-PCR for SARS-CoV-2.
P301	COVID-19 case was identified as a positive post-baseline RT-PCR test result, together with eligible symptoms as follows: A positive post-baseline PCR result **AND** 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 1 of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
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: Absence of COVID-19 symptoms, **AND** at least 1 from below: bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, **OR** Positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.
SARS-CoV-2 infection (regardless of symptoms)	A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: 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) post-baseline, **OR** Positive RT-PCR test post-baseline.

Source: Table 8 of P203 Clinical Study Report – Parts 1A and 1B.

Analysis of Safety:

All safety data were summarized descriptively. Solicited ARs and unsolicited AEs were summarized in the Solicited Safety Set (SSS) and Safety Set (SS), respectively, where the SSS was a subset of the SS, which was a subset of the RS. Within the SSS, First and Second Injection SSS were defined. All four analysis sets are defined below:

- SS: All randomized participants who received at least 1 dose of IP.
  - SSS: Participants in the SS who contributed any solicited AR data.
    - First Injection SSS: Participants in the SSS who received at least one dose of IP.
    - Second Injection SSS: Participants in the SSS who received both doses of IP.

Subgroup analyses were performed by baseline SARS-CoV-2 status, age category, sex, race, ethnicity, and race and ethnicity.

Multiplicity Adjustment:

The success criterion for P203 – Part 1A was that both co-primary immunogenicity endpoints meet their respective success criteria for the immunogenicity analyses at Day 57. Thus, no multiplicity adjustments were necessary.

Sample Size Determination:

The sample size of this study was driven by both safety and immunogenicity. For safety, approximately 3700 participants were planned to be randomly assigned in a 2:1 ratio to receive mRNA-1273 or placebo. With approximately 2500 participants exposed to mRNA-1273, the study had at least a 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

For immunogenicity, approximately 362 participants who received mRNA-1273 were selected for the IS, with a target of 289 participants in the PPIS (assuming a non-evaluable rate of 20%). For GMR, assuming a non-inferiority margin of 0.67, a true GMR of 1, and a standard deviation (SD) of 1.5 for natural log-transformed titers, 289 participants in the PPIS yielded approximately 90% power to demonstrate non-inferiority in terms of GMR at the one-sided alpha = 0.025 level. For SRR difference, assuming a non-inferiority margin of -10% and a true SRR difference of 0% with SRRs of 85% in both groups, 289 participants in the PPIS yielded approximately 90% power to demonstrate non-inferiority of SRR difference at the one-sided alpha = 0.025 level.

Part 1B

Analysis of Safety:

All safety data were summarized descriptively. Unsolicited AEs were summarized in the Long-Term Safety Set (LTSS), which was defined as:

- LTSS: Participants who received at least one dose of mRNA-1273.

6.2.10 Study Population and Disposition

Part 1A

Table 3 displays the dispositions of the randomized population for P203 – Part 1A. A total of 3733 participants were included in the RS (1243 in the placebo group and 2490 in the mRNA-1273 group).

Overall, 78.6% of participants in the placebo group and 8.9% of participants in the mRNA-1273 group discontinued from the study prior to unblinding. This was because on 10 May 2021, a non-study vaccine was authorized for individuals 12 YOA and older. Although attempts to maintain study blinding were implemented according to the Applicant, most study participants requested unblinding to learn their study group status, and the majority of placebo recipients discontinued the study to seek the non-study COVID-19 vaccine. Access to mRNA-1273 was not offered to placebo participants at the time the non-study COVID-19 vaccine was authorized.

Table 3: Participant Disposition for P203 – Part 1A – RS

-	**Placebo N=1243 n (%)**	**mRNA-1273 N=2490 n (%)**
Number of participants	-	-
Received Dose 1	1240 (99.8)	2486 (99.8)
Received Dose 2	1222 (98.3)	2480 (99.6)
Completed study vaccine schedule	1222 (98.3)	2480 (99.6)
Discontinued study vaccine[a]	18 (1.4)	6 (0.2)
Reason for discontinuation of study vaccine	-	-
AE	0	3 (0.1)
COVID-19 infection	0	1 (<0.1)
Other	0	2 (<0.1)
Lost to follow-up	6 (0.5)	2 (<0.1)
Withdrawal of consent by participant	9 (0.7)	1 (<0.1)
COVID-19 non-infection related	1 (<0.1)	0
Other	8 (0.6)	1 (<0.1)
Other	2 (0.2)	0
Missing	1 (<0.1)	0
Discontinued from Study prior to unblinding[b]	977 (78.6)	221 (8.9)
Reason for discontinuation of Study	-	-
AE	0	1 (<0.1)
Other	0	1 (<0.1)
Lost to follow-up	13 (1.0)	55 (2.2)
Physician decision	0	2 (<0.1)
Protocol deviation	2 (0.2)	1 (<0.1)
Participant received another COVID-19 vaccine under EUA	645 (51.9)	38 (1.5)
Withdrawal of consent by participant	89 (7.2)	105 (4.2)
COVID-19 non-infection related[c]	16 (1.3)	1 (<0.1)
Other	73 (5.9)	104 (4.2)
Other	228 (18.3)	19 (0.8)

[a]Study vaccine discontinuation was defined as a participant who received Dose 1 but not Dose 2.
[b]Unblinding was defined as the earliest date of unblinding, non-study COVID-19 vaccination, crossover dose, or BD.
[c]Refers to situations related to pandemic conditions (e.g, reluctance to attend site visits because of concerns regarding SARS-CoV-2 transmissibility) rather than to SARS-CoV-2 infection or COVID-19 in the study participant.
Source: Table 11 of P203 Clinical Study Report – Parts 1A and 1B.

Table 4 displays the sample size in each analysis set by treatment group for P203 – Part 1A. In each analysis set, the numbers of participants were generally balanced between treatment groups. A subset of 374 participants who received mRNA-1273 was selected for the IS, where 340 participants met the criteria for the PPIS. In P301, a subset of 340 participants who received mRNA-1273 was selected for the IS, where 295 participants met the criteria for the PPIS.

Table 4: Number of Participants in Each Analysis Set for P203 – Part 1A

-	**Placebo n (%)**	**mRNA-1273 n (sss%)**
Randomization Set	1243	2490
Full Analysis Set, n (%)	1240 (99.8)	2486 (99.8)
Per-Protocol Set for Efficacy, n (%)	1044 (84.0)	2142 (86.0)
Modified Intent-to-Treat set, n (%)	1078 (86.7)	2171 (87.2)
Modified Intent-to-Treat-1 set, n (%)	1076 (86.6)	2167 (87.0)
Immunogenicity Subset	-	374
Per-Protocol Immunogenicity Subset, n (%)	-	340 (90.9)
Safety Set	1240	2486
Solicited Safety Set, n (%)	1240 (100)	2485 (>99.9)
First Injection Solicited Safety Set, n (%)	1238 (99.8)	2482 (99.8)
Second Injection Solicited Safety Set, n (%)	1220 (98.4)	2478 (99.7)

Source: Table 12 of P203 Clinical Study Report – Parts 1A and 1B.

Table 5 displays the distributions of demographic characteristics among the treatment groups by study and analysis set. For P203 – Part 1A, the distributions between both treatment groups in the SS and the PPIS were similar. Among participants in the PPIS, aside from age differences, there was a smaller percentage of Hispanic participants in P203 – Part 1A (7.6%) than P301 (26.4%).

Part 1B

For P203 – Part 1B, due to the high number of discontinuations of placebo recipients starting in May 2021, most participants included in the LTSS were those originally randomized to mRNA-1273 in Part 1A. The mRNA-1273 groups in Parts 1A and 1B consisted of the same 2486 participants. Although the placebo-mRNA-1273 group included only 91 participants, the distributions between the treatment groups in the LTSS were generally similar. However, there was a higher percentage of Hispanic participants in the placebo-mRNA-1273 group (25.3%) than the mRNA-1273 group (11.3%). Additionally, there was a higher percentage of participants who had immunologic or virologic evidence of prior COVID-19 infection at pre-Dose 1 of mRNA-1273 (i.e., positive pre-Dose 1 SARS-CoV-2 status) in the placebo-mRNA-1273 group (39.6%) than the mRNA-1273 group (5.9%).

Table 5: Demographic Characteristics by Study and Analysis Set

-	**P203 – Part 1A Placebo (N=1240) SS**	**P203 – Parts 1A and 1B mRNA-1273 (N = 2486) SS/LTSS**	**P203 – Part 1A mRNA-1273 (N=340) PPIS**	**P301 mRNA-1273 (N=295) PPIS**	**P203 – Part 1B Placebo-mRNA-1273 (N=91) LTSS**
Age (years)	-	-	-	-	-
n	1240	2486	340	295	91
Mean (SD)	14.2 (1.6)	14.3 (1.6)	14.4 (1.6)	22.4 (2.2)	14.1 (1.7)
Median	14.0	14.0	14.0	23.0	14.0
Min, Max	12, 17	12, 17	12, 17	18, 25	12, 17
Age group, n (%)	-	-	-	-	-
≥ 12 and <16 years	929 (74.9)	1839 (74.0)	239 (70.3)	-	70 (76.9)
≥ 16 and <18 years	311 (25.1)	647 (26.0)	101 (29.7)	-	21 (23.1)
Gender, n (%)	-	-	-	-	-
Male	632 (51.0)	1283 (51.6)	178 (52.4)	142 (48.1)	48 (52.7)
Female	608 (49.0)	1203 (48.4)	162 (47.6)	153 (51.9)	43 (47.3)
Race, n (%)	-	-	-	-	-
Caucasian	1040 (83.9)	2084 (83.8)	284 (83.5)	206 (69.8)	82 (90.1)
African American	42 (3.4)	83 (3.3)	4 (1.2)	29 (9.8)	2 (2.2)
Asian	80 (6.5)	142 (5.7)	15 (4.4)	30 (10.2)	3 (3.3)
American Indian or Alaska native	7 (0.6)	12 (0.5)	0	3 (1.0)	1 (1.1)
Native Hawaiian or other Pacific Islander	0	3 (0.1)	1 (0.3)	2 (0.7)	0
Multiracial	50 (4.0)	118 (4.7)	19 (5.6)	14 (4.7)	3 (3.3)
Other	9 (0.7)	27 (1.1)	7 (2.1)	8 (2.7)	0
Not reported	11 (0.9)	11 (0.4)	6 (1.8)	3 (1.0)	0
Unknown	1 (<0.1)	6 (0.2)	4 (1.2)	0	0
Ethnicity, n (%)	-	-	-	-	-
Hispanic or Latino	152 (12.3)	280 (11.3)	26 (7.6)	78 (26.4)	23 (25.3)
Not Hispanic or Latino	1076 (86.8)	2186 (87.9)	304 (89.4)	215 (72.9)	68 (74.7)
Not reported	10 (0.8)	19 (0.8)	9 (2.6)	0	0
Unknown	2 (0.2)	1 (<0.1)	1 (0.3)	2 (0.7)	0
Race and ethnicity group, n (%)[a]	-	-	-	-	-
Caucasian non-Hispanic	911(73.5)	1856 (74.7)	266 (78.2)	145 (49.2)	60 (65.9)
Communities of Color	326 (26.3)	626 (25.2)	70 (20.6)	150 (50.8)	31 (34.1)
Missing	3 (0.2)	4 (0.2)	4 (1.2)	0	0
Weight (kg)	-	-	-	-	-
n	1240	2486	340	294	91
Mean (SD)	61.0 (16.4)	61.3 (15.9)	61.5 (14.8)	77.6 (19.3)	61.2 (16.5)
Median	57.8	58.9	59.6	73.6	56.9
Min, Max	30.3, 160.8	27.8, 184.1	29.1, 130.1	44.0, 158.2	35.0, 115.9

Table 5: Demographic Characteristics by Study and Analysis Set (continued)

-	**P203 – Part 1A Placebo (N=1240) SS**	**P203 – Parts 1A and 1B mRNA-1273 (N = 2486) SS/LTSS**	**P203 – Part 1A mRNA-1273 (N=340) PPIS**	**P301 mRNA-1273 (N=295) PPIS**	**P203 – Part 1B Placebo-mRNA-1273 (N=91) LTSS**
Height (cm)	-	-	-	-	-
n	1240	2486	340	294	91
Mean (SD)	165.6 (10.0)	166.0 (10.0)	166.4 (9.2)	171.2 (9.3)	165.7 (10.0)
Median	165.1	165.5	166.2	170.6	164.5
Min, Max	122.6, 192.0	104.0, 203.2	137.5, 192.0	147.3, 201.9	143.3, 190.8
Body mass index (kg/m2)	-	-	-	-	-
n	1240	2486	340	294	91
Mean (SD)	22.1 (5.1)	22.1 (4.9)	22.1 (4.4)	26.4 (5.9)	22.2 (5.2)
Median	20.9	21.1	21.2	24.9	20.9
Min, Max	14.8, 62.7	11.0, 76.7	14.7, 42.0	16.7, 48.7	15.1, 38.2
BMI subgroup, n (%)	-	-	-	-	-
< 30 kg/m2	1149 (92.7)	2320 (93.3)	318 (93.5)	226 (76.6)	80 (87.9)
≥ 30 kg/m2	91 (7.3)	166 (6.7)	22 (6.5)	68 (23.1)	11 (12.1)
Missing	0	0	0	1 (0.3)	0
BMI subgroup, n (%)	-	-	-	-	-
Obesity[b]	225 (18.1)	451 (18.1)	59 (17.4)	68 (23.1)	15 (16.5)
Non-obesity	1015 (81.9)	2035 (81.9)	281 (82.6)	226 (76.6)	76 (83.5)
Missing	0	0	0	1 (0.3)	0
Pre-Dose 1[c] RT-PCR results, n (%)	-	-	-	-	-
Negative	1143 (92.2)	2311 (93.0)	340 (100)	295 (100)	83 (91.2)
Positive	9 (0.7)	13 (0.5)	0	0	3 (3.3)
Missing	88 (7.1)	162 (6.5)	0	0	5 (5.5)
Pre-Dose 1[c] Elecsys Anti-SARS-CoV-2 results, n (%)	-	-	-	-	-
Negative	1156 (93.2)	2304 (92.7)	340 (100)	295 (100)	53 (58.2)
Positive	64 (5.2)	139 (5.6)	0	0	34 (37.4)
Missing	20 (1.6)	43 (1.7)	0	0	4 (4.4)
Pre-Dose 1[c] SARS-CoV-2 status, n (%)[d]	-	-	-	-	-
Negative	1078 (86.9)	2171 (87.3)	340 (100)	295 (100)	51 (56.0)
Positive	70 (5.6)	147 (5.9)	0	0	36 (39.6)
Missing	92 (7.4)	168 (6.8)	0	0	4 (4.4)

[a]Caucasian non-Hispanic was defined as Caucasian and non-Hispanic, and Communities of Color included all the others whose race or ethnicity was not unknown, unreported, or missing.
[b]Obesity was defined as BMI ≥ 95th percentile of the World Health Organization growth reference data for P203 and BMI ≥ 30 kg/m2 for P301.
[c]Pre-Dose 1 was defined as pre-Dose 1 of either mRNA-1273 or placebo for every group but P203 – Part 1B placebo-mRNA-1273, where it was defined as pre-Dose 1 of mRNA-1273.

[d]Pre-Dose 1 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.
Source: Adapted from Tables 16, 17, and 19 of P203 Clinical Study Report – Parts 1A and 1B.

6.2.11 Efficacy Analyses

Part 1A – Co-Primary Immunogenicity Endpoints

Table 6 displays both the geometric least squares means (GLSMs) and SRRs of Day 57 nAb titers for both adolescents and young adults. The success criteria for both the GMR (GMR = 1.1, 95% CI = 0.9 to 1.2) and SRR difference (SRR difference = -0.2%, 95% CI = -2.1% to 1.9%) were met for both the lower bounds of the 95% CIs and the point estimates.

Across the subgroups of age category, sex, race, ethnicity, and race and ethnicity, no meaningful differences in GMRs or SRR differences were observed.

Table 6: Analyses of Co-Primary Immunogenicity Endpoints at Day 57 for PPIS for both P203 – Part 1A and P301

-	**P203 – Part 1A Adolescents 12 to < 18 YOA**	**P301 Young adults 18 – 25 YOA**
N	340	295
GLSM (95% CI)[a]	1401.7 (1276.2, 1539.5)	1299.9 (1175.4, 1437.5)
GMR (95% CI)[a]	1.1 (0.9, 1.2)	-
Seroresponse Rate, % (95% CI)[b,c]	336/340 98.8 (97.0, 99.7)	292/295 99.0 (97.1, 99.8)
SRR Difference, % (95% CI)[d]	-0.2 (-2.1, 1.9)	-

[a]Based on ANCOVA modeling, which used Day 57 log-titers as the dependent variable and group (adolescents vs. young adults) as the only independent variable.
[b]SRR compares Day 57 to pre-Dose 1 titer of the primary series.
[c]95% CI was estimated via the Clopper-Pearson method.
[d]95% CI was estimated via the Miettinen-Nurminen method.
Source: Table 23 of P203 Clinical Study Report – Parts 1A and 1B.

Reviewer's Comment:

- *The immunogenicity (Sections 6.2.11, 6.3.11, 6.4.11, 6.5.11), efficacy (Section 6.2.11), and safety (Sections 6.2.12, 6.3.12, 6.4.12, 6.5.12) analyses were verified based on data submitted in the Standard Data Tabulation Model format, and the results were consistent with those reported by the Applicant.*

Part 1A – Secondary Efficacy Endpoint

Tables 7 and 8 display the results of the descriptive efficacy analyses for the PPE and mITT1, respectively. Figure 1 displays the cumulative incidence curve for the P301 case definition starting 14 days after Dose 2 for the PPE.

Starting 14 days after Dose 2, in the PPE for the CDC case definition, there were 2 and 9 COVID-19 cases in the mRNA-1273 and placebo groups, respectively, with an estimated VE = 0.90 (95% CI = 0.51 to 0.99). Similarly, for the P301 case definition, there were 0 and 6 cases in the mRNA-1273 and placebo groups, respectively, with an estimated VE = 1.00 (95% CI = 0.61 to Not Estimated [NE]). For both the asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection case definitions, there were more cases in both treatment groups with VEs of 0.44 (95% CI = -0.17 to 0.72) and 0.60 (95% CI = 0.27 to 0.79), respectively.

Starting 14 days after Dose 1, in the mITT1, for the CDC, P301, asymptomatic SARS-CoV-2 infection, and SARS-CoV-2 infection case definitions, the estimated VEs were 0.91 (95% CI = 0.67 to 0.98), 1.00 (95% CI = 0.77 to NE), 0.62 (95% CI = 0.33 to 0.79), and 0.72 (95% CI = 0.54 to 0.83), respectively.

Table 7: Analyses of Secondary Efficacy Endpoints Starting 14 Days After Dose 2 as of 31 May 2021 for P203 – Part 1A – PPE

-	**mRNA-1273 (N=2142)** **Cases** **IR (95% CI)**	**Placebo (N=1044)** **Cases** **IR (95% CI)**	**VE (95% CI)**
CDC Case Definition	2 3.29 (0.40, 11.87)	9 32.39 (14.81, 61.48)	0.90 (0.51, 0.99)
P301 Case Definition	0 0 (NE, 6.06)	6 21.54 (7.90, 46.88)	1.00 (0.61, NE)
Asymptomatic SARS-CoV-2 Infection	20 33.05 (20.19, 51.04)	16 58.55 (33.46, 95.07)	0.44 (-0.17, 0.72)
SARS-CoV-2 Infection	22 36.35 (22.78, 55.04)	25 91.48 (59.20, 135.04)	0.60 (0.27, 0.79)

IR = Incidence Rate; NE = Not Estimated.
Source: Table 24 of P203 Clinical Study Report – Parts 1A and 1B.

Reviewer's Comment:

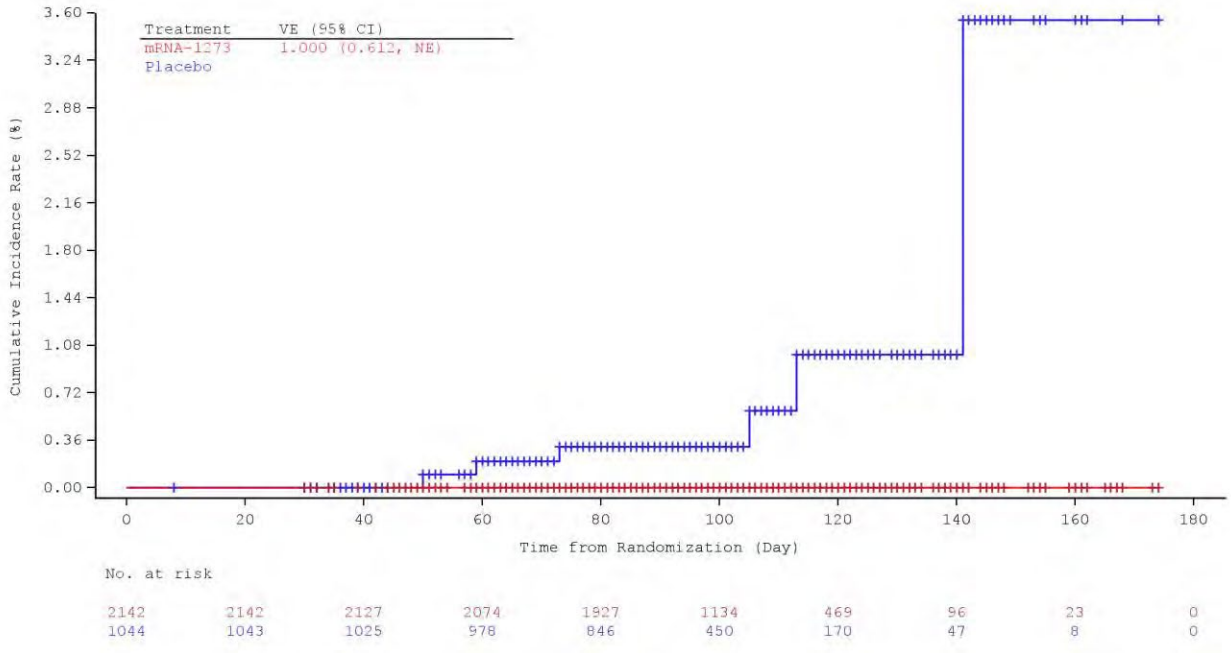
- *For the PPE, person-years were based on follow-up time starting from Dose 1 for all subjects. However, as cases were not counted before 14 days post Dose 2, subjects were not effectively at risk until 14 days after Dose 2. I re-estimated the incidence rates and VE based on person-years starting from 14 days post Dose 2. For all endpoints, the VEs were within 3 percentage points of the VEs displayed in Table 7.*

Table 8: Sensitivity Analyses of Secondary Efficacy Endpoints Starting 14 Days After Dose 1 as of 31 May 2021 for P203 – Part 1A – mITT1

-	**mRNA-1273 (N=2167)** **Cases** **IR (95% CI)**	**Placebo (N=1076)** **Cases** **IR (95% CI)**	**VE (95% CI)**
CDC Case Definition	3 4.87 (1.00, 14.22)	15 52.68 (29.49, 86.90)	0.91 (0.67, 0.98)
P301 Case Definition	0 3.29 (NE, 5.98)	9 31.52 (14.41, 59.83)	1.00 (0.77, NE)
Asymptomatic SARS-CoV-2 Infection	24 39.15 (25.08, 58.25)	29 103.61 (69.39, 148.81)	0.62 (0.33, 0.79)
SARS-CoV-2 Infection	27 44.04 (29.02, 64.07)	44 157.22 (114.24, 211.06)	0.72 (0.54, 0.83)

IR = Incidence Rate; NE = Not Estimated.
Source: Table 25 of P203 Clinical Study Report – Parts 1A and 1B.

Figure 1: Cumulative Incidence Curve of COVID-19 Starting 14 Days After Dose 2 as of 31 May 2021 for P203 – Part 1A – PPE – P301 Case Definition



Source: Figure 6 of P203 Clinical Study Report – Parts 1A and 1B.

6.2.12 Safety Analyses

Part 1A – Solicited ARs

Table 9 displays both local and systemic ARs within 7 days after Dose 1 and Dose 2 in both the mRNA-1273 and placebo groups for the First Injection SSS and Second Injection SSS.

Rates of both local and systemic ARs were generally higher in the mRNA-1273 group than the placebo group for both doses. Rates of local ARs were similar after Dose 1 and Dose 2 in the mRNA-1273 group except that there was a slightly higher rate of Erythema after Dose 2 than

Dose 1. For both doses, injection site pain was the most frequently reported solicited local AR in the mRNA-1273 group. Rates of systemic ARs were generally higher after Dose 2 than Dose 1 in the mRNA-1273 group. For both doses, fatigue and headache were the most frequently reported solicited systemic ARs in the mRNA-1273 group.

Across the subgroups defined by baseline SARS-CoV-2 status, age category, race, ethnicity, and race and ethnicity, no meaningful differences in solicited ARs were observed. Females generally reported more solicited systemic ARs after both Dose 1 and Dose 2.

Table 9: Summary of Both Solicited Local and Systemic ARs Within 7 Days After Dose 1 and Dose 2 by Grade for P203 – Part 1A – First Injection SSS and Second Injection SSS

-	**mRNA-1273 Dose 1 (N=2482) n (%)**	**mRNA-1273 Dose 2 (N=2478) n (%)**	**Placebo Dose 1 (N=1238) n (%)**	**Placebo Dose 2 (N=1220) n (%)**
Local ARs, Any Grade	2339 (94.2)	2314 (93.4)	455 (36.8)	398 (32.6)
Local ARs, Grade 3	171 (6.9)	220 (8.9)	1 (<0.1)	3 (0.2)
Pain, Any Grade	2310 (93.1)	2290 (92.4)	431 (34.8)	370 (30.3)
Pain, Grade 3[a]	133 (5.4)	126 (5.1)	1 (<0.1)	3 (0.2)
Axillary swelling/tenderness, Any Grade	576 (23.2)	519 (21.0)	101 (8.2)	61 (5.0)
Axillary swelling/tenderness, Grade 3[a]	11 (0.4)	7 (0.3)	0	0
Swelling (hardness), Any Grade	401 (16.2)	508 (20.5)	12 (1.0)	12 (1.0)
Swelling (hardness), Grade 3[b]	27 (1.1)	56 (2.3)	0	0
Erythema (redness), Any Grade	329 (13.3)	484 (19.5)	8 (0.6)	11 (0.9)
Erythema (redness), Grade 3[b]	22 (0.9)	72 (2.9)	0	0
Systemic ARs, Any Grade	1701 (68.5)	2134 (86.1)	687 (55.5)	561 (46.0)
Systemic ARs, Grade 3	108 (4.4)	341 (13.8)	36 (2.9)	25 (2.0)
Systemic ARs, Grade 4	0	3 (0.1)	0	1 (<0.1)
Fatigue, Any Grade	1188 (47.9)	1679 (67.8)	453 (36.6)	353 (28.9)
Fatigue, Grade 3[c]	33 (1.3)	188 (7.6)	18 (1.5)	10 (0.8)
Headache, Any Grade	1106 (44.6)	1739 (70.2)	477 (38.5)	371 (30.4)
Headache, Grade 3[d]	56 (2.3)	112 (4.5)	17 (1.4)	14 (1.1)
Headache, Grade 4[e]	0	1 (<0.1)	0	0
Myalgia, Any Grade	670 (27.0)	1155 (46.6)	205 (16.6)	153 (12.5)
Myalgia, Grade 3[c]	24 (1.0)	129 (5.2)	10 (0.8)	3 (0.2)
Arthralgia, Any Grade	371 (15.0)	716 (28.9)	143 (11.6)	113 (9.3)
Arthralgia, Grade 3[c]	15 (0.6)	57 (2.3)	5 (0.4)	2 (0.2)
Chills, Any Grade	456 (18.4)	1066 (43.0)	138 (11.1)	97 (8.0)
Chills, Grade 3[f]	4 (0.2)	11 (0.4)	1 (<0.1)	0
Nausea/vomiting, Any Grade	281 (11.3)	591 (23.9)	109 (8.8)	106 (8.7)
Nausea/vomiting, Grade 3[g]	2 (<0.1)	2 (<0.1)	0	0
Nausea/vomiting, Grade 4[h]	0	1 (<0.1)	0	0
Fever, Any Grade	57 (2.3)	298 (12.0)	11 (0.9)	12 (1.0)
Fever, Grade 3[i]	9 (0.4)	48 (1.9)	1 (<0.1)	1 (<0.1)
Fever, Grade 4[j]	0	1 (<0.1)	0	1 (<0.1)
Use of antipyretic or pain medication	748 (30.1)	1242 (50.1)	118 (9.5)	108 (8.9)

[a]Grade 3 pain and axillary swelling/tenderness is defined as: any use of prescription pain reliever; prevents daily activity.
[b]Grade 3 swelling and erythema is defined as: >100 mm / >10 cm.
[c]Grade 3 fatigue, myalgia, arthralgia is defined as: significant; prevents daily activity.
[d]Grade 3 headache is defined as: significant; any use of prescription pain reliever or prevents daily activity.
[e]Grade 4 headache is defined as: requires emergency room visit or hospitalization.
[f]Grade 3 chills is defined as: prevents daily activity and requires medical intervention.
[g]Grade 3 nausea/vomiting is defined as: prevents daily activity, requires outpatient intravenous hydration.
[h]Grade 4 nausea/vomiting is defined as: requires emergency room visit or hospitalization for hypotensive shock.
[i]Grade 3 fever is defined as: ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j]Grade 4 fever is defined as: >40.0°C / >104.0°F.

Source: Adapted from Tables 28 and 29 of P203 Clinical Study Report – Parts 1A and 1B.

Part 1A – Unsolicited AEs

Table 10 displays unsolicited AEs up to 28 days after any injection in both the mRNA-1273 and placebo groups for the SS.

For unsolicited AEs regardless of relationship to study vaccination up to 28 days after any injection, comparing the mRNA-1273 group to the placebo group, there were similar or slightly higher percentages of unsolicited AEs (23.4% and 19.1%, respectively), MAAEs (7.4% and 6.9%, respectively), Grade 3 AEs (0.8% and 0.3%, respectively), and SAEs (0.1% and < 0.1%, respectively). Additionally, in the mRNA-1273 group, 0.1% of participants had unsolicited AEs that led to discontinuation from the study vaccine and 1 participant had an AESI of appendicitis that was not considered related to study vaccination by the investigator. No events of myocarditis, pericarditis, or MIS-C were reported. No unsolicited AEs that led to discontinuation from participation in the study or death were reported.

For unsolicited AEs considered related to study vaccination by the investigator, comparing the mRNA-1273 group to the placebo group, there were higher percentages of related unsolicited AEs (15.0% and 7.9%, respectively), related MAAEs (1.0% and 0.2%, respectively), and related Grade 3 AEs (0.6% and 0.2%, respectively). There was one participant who had an unsolicited AE that led to discontinuation from the study vaccine in the mRNA-1273 group that was considered as related to study vaccination by the investigator. No related SAEs or related AESIs as determined by the investigator were reported.

Across the subgroups defined by baseline SARS-CoV-2 status, age category, sex, race, ethnicity, and race and ethnicity, no meaningful differences in unsolicited AEs were observed.

Table 10: Summary of Unsolicited AEs up to 28 Days After Any Injection for P203 – Part 1A – SS

-	**mRNA-1273 (N=2486) n (%)**	**Placebo (N=1240) n (%)**
Unsolicited AEs regardless of relationship to study vaccination	-	-
All	582 (23.4)	237 (19.1)
Serious	3 (0.1)	1 (<0.1)
Medically-attended	183 (7.4)	85 (6.9)
Leading to discontinuation from study vaccine	3 (0.1)	0
Grade 3	19 (0.8)	4 (0.3)
Non-serious[a]	579 (23.3)	236 (19.0)
Grade 3	16 (0.6)	3 (0.2)
At least 1 non-serious[b]	581 (23.4)	236 (19.0)
Grade 3	16 (0.6)	3 (0.2)
Special interest (AESI)	1 (<0.1)	0
Unsolicited AEs related to study vaccination	-	-
All	374 (15.0)	98 (7.9)
Medically-attended	25 (1.0)	2 (0.2)
Leading to discontinuation from study vaccine	1 (<0.1)	0
Grade 3	14 (0.6)	3 (0.2)
Non-serious[a]	374 (15.0)	98 (7.9)
Grade 3	14 (0.6)	3 (0.2)
At least 1 non-serious[b]	374 (15.0)	98 (7.9)
Grade 3	14 (0.6)	3 (0.2)

[a]Participants without any SAE and with any nonserious AE.
[b]Participants with at least one nonserious AE regardless of reporting any SAE or not.
Source: Table 34 of P203 Clinical Study Report – Parts 1A and 1B.

Part 1B

Table 11 displays unsolicited AEs up to EoS after any injection of mRNA-1273 in both the mRNA-1273 and placebo-mRNA-1273 groups, as well as the total, for the LTSS. For the mRNA-1273 group, follow-up began on Day 1 of Part 1A. For the placebo-mRNA-1273 group, follow-up began from crossover dose. After Dose 2 as of EoS, the median follow-up was 312 and 71 days in the mRNA-1273 and placebo-mRNA-1273 groups, respectively.

For unsolicited AEs regardless of relationship to study vaccination, a total of 55.4%, 0.9%, 39.3%, 1.9%, and 0.5% of participants reported unsolicited AEs, SAEs, MAAEs, Grade 3 AEs, and AESIs, respectively up to EoS. According to the Applicant, the elevated rates of both unsolicited AEs and MAAEs were primarily due to a higher case rate of COVID-19, which likely reflected the Omicron BA.1 surge that was observed during the months of December 2021 and January 2022 which overlapped with the follow-up period for P203 – Part 1B. No additional unsolicited AEs that led to discontinuation from the study vaccine were reported. No events of myocarditis, pericarditis, or MIS-C were reported. No unsolicited AEs that led to discontinuation from participation in the study were reported, and no deaths were reported.

For unsolicited AEs considered related to study vaccination by the investigator, a total of 15.4%, 1.1%, and 0.6% of participants reported related unsolicited AEs, related MAAEs, and related

Grade 3 AEs, respectively. No related SAEs or related AESIs as determined by the investigator were reported.

Table 11: Summary of Unsolicited AEs up to EoS for P203 – Part 1B – LTSS

-	**mRNA-1273 (N=2486) n (%)**	**Placebo-mRNA-1273 (N=91) n (%)**	**Total (N=2577) n (%)**
Unsolicited AEs regardless of relationship to study vaccination	-	-	-
All	1398 (56.2)	29 (31.9)	1427 (55.4)
Serious	21 (0.8)	1 (1.1)	22 (0.9)
Fatal	0	0	0
Medically-attended	991 (39.9)	23 (25.3)	1014 (39.3)
Leading to discontinuation from study vaccine	3 (0.1)	0	3 (0.1)
Grade 3	49 (2.0)	1 (1.1)	50 (1.9)
Non-serious[a]	1377 (55.4)	28 (30.8)	1405 (54.5)
Grade 3	32 (1.3)	0	32 (1.2)
At least 1 non-serious[b]	1394 (56.1)	29 (31.9)	1423 (55.2)
Grade 3	34 (1.4)	0	34 (1.3)
Special interest (AESI)	13 (0.5)	0	13 (0.5)
Unsolicited AEs related to study vaccination	-	-	-
All	383 (15.4)	8 (8.8)	391 (15.2)
Medically-attended	27 (1.1)	2 (2.2)	29 (1.1)
Leading to discontinuation from study vaccine	1 (<0.1)	0	1 (<0.1)
Grade 3	15 (0.6)	0	15 (0.6)
Non-serious[a]	383 (15.4)	8 (8.8)	391 (15.2)
Grade 3	15 (0.6)	0	15 (0.6)
At least 1 non-serious[b]	383 (15.4)	8 (8.8)	391 (15.2)
Grade 3	15 (0.6)	0	15 (0.6)

For placebo-mRNA-1273 group, only AEs occurring after the crossover mRNA-1273 Dose 1 were included; for mRNA-1273 group, any AEs occurring after mRNA-1273 Dose 1 were included.
[a]Participants without any SAE and with any nonserious AE.
[b]Participants with at least one nonserious AE regardless of reporting any SAE or not.
Source: Table 38 of P203 Clinical Study Report – Parts 1A and 1B.

6.3 Clinical Study P203 – Part 1C

Title of Study: 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 YOA – mRNA-1273 Booster Phase

Dates:
1. Study initiation date (First Subject First Visit): 27 December 2021
2. Data cutoff date for safety analyses: 15 August 2022

6.3.1 Objectives

Primary Immunogenicity Objective:

1. To infer effectiveness of the 50 μg of mRNA-1273 BD by establishing non-inferiority of nAb response after the BD compared to the primary series of mRNA-1273 in participants 18 – 25 YOA from P301.

Safety Objective:

1. To evaluate the safety and reactogenicity of 50 μg BD of mRNA-1273.

6.3.2 Design Overview

P203 – Part 1C was an open-label homologous BD phase designed to offer participants in P203 – Parts 1A and 1B who were at least 5 months from the second dose of mRNA-1273 the option to request a BD of 50 μg mRNA-1273. For immunogenicity, blood samples were collected from a random subset of participants at baseline (i.e., pre-BD) and Day 29 (i.e., 28 days after BD). Vaccine effectiveness was inferred from bridging the immune responses at Day 29 to those at Day 57 of young adults 18 to 25 YOA from P301 who received mRNA-1273 primary series. The endpoint selected for immunobridging to P301 was the pseudovirus nAb titer. For safety, solicited ARs were collected through 7 days after the BD. Unsolicited AEs (including MAAEs, SAEs, and AESIs) were collected through 28 days after the BD and up to the data cutoff.

6.3.3 Population

Subjects 12 to 17 YOA at the time of enrollment in P203 – Part 1A were enrolled in P203 – Part 1C.

6.3.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 50 μg mRNA-1273 was administered.

6.3.6 Sites and Centers

The study was conducted at 25 sites in the U.S.

6.3.7 Surveillance/Monitoring

Please refer to the clinical review.

6.3.8 Endpoints and Success Criteria

Co-Primary Immunogenicity Endpoints:

1. GMR and SRR[a] difference between P203 – Part 1C BD recipients (12 to 17 YOA) at Day 29 and P301 primary series recipients (18 to 25 YOA) at Day 57.

- The lower bound of the two-sided 95% CI of the GMR (adolescents to young adults) is > 0.67 AND the GMR point estimate is > 0.8 (i.e., non-inferiority).
- The lower bound of the two-sided 95% CI of the SRR difference (adolescents minus young adults) is > -10% (i.e., non-inferiority).

[a]Seroresponse was defined as titer change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ. Supplementary analyses of titer change from pre-BD for P203 – Part 1C and pre-Dose 1 of the primary series for P301 were also conducted.

Safety Endpoints:

1. In all participants:
   - Solicited local and systemic ARs through 7 days after BD.
   - Unsolicited AEs, including MAAEs, SAEs, AESIs, and AEs leading to study discontinuation, through 28 days after BD.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity:

For nAb titers at Day 29 (for P203 – Part 1C) and Day 57 (for P301), the 95% CI for the GMR was estimated based on the t-distribution of the log-titers. The 95% CIs for the SRR differences were estimated via the Miettinen-Nurminen method.

For P301, the immunogenicity analyses were conducted on the PPIS, which was a subset of the IS, which was a subset of the FAS. For P203 – Part 1C, the immunogenicity analyses were conducted on the PPIS – Pre-booster SARS-CoV-2 Negative (PPIS-NEG). All four analysis sets are defined below:

- FAS: All randomized participants who received at least 1 injection of IP (i.e., at least one dose for P301 or BD for P203 – Part 1C).
  - IS: A subset of participants in the FAS selected for immunogenicity testing.
    - PPIS: Participants in the IS who were seronegative at pre-Dose 1, received planned doses of IP per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that impacted key or critical data.
      - PPIS-NEG: For P203 – Part 1C, participants in the PPIS who were additionally seronegative pre-BD.

Subgroup analyses were performed by sex (i.e., male or female), race (i.e., African American, Caucasian, or Other), ethnicity (i.e., Hispanic/Latino or not Hispanic/Latino), race and ethnicity (i.e., non-Hispanic Caucasian or Communities of Color), and BMI (i.e., <30 kg/m2, ≥30 kg/m2).

Analysis of Safety:

All safety data were summarized descriptively. Solicited ARs and unsolicited AEs were summarized in the SSS and SS, respectively, where the SSS was a subset of the SS. Both analysis sets are defined below:

- SS: All randomized participants who received a BD.
  - SSS: Participants in the SS who contributed any solicited AR data.

Subgroup analyses were performed by pre-booster SARS-CoV-2 status, age category (≥12 to <16 years and ≥16 to <18 years), sex, and race and ethnicity.

Multiplicity Adjustment:

The success criterion for P203 – Part 1C was that both GMR and SRR difference meet their respective success criteria for non-inferiority at the immunogenicity analyses at Day 29 for P203 – Part 1C versus Day 57 for P301. Thus, no multiplicity adjustments were necessary.

Sample Size Determination:

The sample size was driven by both safety and immunogenicity. For safety, at least 1,000 participants were expected to receive the BD. Assuming a true AE rate of 0.25%, there was a 90% probability to observe at least 1 participant with an AE.

For immunogenicity, the sample size was determined from power calculations for the success criterion of rejecting both null hypotheses for the co-primary endpoints. A total of 400 participants who received the BD were planned to be selected for the IS, with a target of 289 participants in the PPIS-NEG (assuming a non-evaluable rate of approximately 28% primarily due to SARS-CoV-2 infection pre-BD). For the GMR, assuming a non-inferiority margin of 0.67, a true GMR of 1, and an SD of 1.5 for natural log-transformed titers, 289 participants in the PPIS-NEG yielded 90% power to demonstrate non-inferiority of GMR at the one-sided alpha = 0.025 level. For SRR difference, assuming a non-inferiority margin of -10% and a true SRR difference of 0% with SRRs of 90% in both groups, 289 participants in the PPIS-NEG yielded 90% power to demonstrate non-inferiority of SRR difference at the one-sided alpha = 0.025 level.

6.3.10 Study Population and Disposition

Table 12 displays the dispositions of the BD population for the FAS, where a total of 1405 participants were included.

Table 12: Participant Disposition for P203 – Part 1C – FAS

-	**mRNA-1273 N=1405 n (%)**
Number of participants	-
Received injection	1405 (100)
Discontinued from study	48 (3.4)
Reason for discontinuation of study	-
Lost to follow-up	12 (0.9)
Protocol deviation	2 (0.1)
Study terminated by sponsor	1 (<0.1)
Withdrawal of consent by participant	30 (2.1)
COVID-19 non-infection related	2 (0.1)
Other	28 (2.0)
Other	3 (0.2)

Source: Table 6 of P203 – Part 1C Interim Clinical Study Report.

Table 13 displays the sample size in each analysis set. A subset of 374 participants who received BD were selected for the IS, where 264 participants met the criteria for the PPIS-NEG. In P301, a subset of 340 participants who received mRNA-1273 primary series were selected for the IS, where 295 participants met the criteria for the PPIS.

Table 13: Number of Participants in Each Analysis Set

-	**P203 – Part 1C mRNA-1273**
Full Analysis Set	1405
Immunogenicity Subset, n (%)	374 (26.6)
Per-Protocol Immunogenicity Subset, n (%)	327 (23.3)
Per-Protocol Immunogenicity Subset - Pre-booster SARS-CoV-2 Negative, n (%)	264 (18.8)
Safety Set	1405
Solicited Safety Set, n (%)	1351 (96.2)

Source: Table 7 of P203 – Part 1C Interim Clinical Study Report.

Table 14 displays the distributions of demographic characteristics by study and analysis set. For P203 – Part 1C, the distributions between the SS and the PPIS-NEG were similar. Aside from age differences, there was a smaller percentage of Hispanic participants in the PPIS-NEG for P203 – Part 1C (12.5%) than the PPIS for P301 (26.1%).

Table 14: Participant Demographics and Baseline Characteristics for P203 – Part 1C – SS and PPIS-NEG and P301 – PPIS

-	**P203 – Part 1C mRNA-1273 N=1405 n (%) SS**	**P203 – Part 1C mRNA-1273 N=264 n (%) PPIS-NEG**	**P301 18 – 25 YOA N=295 n (%) PPIS**
Age (years)	-	-	-
n	1405	264	295
Mean (SD)	14.1 (1.5)	13.9 (1.5)	22.4 (2.2)
Median	14.0	14.0	23.0
Min, Max	12, 17	12, 17	18, 25
Age subgroup	-	-	-
≥12 and <16 years	1126 (80.1)	218 (82.6)	-
≥16 and <18 years	279 (19.9)	46 (17.4)	-
Sex, n (%)	-	-	-
Male	723 (51.5)	134 (50.8)	143 (48.5)
Female	682 (48.5)	130 (49.2)	152 (51.5)
Race, n (%)	-	-	-
White	1193 (84.9)	232 (87.9)	206 (69.8)
Black or African American	44 (3.1)	4 (1.5)	29 (9.8)
Asian	69 (4.9)	9 (3.4)	30 (10.2)
American Indian or Alaska Native	7 (0.5)	0	3 (1.0)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	0	2 (0.7)
Multiracial	73 (5.2)	15 (5.7)	14 (4.7)
Other	10 (0.7)	3 (1.1)	8 (2.7)
Not reported	4 (0.3)	1 (0.4)	3 (1.0)
Unknown	4 (0.3)	0	0
Ethnicity, n (%)	-	-	-
Hispanic or Latino	188 (13.4)	33 (12.5)	77 (26.1)
Not Hispanic or Latino	1206 (85.8)	229 (86.7)	216 (73.2)
Not reported	11 (0.8)	2 (0.8)	0
Unknown	0	0	2 (0.7)
Weight (kg)	-	-	-
n	1405	264	294
Mean (SD)	60.9 (16.8)	59.5 (15.8)	77.6 (19.3)
Median	57.9	57.2	73.6
Min, Max	27.8, 184.1	35.6, 184.1	44.0, 158.2
Height (cm)	-	-	-
n	1405	264	294
Mean (SD)	165.0 (9.7)	164.8 (9.4)	171.3 (9.2)
Median	165.1	165.1	170.7
Min, Max	116.0, 194.0	137.1, 194.0	147.5, 201.9
BMI (kg/m^2)	-	-	-
n	1405	264	294
Mean (SD)	22.2 (5.3)	21.9 (5.6)	26.4 (5.9)
Median	21.1	20.6	24.9
Min, Max	14.7, 76.7	15.3, 76.7	16.7, 48.7
Pre-booster RT-PCR results, n (%)	-	-	-
Negative	1213 (86.3)	264 (100)	-
Positive	105 (7.5)	0	-
Missing	87 (6.2)	0	-

Table 14: Participant Demographics and Baseline Characteristics for P203 – Part 1C – SS and PPIS-NEG and P301 – PPIS (continued)

-	**P203 – Part 1C mRNA-1273 N=1405 n (%) SS**	**P203 – Part 1C mRNA-1273 N=264 n (%) PPIS-NEG**	**P301 18 – 25 YOA N=295 n (%) PPIS**
Pre-booster Elecsys anti-SARS-CoV-2 results, n (%)	-	-	-
Negative	862 (61.4)	264 (100)	-
Positive	531 (37.8)	0	-
Missing	12 (0.9)	0	-
Pre-booster SARS-CoV-2 status, n (%)[a]	-	-	-
Negative	752 (53.5)	264 (100)	-
Positive	597 (42.5)	0	-
Missing	56 (4.0)	0	-
Time since primary series Dose 2 to booster (days)	-	-	-
Mean (SD)	317.6 (39.7)	299.7 (14.6)	-
Median	315.0	295.0	-
Min, Max	63, 514	274, 357	-

[a]Pre-booster SARS-CoV-2 Status: Positive if there was immunologic or virologic evidence of prior infection, 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.
Source: Adapted from Tables 10, 11, and 14.1.6.5.1 of P203 – Part 1C Interim Clinical Study Report.

6.3.11 Immunogenicity Analyses

Table 15 displays both the GMTs and SRRs for both adolescents at Day 29 and young adults at Day 57. The success criteria for both the GMR (GMR = 5.1, 95% CI = 4.5 to 5.7) and SRR difference (SRR difference = 0.7%, 95% CI = -0.8% to 2.4%) were met for the lower bounds of the 95% CIs. The success criterion was also met for the GMR point estimate.

Table 15 also displays the supplementary immunogenicity analyses of the secondary definition of SRR comparing the Day 29 to pre-BD titers for P203 – Part 1C and the Day 57 to pre-Dose 1 of the primary series titers for P301. The SRR difference was -2.7% with 95% CI = -5.8% to -0.5%.

Across the subgroups defined by sex, race, ethnicity, race and ethnicity, and BMI, no meaningful differences in GMRs or SRR differences were observed.

Table 15: Immunogenicity Analyses of Pseudovirus nAb Titer at Day 29 for P203 – Part 1C – PPIS-NEG Set and Day 57 for P301 – PPIS

-	**P203 – Part 1C Adolescents 12 to 17 YOA**	**P301 Young adults 18 – 25 YOA**
N	264	295
GMT (95% CI)[a]	7102.0 (6553.2, 7696.8)	1400.4 (1281.1, 1530.8)
GMR (95% CI)[a]	5.1 (4.5, 5.7)	-
SRR, % (95% CI)[b,c]	264/264 100.0 (98.6, 100.0)	292/294 99.3 (97.6, 99.9)
SRR Difference, % (95% CI)[b,d]	0.7 (-0.8, 2.4)	-
SRR, % (95% CI)[e,c]	255/264 96.6 (93.6, 98.4)	292/294 99.3 (97.6, 99.9)
SRR Difference, % (95% CI)[e,d]	-2.7 (-5.8, -0.5)	-

[a]95% CI for GMT and GMR was calculated based on the t-distribution.
[b]SRR compares the Day 29 titer for P203 – Part 1C and the Day 57 titer for P301 to the pre-Dose 1 titer of the primary series.
[c]95% CI was calculated by Clopper-Pearson method.
[d]95% CI was calculated by Miettinen-Nurminen method.
[e]SRR compares the Day 29 titer to the pre-BD titer for P203 – Part 1C and the Day 57 titer to the pre-Dose 1 titer of the primary series for P301.
Source: Adapted from Tables 12 and 14.2.1.2.3.5.1.5 of P203 – Part 1C Interim Clinical Study Report.

6.3.12 Safety Analyses

Table 16 displays both local and systemic ARs, respectively, within 7 days after BD in the SSS. Injection site pain was the most frequent solicited local AR, while fatigue and headache were the most frequent solicited systemic ARs.

Across the subgroups of both age category and race and ethnicity, no meaningful differences in the rates of solicited ARs were observed. Both pre-booster SARS-CoV-2 negative and female participants generally reported more solicited systemic ARs.

Table 16: Summary of Solicited Local and Systemic ARs Within 7 Days After BD – SSS

Event	**P203 – Part 1C mRNA-1273 N=1351 n (%)**
Local ARs, Any Grade	1236 (91.5)
Local ARs, Grade 3	62 (4.6)
Pain, Any Grade	1224 (90.6)
Pain, Grade 3[a]	44 (3.3)
Axillary swelling/tenderness, Any Grade	375 (27.8)
Axillary swelling/tenderness, Grade 3[a]	5 (0.4)
Swelling (hardness), Any Grade	180 (13.3)
Swelling (hardness), Grade 3[b]	10 (0.7)
Erythema (redness), Any Grade	121 (9.0)
Erythema (redness), Grade 3[b]	10 (0.7)
Systemic ARs, Any Grade	1024 (75.9)
Systemic ARs, Grade 3	111 (8.2)
Fatigue, Any Grade	784 (58.1)
Fatigue, Grade 3[c]	54 (4.0)
Headache, Any Grade	760 (56.3)
Headache, Grade 3[d]	29 (2.1)
Myalgia, Any Grade	542 (40.1)
Myalgia, Grade 3[c]	49 (3.6)
Arthralgia, Any Grade	322 (23.9)
Arthralgia, Grade 3[c]	18 (1.3)
Chills, Any Grade	408 (30.2)
Chills, Grade 3[e]	7 (0.5)
Nausea/vomiting, Any Grade	241 (17.9)
Nausea/vomiting, Grade 3[f]	2 (0.1)
Fever, Any Grade	81 (6.1)
Fever, Grade 3[g]	8 (0.6)
Use of antipyretic or pain medication	511 (39.2)

[a]Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[b]Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[c]Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[d]Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[e]Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[f]Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.
[g]Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
Source: Table 17 of P203 – Part 1C Interim Clinical Study Report.

Table 17 displays unsolicited AEs up to 28 days after the BD in the SS. For unsolicited AEs regardless of relationship to study vaccination, 14.9%, 8.5%, and 0.3% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively. No deaths, SAEs, AESIs, events of myocarditis, pericarditis, MIS-C, or unsolicited AEs leading to study discontinuation were reported. For unsolicited AEs considered by the investigator to be related to study vaccination, 4.2%, 0.1%, and 0.2% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively.

After the BD as of the data cutoff, the median follow-up was 116 days. Up to the data cutoff, for unsolicited AEs regardless of relationship to study vaccination, 32.7%, 26.2%, 0.7%, 0.4%, and 0.1% of participants reported unsolicited AEs, MAAEs, Grade 3 unsolicited AEs, SAEs, and AESIs, respectively. No deaths, events of myocarditis, pericarditis, MIS-C, or unsolicited AEs leading to study discontinuation were reported. For unsolicited AEs considered by the investigator to be related to study vaccination, 4.5%, 0.2%, and 0.3% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively. No related SAEs or related AESIs as determined by the investigator were reported.

Up to 28 days after the BD or the data cutoff, across the subgroups of pre-booster SARS-CoV-2 status, age category, sex, and race and ethnicity, no meaningful differences in the rates of unsolicited AEs were observed.

Table 17: Summary of Unsolicited AEs up to 28 Days After BD – SS

Event	**P203 – Part 1C mRNA-1273 N=1405 n (%)**
Unsolicited AEs regardless of relationship to study vaccination	-
All	209 (14.9)
Medically-attended	119 (8.5)
Grade 3	4 (0.3)
Non-serious[a]	209 (14.9)
Grade 3	4 (0.3)
At least 1 non-serious event[b]	209 (14.9)
Grade 3	4 (0.3)
Unsolicited AEs related to study vaccination	-
All	59 (4.2)
Medically-attended	2 (0.1)
Grade 3	3 (0.2)
Non-serious[a]	59 (4.2)
Grade 3	3 (0.2)
At least 1 non-serious event[b]	59 (4.2)
Grade 3	3 (0.2)

[a]Participants without any SAE and with any non-serious AE.
[b]Participants with at least one non-serious AE regardless of reporting any SAE or not.
Source: Table 19 of P203 – Part 1C Interim Clinical Study Report.

6.4 Clinical Study P205 – Parts H and F

Title of Study: A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants – mRNA-1273.222 and mRNA-1273 Booster Phases

Part H Dates:
1. Study initiation date (First Subject First Visit): 10 August 2022
2. Data cutoff date for safety analyses: 31 October 2022

Part F Dates:
1. Study initiation date (First Subject First Visit): 18 February 2022
2. Data cutoff date for safety analyses: 20 June 2022

6.4.1 Objectives

Part H

Primary Immunogenicity Objectives:
1. To demonstrate non-inferiority of the nAb response of a second BD of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second BD against Omicron BA.4/BA.5.

2. To demonstrate superiority of the nAb response of a second BD of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg administered as a second BD against Omicron BA.4/BA.5.

3. To demonstrate non-inferiority of the nAb response of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second BD against the ancestral strain.

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

6.4.2 Design Overview

P205 consisted of eight parts, where Part A consisted of two parts (i.e., Parts A.1 and A.2) and Parts B, C, D, E, F, G, and H each consisted of a single part.

As only Part H was submitted to support the sBLA, this review memo focuses on Part H. As Part F – Cohort 2 (referred to as Part F) was only submitted to support both the immunobridging and safety analyses for Part H, a full review of Part F is not provided in this review memo. Instead, a summary of the design of Part F is provided.

Parts H and F

Parts H and F evaluated 50 µg mRNA-1273.222 (Original and Omicron BA.4/BA.5) and 50 µg mRNA-1273, respectively, administered as a second BD to adults 18 YOA and older who previously received 2 doses of 100 µg mRNA-1273 as a primary series and one BD of 50 µg mRNA-1273, where the second BD was to be administered at least 3 months after the first BD. For both Parts H and F, for immunogenicity, blood samples were collected from a subset of participants at pre-second BD (i.e., baseline) and Day 29 (i.e., 28 days after second BD). Vaccine effectiveness was inferred from bridging the immune responses of adults in P205 – Part H to those of adults from P205 – Part F. The endpoint selected for immunobridging was the pseudovirus nAb ID50 titer. For safety, solicited ARs were collected through 7 days after the second BD. Unsolicited AEs (including MAAEs, SAEs, and AESIs) were collected through 28 days after the second BD and up to the data cutoff.

6.4.3 Population

Subjects 18 YOA and older who previously received 2 doses of 100 µg mRNA-1273 and one dose of 50 µg mRNA-1273 were enrolled.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Part H:

A single dose of 50 µg mRNA-1273.222 was admnistered.

Part F:

A single dose of 50 µg mRNA-1273 was administered.

6.4.6 Sites and Centers

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

6.4.7 Surveillance/Monitoring

Please refer to the clinical review.

6.4.8 Endpoints and Success Criteria

Primary Immunogenicity Endpoints:

1. GMR and SRR[a] difference between P205 – Parts H and F second BD recipients at Day 29 against Omicron BA.4/BA.5.
   - The lower bound of the two-sided 95% CI of the GMR (Part H to F) is > 0.67 (i.e., non-inferiority).
     - The lower bound of the two-sided 95% CI of the GMR (Part H to F) is > 1.0 (i.e., superiority).
   - The lower bound of the two-sided 95% CI of the SRR difference (Part H to F) is > -10% (i.e., non-inferiority).

- The lower bound of the two-sided 95% CI of the SRR difference (Part H to F) is > -5% (i.e., non-inferiority).

2. GMR and SRR[a] difference between P205 – Parts H and F second BD recipients at Day 29 against ancestral strain.
   - The lower bound of the two-sided 95% CI of the GMR (Part H to F) is > 0.67 (i.e., non-inferiority).
   - The lower bound of the two-sided 95% CI of the SRR difference (Part H to F) is > -10% (i.e., non-inferiority).

[a]Seroresponse was defined as titer change from pre-Dose 1 of primary series below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if pre-Dose 1 titer is ≥ LLOQ. Supplementary analyses of titer change from pre-second BD were also conducted.

Safety Endpoints:

1. In all participants:
   - Solicited local and systemic ARs through 7 days after second BD.
   - Unsolicited AEs, including MAAEs, SAEs, AESIs, and AEs leading to study discontinuation, through 28 days after second BD.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity:

GMRs and 95% CIs were estimated via ANCOVA using Day 29 log-titers as the dependent variable and treatment group (Part H vs. Part F), pre-second BD titers, and age category (i.e., 18 – 64 years, ≥65 years) as the independent variables. The 95% CIs for SRR differences were estimated via the stratified Miettinen-Nurminen method adjusted for age category (i.e., 18 – 64 years, ≥65 years).

The immunogenicity analyses were conducted on the PPIS-NEG, which was a subset of the PPIS, which was a subset of the FAS. All three analysis sets are defined below:

- FAS: All randomized participants who received the second BD.
  - PPIS: Participants in the FAS who received planned second BD per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that impacted key or critical data.
    - PPIS-NEG: Participants in the PPIS who were additionally seronegative pre-second BD.

Subgroup analyses were performed by age category, sex (i.e., male or female), race (i.e., African American, Caucasian, or Other), and ethnicity (i.e., Hispanic/Latino or not Hispanic/Latino).

Analysis of Safety:

All safety data were summarized descriptively. Solicited ARs and unsolicited AEs were summarized in the SSS and SS, respectively, where the SSS was a subset of the SS. Both analysis sets are defined below:

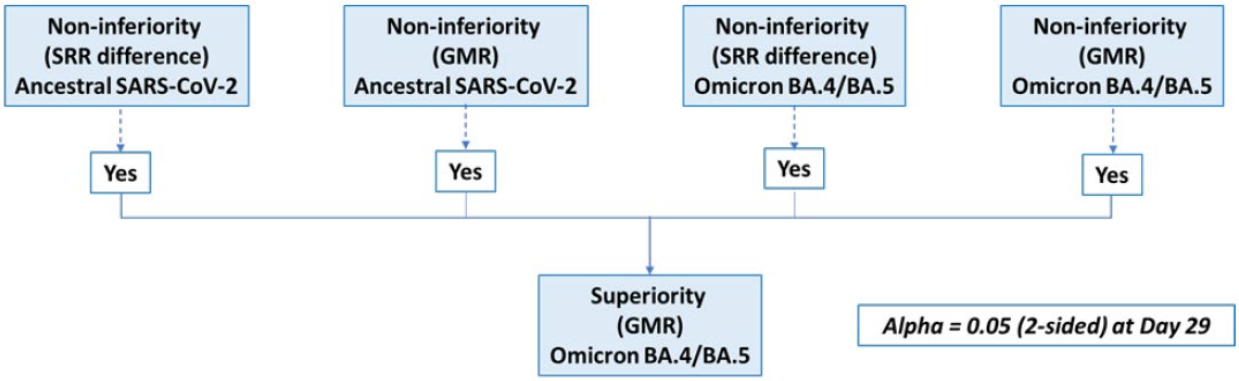
- SS: All randomized participants who received a second BD.
  - SSS: Participants in the SS who contributed any solicited AR data.

For solicited ARs, subgroup analyses were performed by both pre-booster SARS-CoV-2 status and age category. For unsolicited AEs, subgroup analyses were performed only by age category.

Multiplicity Adjustment:

The success criterion for P205 – Part H was that the primary immunogenicity endpoints for both Omicron BA.4/BA.5 and the ancestral strain meet their respective success criteria for non-inferiority in terms of both GMR and SRR difference at the immunogenicity analyses at Day 29. If all of these success criteria were met, then the primary immunogenicity endpoint for Omicron BA.4/BA.5 would additionally be evaluated for superiority in terms of the anti-Omicron BA.4/BA.5 GMR. This testing strategy is displayed in Figure 2.

Figure 2: Statistical Hypotheses Testing Strategy for Part H



Source: Figure 2 of P205 – Part H Interim Clinical Study Report.

Sample Size Determination:

The sample size was driven by both immunogenicity and safety. For safety, with at least 500 participants expected to receive mRNA-1273.222 in Part H and assuming a true AE rate of 1%, there was at least a 90% probability to observe at least 1 participant with an AE.

For immunogenicity, the sample size was determined from power calculations for the rejection of all null hypotheses (including both non-inferiority and superiority) for the primary endpoints. Parts H and F expected to enroll 500 and 375 participants with a target of 300 and 260 participants, respectively, in the PPIS-NEG (assuming non-evaluable rates of approximately 40% and 31%, respectively, primarily due to SARS-CoV-2 infection pre-second BD). There was approximately 60% power to demonstrate all primary immunogenicity objectives at the one-sided alpha = 0.025 level.

For GMR against Omicron BA.4/BA.5, the assumed parameters were a true GMR of 1.5, an SD of 1.5 on natural log scale, and non-inferiority and superiority margins of 0.67 and 1, respectively. For SRR difference against Omicron BA.4/BA.5, the assumed parameters were a true SRR difference of 0% with SRRs of 95% in both groups and non-inferiority margins of both -10% and -5%.

For GMR against the ancestral strain, the assumed parameters were a true GMR of 1.5, an SD of 1.5 on natural log scale, and a non-inferiority margin of 0.67. For SRR difference against the ancestral strain, the assumed parameters were a true SRR difference of 0% with SRRs of 95% in both groups and a non-inferiority margin of -10%.

6.4.10 Study Population and Disposition

Table 18 displays the dispositions of the FAS for both Parts H and F, where a total of 511 and 376 participants were included, respectively.

Table 18: Participant Disposition After Second BD for P205 – Part H and P205 – Part F – FAS

-	**P205 – Part H mRNA-1273.222 N=511 n (%)**	**P205 – Part F mRNA-1273 N=376 n (%)**
Number of participants	-	-
Received injection	511	376
Discontinued from study	4 (0.8)	6 (1.6)
Reason for discontinuation of study	-	-
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)
Other	2 (0.4)	1 (0.3)

Source: Table 8 of P205 – Part H Interim Clinical Study Report.

Table 19 displays the sample size in each analysis set for both Parts H and F. Totals of 209 and 259 participants for Parts H and F, respectively, met the criteria for the PPIS-NEG.

Table 19: Number of Participants in Each Analysis Set for P205 – Part H and P205 – Part F

-	**P205 – Part H mRNA-1273.222**	**P205 – Part F mRNA-1273**
Full Analysis Set	511	376
Per-protocol Immunogenicity Set, n (%)	490 (95.9)	366 (97.3)
Per-protocol Immunogenicity SARS-CoV-2 Negative Set, n (%)	209 (40.9)	259 (68.9)
Safety Set	511	376
Solicited Safety Set, n (%)	508 (99.4)	350 (93.1)

Source: Table 9 of P205 – Part H Interim Clinical Study Report.

Table 20 displays the distributions of demographic characteristics for the FAS for both Parts H and F. Comparing Part H to F, there were smaller percentages of participants ≥65 years (20.5% versus 39.9%) and male participants (38.2% versus 49.5%).

Table 20: Participant Demographics and Baseline Characteristics for P205 – Part H and P205 – Part F – FAS

-	**P205 – Part H mRNA-1273.222 N=511 n (%)**	**P205 – Part F mRNA-1273 N=376 n (%)**
Age (years)	-	-
n	511	376
Mean (SD)	50.8 (14.8)	57.6 (15.2)
Median	50.0	60.5
Min, Max	19, 89	20, 96
Age subgroup	-	-
>=18 and <65 years	406 (79.5)	226 (60.1)
Mean (SD)	45.5 (11.6)	48.0 (11.4)
Median	46.0	48.5
Min, Max	19, 64	20, 64
>=65 years	105 (20.5)	150 (39.9)
Mean (SD)	71.1 (5.4)	72.1 (6.0)
Median	70.0	70.0
Min, Max	65, 89	65, 96
Sex, n (%)	-	-
Male	195 (38.2)	186 (49.5)
Female	316 (61.8)	190 (50.5)
Race, n (%)	-	-
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, n (%)	-	-
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
Weight (kg)		
n	509	376
Mean (SD)	89.0 (23.8)	88.8 (22.7)
Median	85.9	85.1
Min, Max	37.0, 206.1	46.4, 189.6
Height (cm)		
n	509	376
Mean (SD)	169.1 (10.0)	169.8 (10.4)
Median	169.0	170.0
Min, Max	127.0, 194.3	123.0, 205.0
BMI (kg/m^2)	-	-
n	509	376
Mean (SD)	31.1 (8.0)	30.8 (7.5)
Median	29.9	29.4
Min, Max	13.9, 64.4	18.4, 61.8

Table 20: Participant Demographics and Baseline Characteristics for P205 – Part H and P205 – Part F – FAS (continued)

-	**P205 – Part H mRNA-1273.222 N=511 n (%)**	**P205 – Part F mRNA-1273 N=376 n (%)**
Pre-booster RT-PCR results, n (%)	-	-
Negative	488 (95.5)	366 (97.3)
Positive	10 (2.0)	2 (0.5)
Missing	13 (2.5)	8 (2.1)
Pre-booster Elecsys anti-SARS-CoV-2 results, n (%)	-	-
Negative	226 (44.2)	276 (73.4)
Positive	282 (55.2)	100 (26.6)
Missing	3 (0.6)	0
Pre-booster SARS-CoV-2 status, n (%)[a]	-	-
Negative	216 (42.3)	267 (71.0)
Positive	286 (56.0)	101 (26.9)
Missing	9 (1.8)	8 (2.1)
Time between Dose 2 of primary series to the first BD (days)	-	-
n	509	374
Mean (SD)	274.6 (71.4)	258.0 (56.9)
Median	251.0	242.0
Min, Max	67, 533	170, 438
Time between the first and second BDs (days)	-	-
n	509	374
Mean (SD)	279.9 (41.7)	133.6 (21.5)
Median	289.0	134.0
Min, Max	103, 371	90, 310

[a]Pre-booster SARS-CoV-2 Status: Positive if there was immunologic or virologic evidence of prior infection, 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.
Source: Table 11 of P205 – Part H Interim Clinical Study Report.

6.4.11 Immunogenicity Analyses

Table 21 displays the Day 29 GLSMs and SRRs for both Omicron BA.4/BA.5 and the ancestral strain. Adjusting for both age category and pre-second BD log-titers, the anti-Omicron BA.4/BA.5 GMR was 6.3 with 95% CI = 5.3 to 7.5, while the anti-ancestral strain GMR was 2.0 with 95% CI = 1.7 to 2.3. Adjusting for age category, the anti-Omicron BA.4/BA.5 SRR Difference was 12.1% with 95% CI = 6.9% to 17.3%, while the anti-ancestral strain SRR Difference was 0% with the SRRs in both groups being 100%. The primary immunogenicity endpoints met their respective success criteria for non-inferiority; thus, the success criterion for P205 – Part H was met. Additionally, superiority of anti-Omicron BA.4/BA.5 GMR was met.

Table 21 also displays the supplementary immunogenicity analyses of the secondary definition of SRR comparing post-second BD to pre-second BD titers. After adjusting for age category, the anti-Omicron BA.4/BA.5 SRR Difference was 53.9% with 95% CI = 46.7% to 61.2%, while the anti-ancestral strain SRR Difference was 37.3% with 95% CI = 29.0% to 45.6%.

Across the subgroups of age category, sex, race, and ethnicity, no meaningful differences in GMRs or SRR differences were observed.

Table 21: Immunogenicity Analyses of Pseudovirus nAb ID50 at Day 29 for P205 – Parts H and F – PPIS-NEG Set

-	**P205 – Part H**	**P205 – Part F**
N	209	259
Omicron BA.4/BA.5	-	-
GLSM (95% CI)[a]	2747.3 (2399.2, 3145.9)	436.7 (389.1, 490.0)
GMR (95% CI)[a]	6.3 (5.3, 7.5)	-
SRR, % (95% CI)[b,c]	205/209 98.1 (95.2, 99.5)	222/257 86.4 (81.6, 90.3)
SRR Difference, % (95% CI)[b,d]	12.1 (6.9, 17.3)	-
SRR, % (95% CI)[e,c]	190/209 90.9 (86.2, 94.4)	98/259 37.8 (31.9, 44.0)
SRR Difference, % (95% CI)[e,d]	53.9 (46.7, 61.2)	-
N	209	259
Ancestral Strain	-	-
GLSM (95% CI)[a]	9555.8 (8593.6, 10625.7)	4882.2 (4457.7, 5347.1)
GMR (95% CI)[a]	2.0 (1.7, 2.3)	-
SRR, % (95% CI)[b,c]	209/209 100.0 (98.3, 100.0)	259/259 100.0 (98.6, 100.0)
SRR Difference, % (95% CI)[b,d]	0	-
SRR, % (95% CI)[e,c]	168/209 80.4 (74.3, 85.5)	111/259 42.9 (36.7, 49.1)
SRR Difference, % (95% CI)[e,d]	37.3 (29.0, 45.6)	-

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable and treatment group (Part H vs. Part F), pre-second BD titers, and age category (i.e., 18 – 64 years, ≥65 years) as the independent variables.
[b]SRR compared post-second BD titer to pre-Dose 1 titer of the primary series.
[c]95% CI was calculated by Clopper-Pearson method.
[d]95% CI was calculated by stratified Miettinen-Nurminen method adjusted for age category. The SRR Difference was a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences.
[e]SRR compared post-second BD titer to pre-second BD titer.
Source: Adapted from both Tables 14 and 17 of P205 – Part H Interim Clinical Study Report.

Reviewer's Comments:

- *For Omicron BA.4/BA.5, pseudovirus nAb ID50 titers above the upper limit of quantitation (ULOQ) were not imputed to the ULOQ. At Day 29, 27/209 and 0/259 subjects in P205 – Part H and P205 – Part F, respectively, had pseudovirus nAb ID50 titer > ULOQ. I ran a sensitivity analysis of the GMR imputing the ULOQ for pseudovirus nAb ID50 titers > ULOQ. Adjusting for both age category and pre-second BD log-titers, the anti-Omicron BA.4/BA.5 GMR was 5.7 with 95% CI = 4.9 to 6.7. Therefore, the results of the sensitivity analysis confirmed the immunobridging conclusions.*

- *For the PPIS-NEG, the time between the first and second BD as measured in days was substantially longer in Part H (with a median of 288 days over 209 subjects) than Part F (with a median of 133 days over 258 subjects — 1 subject was missing this information). Compared to Part F, a longer time between the first and second BD for Part H may have lowered the pre-second BD titer, allowing seroresponse to be achieved with a lower post-second BD titer. While the ANCOVA for GMR adjusted for pre-second BD titers, the stratified Miettinen-Nurminen method for SRR Difference only adjusted for age category. I conducted a sensitivity analysis of the stratified Miettinen-Nurminen method for SRR Difference which adjusted for, in addition to age category, an indicator variable for time between the first and second BD greater than the median across both Parts H and F (i.e., 154 days over 467 subjects). After adjusting for both age category and time between the first and second BD, the anti-Omicron BA.4/BA.5 SRR Difference was 47.7% with 95% CI = 33.4% to 61.9%, while the anti-ancestral strain SRR Difference was 30.9% with 95% CI = 16.0% to 45.9%.*

6.4.12 Safety Analyses

Table 22 displays both local and systemic ARs by age category within 7 days after second BD in the SSS.

Rates of solicited local ARs were generally similar between Parts H and F and slightly higher for participants ages 18 – 64 years compared to participants ≥ 65 years. Across both parts and age categories, injection site pain was the most frequently reported solicited local AR. No meaningful differences in solicited local ARs were observed between pre-booster SARS-CoV-2 positive or negative participants.

Rates of solicited systemic ARs were generally similar between Parts H and F and slightly higher for participants ages 18 – 64 years compared to participants ≥ 65 years. Across both parts and age categories, fatigue was the most frequently reported solicited systemic AR. Pre-booster SARS-CoV-2 negative participants generally reported more solicited systemic ARs.

Table 22: Summary of Solicited Local and Systemic ARs Within 7 Days After Second BD for P205 – Parts H and F by Age Category (SSS)

Event	P205 – Part H mRNA-1273.222 18 – 64 years N=403 n (%)	P205 – Part F mRNA-1273 18 – 64 years N=210 n (%)	P205 – Part H mRNA-1273.222 ≥ 65 years N=105 n (%)	P205 – Part F mRNA-1273 ≥ 65 years N=140 n (%)
Local ARs, Any Grade	347 (86.3)	179 (85.2)	73 (69.5)	99 (70.7)
Local ARs, Grade 3	23 (5.7)	9 (4.3)	5 (4.8)	3 (2.1)
Pain, Any Grade	347 (86.3)	174 (82.9)	71 (67.6)	94 (67.1)
Pain, Grade 3[a]	19 (4.7)	4 (1.9)	1 (1.0)	0
Axillary swelling/tenderness, Any Grade	91 (22.6)	38 (18.1)	15 (14.3)	15 (10.7)
Axillary swelling/tenderness, Grade 3[a]	1 (0.2)	4 (1.9)	0	0
Swelling (hardness), Any Grade	32 (8.0)	14 (6.7)	8 (7.6)	8 (5.7)
Swelling (hardness), Grade 3[b]	2 (0.5)	2 (1.0)	3 (2.9)	3 (2.1)
Erythema (redness), Any Grade	17 (4.2)	10 (4.8)	6 (5.7)	3 (2.1)
Erythema (redness), Grade 3[b]	3 (0.7)	1 (0.5)	2 (1.9)	1 (0.7)
Systemic ARs, Any Grade	307 (76.2)	148 (70.5)	65 (61.9)	83 (59.3)
Systemic ARs, Grade 3	30 (7.4)	9 (4.3)	5 (4.8)	7 (5.0)
Fatigue, Any Grade	243 (60.3)	114 (54.3)	61 (58.1)	65 (46.8)
Fatigue, Grade 3[c]	14 (3.5)	7 (3.3)	3 (2.9)	4 (2.9)
Headache, Any Grade	210 (52.2)	99 (47.1)	39 (37.1)	44 (31.7)
Headache, Grade 3[d]	11 (2.7)	1 (0.5)	1 (1.0)	1 (0.7)
Myalgia, Any Grade	197 (49.0)	89 (42.4)	38 (36.2)	45 (32.4)
Myalgia, Grade 3[c]	17 (4.2)	8 (3.8)	3 (2.9)	5 (3.6)
Arthralgia, Any Grade	145 (36.1)	68 (32.4)	32 (30.5)	42 (30.2)
Arthralgia, Grade 3[c]	9 (2.2)	2 (1.0)	0	1 (0.7)
Chills, Any Grade	96 (23.9)	54 (25.7)	16 (15.2)	20 (14.4)
Chills, Grade 3[e]	3 (0.7)	0	1 (1.0)	1 (0.7)
Nausea/vomiting, Any Grade	67 (16.7)	27 (12.9)	4 (3.8)	8 (5.8)
Nausea/vomiting, Grade 3[f]	1 (0.2)	0	0	0
Fever, Any Grade	16 (4.0)	9 (4.3)	4 (3.8)	2 (1.4)
Fever, Grade 3[g]	1 (0.2)	0	0	0
Use of antipyretic or pain medication	159 (39.5)	67 (31.9)	38 (36.2)	40 (28.6)

[a]Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[b]Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[c]Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[d]Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[e]Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[f]Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.
[g]Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
Source: Table 11 of Summary of Clinical Safety.

Table 23 displays unsolicited AEs up to 28 days after the second BD in the SS. For unsolicited AEs regardless of relationship to study vaccination, comparing Part H to F, there were similar percentages of unsolicited AEs (22.7% and 21.3%, respectively), MAAEs (13.7% and 15.2%, respectively), Grade 3 unsolicited AEs (1.0% and 0.8%, respectively), and SAEs (0.6% and

0.3%, respectively). No events of myocarditis, pericarditis, AESIs, or unsolicited AEs that led to discontinuation from participation in the study were reported. One death was reported in Part H which the investigator attributed to an SAE of subarachnoid hemorrhage that occurred 7 days after the second BD. For unsolicited AEs considered by the investigator to be related to study vaccination, comparing Part H to F, there were similar percentages of both unsolicited AEs (7.8% and 5.6%, respectively) and Grade 3 unsolicited AEs (0.4% and 0.5%, respectively). No related MAAEs as determined by the investigator were reported in Part H, while 0.5% was reported in Part F. No related SAEs or related deaths were reported.

After the second BD as of the data cutoffs, the median follow-up was 37 days in Part H and 131 days in Part F. Up to the data cutoff, for unsolicited AEs regardless of relationship to study vaccination in Part H and Part F, the percentages of participants reporting unsolicited AEs were 25.2% and 52.1%, respectively; for MAAEs, 16.2% and 47.9%, respectively; for Grade 3 unsolicited AEs, 1.0% and 2.4%, respectively; and for SAEs, 0.6% and 2.7%, respectively. In both groups, no events of myocarditis, pericarditis, AESIs, or unsolicited AEs leading to study discontinuation were reported. No additional deaths were reported in Part H while one death was reported in Part F which the investigator attributed to hypotension that occurred 64 days after the second BD. For unsolicited AEs considered by the investigator to be related to study vaccination in Part H and Part F, the percentages of participants reporting unsolicited AEs were 7.8% and 5.6%, respectively; and for Grade 3 unsolicited AEs, 0.4% and 0.5%, respectively. No related MAAEs as determined by the investigator were reported in Part H while 0.5% of participants reported related MAAEs in Part F. In both groups, no related SAEs or related deaths as determined by the investigator were reported.

Table 23: Summary of Unsolicited AEs up to 28 Days After Second BD for P205 – Parts H and F – SS

Event	P205 – Part H mRNA-1273.222 N=511 n (%)	P205 – Part F mRNA-1273 N=376 n (%)
Unsolicited AEs regardless of relationship to study vaccination	-	-
All	116 (22.7)	80 (21.3)
Serious	3 (0.6)	1 (0.3)
Fatal	1 (0.2)	0
Medically-attended	70 (13.7)	57 (15.2)
Grade 3	5 (1.0)	3 (0.8)
Non-serious[a]	113 (22.1)	79 (21.0)
Grade 3	2 (0.4)	2 (0.5)
At least 1 non-serious event[b]	115 (22.5)	80 (21.3)
Grade 3	2 (0.4)	2 (0.5)
Unsolicited AEs related to study vaccination	-	-
All	40 (7.8)	21 (5.6)
Medically-attended	0	2 (0.5)
Grade 3	2 (0.4)	2 (0.5)
Non-serious[a]	40 (7.8)	21 (5.6)
Grade 3	2 (0.4)	2 (0.5)
At least 1 non-serious event[b]	40 (7.8)	21 (5.6)
Grade 3	2 (0.4)	2 (0.5)

[a]Participants without any SAE and with any non-serious AE.
[b]Participants with at least one non-serious AE regardless of reporting any SAE or not.
Source: Table 16 of Summary of Clinical Safety.

6.5 Clinical Study P203 – Part 3

Title of Study: 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 YOA – mRNA-1273.222 Single Dose Phase

Dates:
1. Study initiation date (First Subject First Visit): 21 December 2022
2. Data cutoff date for safety analyses: 05 June 2023

6.5.1 Objectives

Co-Primary Immunogenicity Objectives:
1. To demonstrate superiority of the nAb response of a single dose of 50 µg mRNA-1273.222 in vaccine-naïve, baseline SARS-CoV-2 positive participants 12 – 17 YOA from P203 – Part 3 compared to 100 µg mRNA-1273 primary series in baseline SARS-CoV-2 negative participants 18 – 25 YOA from P301 against Omicron BA.4/BA.5.

2. To demonstrate non-inferiority of the nAb response of a single dose of 50 µg mRNA-1273.222 in vaccine-naïve, baseline SARS-CoV-2 positive participants 12 – 17 YOA from

P203 – Part 3 compared to 100 μg mRNA-1273 primary series in baseline SARS-CoV-2 negative participants 18 – 25 YOA from P301 against the ancestral strain.

Safety Objective:

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

6.5.2 Design Overview

P203 – Part 3 evaluated a single dose of 50 μg mRNA-1273.222 in previously unvaccinated adolescents 12 to 17 YOA with evidence of prior SARS-CoV-2 infection. For immunogenicity, blood samples were collected from a subset of participants at Day 1 (i.e., baseline) and Day 29 (i.e., 28 days after single dose). Vaccine effectiveness was inferred from bridging the immune responses of adolescents in P203 – Part 3 to those of young adults 18 to 25 YOA from P301. The endpoint selected for immunobridging was the pseudovirus nAb titer. For safety, solicited ARs were collected through 7 days after the single dose. Unsolicited AEs (including MAAEs, SAEs, and AESIs) were collected through 28 days after the single dose and up to the data cutoff.

Six months after the single dose of 50 μg mRNA-1273.222 is administered, subjects will receive a second dose of 50 μg mRNA-1273.222. However, results for the second dose were not submitted to the sBLA and thus are not covered in this review memo.

6.5.3 Population

Subjects 12 – 17 YOA who were COVID-19 vaccine-naïve and baseline SARS-CoV-2 positive were enrolled.

6.5.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 50 μg mRNA-1273.222 was administered.

6.5.6 Sites and Centers

The number of sites was not provided.

6.5.7 Surveillance/Monitoring

Please refer to the clinical review.

6.5.8 Endpoints and Success Criteria

Co-Primary Immunogenicity Endpoints:

1. GMR against Omicron BA.4/BA.5 between P203 – Part 3 single dose recipients (12 to 17 YOA) at Day 29 and P301 primary series recipients (18 to 25 YOA) at Day 57.
    - The lower bound of the two-sided 95% CI of the GMR (adolescents divided by young adults) is > 1.0 (i.e., superiority).

2. GMR against the ancestral strain between P203 – Part 3 single dose recipients (12 to 17 YOA) at Day 29 and P301 primary series recipients (18 to 25 YOA) at Day 57.
    - The lower bound of the two-sided 95% CI of the GMR (adolescents divided by young adults) is > 0.67 (i.e., non-inferiority).

Secondary Immunogenicity Endpoints:

1. SRR[a] difference against Omicron BA.4/BA.5 between P203 – Part 3 single dose recipients (12 to 17 YOA) at Day 29 and P301 primary series recipients (18 to 25 YOA) at Day 57.
2. SRR[a] difference against the ancestral strain between P203 – Part 3 single dose recipients (12 to 17 YOA) at Day 29 and P301 primary series recipients (18 to 25 YOA) at Day 57.

[a]Seroresponse was defined as titer change from baseline (pre-single dose for P203 – Part 3 or pre-Dose 1 of the primary series for P301) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

Safety Endpoints:

1. In all participants:
    - Solicited local and systemic ARs through 7 days after single dose.
    - Unsolicited AEs, including MAAEs, SAEs, AESIs, and AEs leading to study discontinuation, through 28 days after single dose.

6.5.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity:

GMRs were estimated via ANCOVA using Day 29 (for P203 – Part 3) or Day 57 (for P301) log-titers as the dependent variable and group (P203 – Part 3 vs. P301) as the only independent variable. The 95% CIs for the SRR differences were estimated via the Miettinen-Nurminen method.

The immunogenicity analyses were conducted on the Per-Protocol Immunogenicity Subset-Positive (PPIS-POS), which was a subset of the PPIS, which was a subset of the IS, which was a subset of the FAS. All four analysis sets are defined below:

- FAS: All randomized participants who received a single dose.
    - IS: A subset of participants in the FAS selected for immunogenicity testing.
        - PPIS: Participants in the FAS who received the single dose per schedule, complied with immunogenicity testing schedule, and had no major protocol deviations that impacted key or critical data.
            - PPIS-POS: Participants in the PPIS who were additionally seropositive pre-single dose.

Subgroup analyses were performed by sex (i.e., male or female), race (i.e., African American, Caucasian, or Other), and country (i.e., U.S. or Dominican Republic [D.R.]).

Analysis of Safety:

All safety data were summarized descriptively. Solicited ARs and unsolicited AEs were summarized in the SSS and SS, respectively, where the SSS was a subset of the SS. Both analysis sets are defined below:

- SS: All randomized participants who received a single dose.
  - SSS: Participants in the SS who contributed any solicited AR data.

No subgroup analyses of the safety data were performed.

Multiplicity Adjustment:

The success criterion for P203 – Part 3 was that both co-primary immunogenicity endpoints meet their respective success criteria for superiority and non-inferiority of GMR against Omicron BA.4/BA.5 and the ancestral strain, respectively, at the immunogenicity analyses at Day 29 for P203 – Part 3 versus Day 57 for P301. Thus, no multiplicity adjustments were necessary.

6.5.10 Study Population and Disposition

Table 24 displays the disposition of the FAS for P203 – Part 3, where a total of 379 participants were included.

Table 24: Participant Disposition for P203 – Part 3 – FAS

-	**mRNA-1273.222 N=379 n (%)**
Number of participants	-
Received first injection in Part 3	379 (100)
Discontinued study vaccine[a]	10 (2.6)
Reason for discontinuation of study vaccine:	-
Lost to follow-up	1 (0.3)
Withdrawal of consent by participant:	6 (1.6)
Other	6 (1.6)
Missing	3 (0.8)
Discontinued from study	10 (2.6)
Reason for discontinuation of study:	-
Lost to follow-up	1 (0.3)
Withdrawal of consent by participant	6 (1.6)
Other	6 (1.6)
Other	3 (0.8)

[a]Study Vaccine Discontinuation was defined as a participant who discontinued before receiving the second injection.
Source: Table 1 of P203 – Part 3 Clinical Overview.

Table 25 displays the sample size in each analysis set for P203 – Part 3. A total of 245 participants met the criteria for the PPIS-POS. In P301, a subset of 340 participants who received mRNA-1273 were selected for the IS, where 295 participants met the criteria for the PPIS.

Table 25: Number of Participants in Each Analysis Set for P203 – Part 3

-	**P203 – Part 3 mRNA-1273.222 N=379 n (%)**	**P301 mRNA-1273 18 – 25 YOA n (%)**
Full Analysis Set	379	-
Immunogenicity Subset	247	340
Per-Protocol Immunogenicity Subset, n (%)	246 (99.6)	295 (86.8)
Per-Protocol Immunogenicity Subset-Positive n (%)	245 (99.2)	-
Safety Set	379	-
Solicited Safety Set, n (%)	378 (99.7)	-

Source: Table 2 of P203 – Part 3 Clinical Overview.

Table 26 displays the distributions of demographic characteristics for the FAS in P203 – Part 3.

Table 26: Participant Demographics and Baseline Characteristics for P203 – Part 3 – FAS

-	**mRNA-1273.222 N=379 n (%)**
Age (years)	-
n	379
Mean (SD)	13.8 (1.6)
Median	14.0
Min, Max	12, 17
Age group, n (%)	-
≥12 and <16 years	306 (80.7)
≥16 and <18 years	73 (19.3)
Gender, n (%)	-
Male	200 (52.8)
Female	179 (47.2)
Race, n (%)	-
White	39 (10.3)
Black	122 (32.2)
Multiracial	3 (0.8)
Other[a]	215 (56.7)
Ethnicity, n (%)	-
Hispanic or Latino	358 (94.5)
Not Hispanic or Latino	21 (5.5)
Race and ethnicity group, n (%)[b]	-
White non-Hispanic	5 (1.3)
Communities of Color	374 (98.7)
Country, n (%)	-
U.S.	54 (14.2)
D.R.	325 (85.8)
Weight (kg)	-
N	379
Mean (SD)	55.6 (17.4)
Median	52.7
Min, Max	20.4, 141.0
Height (cm)	-
N	379
Mean (SD)	160.5 (11.1)
Median	161.0
Min, Max	68.0, 188.0
Body mass index (kg/m^2)	-
N	379
Mean (SD)	21.6 (7.5)
Median	19.8
Min, Max	7.5, 116.2
BMI subgroup, n (%)	-
<30 kg/m^2	353 (93.1)
≥30 kg/m^2	26 (6.9)
BMI subgroup (obesity[c] vs non-obesity), n (%)	-
Obesity	68 (17.9)
Non-obesity	311 (82.1)

Table 26: Participant Demographics and Baseline Characteristics for P203 – Part 3 – FAS (continued)

-	**mRNA-1273.222 N=379 n (%)**
Baseline RT-PCR results, n (%)	-
Negative	315 (83.1)
Positive	2 (0.5)
Missing	62 (16.4)
Baseline Elecsys anti-SARS-CoV-2 results, n (%)	-
Negative	1 (0.3)
Positive	378 (99.7)
Baseline SARS-CoV-2 status, n (%)[c]	-
Negative	1 (0.3)
Positive	378 (99.7)

[a]Other category included Mestizo and Caribbean.
[b]White non-Hispanic was defined as White and non-Hispanic, and Communities of Color included all the others whose race or ethnicity was not unknown, unreported or missing.
[c]Obesity was defined as BMI ≥95th percentile of the WHO growth reference data.
[d]Baseline SARS-CoV-2 Status: Positive if there was immunologic or virologic evidence of prior infection, 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.
Source: Table 3 of P203 – Part 3 Clinical Overview.

6.5.11 Immunogenicity Analyses

Table 27 displays the GLSMs and SRRs against both Omicron BA.4/BA.5 and the ancestral strain for both adolescents at Day 29 and young adults at Day 57. The success criteria for the GMR against both Omicron BA.4/BA.5 (GMR = 49.0, 95% CI = 44.2 to 54.2) and the ancestral strain (GMR = 4.2, 95% CI = 3.7 to 4.9) were met for the lower bounds of the 95% CIs. The anti-Omicron BA.4/BA.5 SRR Difference was 94.7% with 95% CI = 91.1% to 96.9%, while the anti-ancestral strain SRR Difference was -4.7% with 95% CI = -8.4% to -2.1%.

Across the subgroups of sex, race, and country, no meaningful differences in GMRs were observed.

Table 27: Immunogenicity Analyses of Pseudovirus nAb at Day 29 for P203 – Part 3 – PPIS-POS Set

-	**P203 – Part 3 Adolescents 12 to < 18 YOA**	**P301 Young adults 18 – 25 YOA**
N	245	294
Omicron BA.4/BA.5	-	-
GLSM (95% CI)[a]	2771.0 (2570.0, 2987.6)	56.6 (52.8, 60.6)
GMR (95% CI)[a]	49.0 (44.2, 54.2)	-
SRR, % (95% CI)[b,c]	232/245 94.7 (91.1, 97.1)	0/294 0 (0, 1.2)
SRR Difference, % (95% CI)[b,d]	94.7 (91.1, 96.9)	-
Ancestral Strain	243	294
GLSM (95% CI)[a]	7187.1 (6480.5, 7970.8)	1692.3 (1540.6, 1858.9)
GMR (95% CI)[a]	4.2 (3.7, 4.9)	-
SRR, % (95% CI)[b,c]	228/241 94.6 (91.0, 97.1)	292/294 99.3 (97.6, 99.9)
SRR Difference, % (95% CI)[b,d]	-4.7 (-8.4, -2.1)	-

[a]Based on ANCOVA modeling, which used Day 29 (for P203 – Part 3) or Day 57 (for P301) log-titers as the dependent variable and group (adolescents vs. young adults) as the only independent variable.
[b]SRR compares the Day 29 titer to the pre-single dose titer for P203 – Part 3 and the Day 57 titer to the pre-Dose 1 titer of the primary series for P301.
[c]95% CI was calculated by Clopper-Pearson method.
[d]95% CI was calculated by Miettinen-Nurminen method.
Source: Adapted from both Tables 7 and 8 of P203 – Part 3.

6.5.12 Safety Analyses

Table 28 displays both local and systemic ARs within 7 days after a 1) single dose in the SSS for P203 – Part 3; 2) Dose 2 in the Second Injection SSS for P203 – Part 1A; and 3) BD in the SSS for P203 – Part 1C.

In P203 – Part 3, injection site pain was the most frequent solicited local AR, while headache was the most frequent solicited systemic AR. Compared to subjects from both P203 – Part 1A and P203 – Part 1C, subjects from P203 – Part 3 reported generally fewer local and systemic ARs.

Table 28: Summary of Solicited Local and Systemic ARs Within 7 Days After 1) a Single Dose in the SSS for P203 – Part 3; 2) Dose 2 in the Second Injection SSS for P203 – Part 1A; and 3) BD in the SSS for P203 – Part 1C

-	**P203 – Part 3 mRNA-1273.222 Single Dose (N=378) n (%)**	**P203 – Part 1A mRNA-1273 Dose 2 (N=2478) n (%)**	**P203 – Part 1C mRNA-1273 BD (N=1351) n (%)**
Local ARs, Any Grade	169 (44.7)	2314 (93.4)	1236 (91.5)
Local ARs, Grade 3	10 (2.6)	220 (8.9)	62 (4.6)
Pain, Any Grade	161 (42.6)	2290 (92.4)	1224 (90.6)
Pain, Grade 3[a]	4 (1.1)	126 (5.1)	44 (3.3)
Axillary swelling or tenderness, Any Grade	43 (11.4)	519 (21.0)	375 (27.8)
Axillary swelling or tenderness, Grade 3[a]	1 (0.3)	7 (0.3)	5 (0.4)
Erythema (Redness), Any Grade	11 (2.9)	484 (19.5)	121 (9.0)
Erythema (Redness), Grade 3[b]	6 (1.6)	72 (2.9)	10 (0.7)
Swelling (Hardness), Any Grade	10 (2.6)	508 (20.5)	180 (13.3)
Swelling (Hardness), Grade 3[b]	3 (0.8)	56 (2.3)	10 (0.7)
Systemic ARs, Any Grade	150 (39.7)	2134 (86.1)	1024 (75.9)
Systemic ARs, Grade 3	16 (4.2)	341 (13.8)	111 (8.2)
Systemic ARs, Grade 4	2 (0.5)	3 (0.1)	0
Fatigue, Any Grade	46 (12.2)	1679 (67.8)	784 (58.1)
Fatigue, Grade 3[c]	0	188 (7.6)	54 (4.0)
Headache, Any Grade	104 (27.6)	1739 (70.2)	760 (56.3)
Headache, Grade 3[d]	5 (1.3)	112 (4.5)	29 (2.1)
Headache, Grade 4[e]	0	1 (<0.1)	0
Myalgia, Any Grade	59 (15.6)	1155 (46.6)	542 (40.1)
Myalgia, Grade 3[c]	1 (0.3)	129 (5.2)	49 (3.6)
Arthralgia, Any Grade	37 (9.8)	716 (28.9)	322 (23.9)
Arthralgia, Grade 3[c]	1 (0.3)	57 (2.3)	18 (1.3)
Chills, Any Grade	20 (5.3)	1066 (43.0)	408 (30.2)
Chills, Grade 3[f]	1 (0.3)	11 (0.4)	7 (0.5)
Nausea/Vomiting, Any Grade	18 (4.8)	591 (23.9)	241 (17.9)
Nausea/Vomiting, Grade 3[g]	0	2 (<0.1)	2 (0.1)
Nausea/Vomiting, Grade 4[h]	0	1 (<0.1)	0
Fever, Any Grade	31 (8.2)	298 (12.0)	81 (6.1)
Fever, Grade 3[i]	10 (2.6)	48 (1.9)	8 (0.6)
Fever, Grade 4[j]	2 (0.5)	1 (<0.1)	0

[a]Grade 3 pain and axillary swelling/tenderness was defined as: any use of prescription pain reliever; prevents daily activity.
[b]Grade 3 swelling and erythema was defined as: >100 mm / >10 cm.
[c]Grade 3 fatigue, myalgia, arthralgia was defined as: significant; prevents daily activity.
[d]Grade 3 headache was defined as: significant; any use of prescription pain reliever or prevents daily activity.
[e]Grade 4 headache was defined as: requires emergency room visit or hospitalization.
[f]Grade 3 chills was defined as: prevents daily activity and requires medical intervention.
[g]Grade 3 nausea/vomiting was defined as: prevents daily activity, requires outpatient intravenous hydration.
[h]Grade 4 nausea/vomiting was defined as: requires emergency room visit or hospitalization for hypotensive shock.

[i]Grade 3 fever was defined as: ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j]Grade 4 fever was defined as: >40.0°C / >104.0°F.
Source: Table 9 of P203 – Part 3.

Table 29 displays unsolicited AEs up to 28 days after a single dose in the SS. For unsolicited AEs regardless of relationship to study vaccination, 12.9%, 9.5%, and 0.8% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively. No deaths, SAEs, AESIs, events of myocarditis, pericarditis, MIS-C, or unsolicited AEs leading to study discontinuation were reported. For unsolicited AEs related to study vaccination as determined by the investigator, 3.7%, 1.8%, and 0.3% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively.

After the single dose as of the data cutoff, the median follow-up was 35 days. Up to the data cutoff, for unsolicited AEs regardless of relationship to study vaccination, 16.9%, 12.4%, 0.8%, and 0.8% of participants reported unsolicited AEs, MAAEs, Grade 3 unsolicited AEs, and SAEs, respectively. No deaths, AESIs, events of myocarditis, pericarditis, MIS-C, or unsolicited AEs leading to study discontinuation were reported. For unsolicited AEs considered by the investigator to be related to study vaccination, 3.7%, 1.8%, and 0.3% of participants reported unsolicited AEs, MAAEs, and Grade 3 unsolicited AEs, respectively. No related SAEs as determined by the investigator were reported.

Table 29: Summary of Unsolicited AEs up to 28 Days[a] After Single Dose – SS

-	**mRNA-1273.222 Single Dose (N=379) n (%)**
Unsolicited TEAEs regardless of relationship to study vaccination	-
All	49 (12.9)
Serious	2 (0.5)
Medically-attended	36 (9.5)
Grade 3/severe	3 (0.8)
Non-serious[a]	47 (12.4)
Grade 3/severe	1 (0.3)
At least 1 non-serious[b]	48 (12.7)
Grade 3/severe	1 (0.3)
Unsolicited TEAEs related to study vaccination	-
All	14 (3.7)
Medically-attended	7 (1.8)
Grade 3/severe	1 (0.3)
Non-serious[a]	14 (3.7)
Grade 3/severe	1 (0.3)
At least 1 non-serious[b]	14 (3.7)
Grade 3/severe	1 (0.3)

[a]Only 69% of participants had follow-up of ≥ 28 days.
[b]Participants without any SAE and with any non-serious AE.
[c]Participants with at least one non-serious AE regardless of reporting any SAE or not.
Source: Table 10 of P203 – Part 3.

7. Integrated Overview of Efficacy

No integrated overview of efficacy was submitted.

8. Integrated Overview of Safety

No integrated overview of safety was submitted.

9. Additional Statistical Issues

There are no additional statistical issues.

10. Conclusions

Both immunogenicity and safety data were obtained from the following seven studies to support licensure of the monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older regardless of previous vaccination status: one Phase 3 clinical study, P301; and six Phase 2/3 clinical studies, P203 – Parts 1A, 1B, and 1C; P205 – Parts F and H; and P203 – Part 3. For all studies but P203 – Part 3, all subjects evaluated in the immunogenicity analyses had no evidence of prior SARS-CoV-2 infection at baseline. For P203 – Part 3, all subjects evaluated in the immunogenicity analyses had evidence of prior SARS-CoV-2 infection.

For P203 – Part 1A, the immunogenicity analyses comparing adolescents 12 to 17 YOA to that of young adults 18 to 25 YOA from P301 who received a two-dose, 100 µg mRNA-1273 primary series met the pre-specified immunobridging success criteria (GMR = 1.1, 95% CI = 0.9 to 1.2; SRR difference = -0.2%, 95% CI = -2.1% to 1.9%). For the descriptive efficacy analyses, starting 14 days after Dose 2, the estimated VEs for the CDC and P301 case definitions were 0.90 (95% CI = 0.51 to 0.99) and 1.00 (95% CI = 0.61 to NE), respectively.

For P203 – Part 1C, the immunogenicity analyses comparing adolescents 12 to 17 YOA who received a single BD of 50 µg mRNA-1273 to that of young adults 18 to 25 YOA from P301 who received a two-dose, 100 µg mRNA-1273 primary series met the pre-specified immunobridging success criteria for non-inferiority (GMR = 5.1, 95% CI = 4.5 to 5.7; SRR difference = 0.7%, 95% CI = -0.8% to 2.4%).

For P205 – Part H, the immunogenicity analyses comparing adults 18 YOA and older who received a second BD of 50 µg mRNA-1273.222 to that of adults 18 YOA and older from P205 – Part F who received a second BD of 50 µg mRNA-1273 met the pre-specified immunobridging success criteria for non-inferiority. Adjusting for both age category and pre-second BD log-titers, the anti-Omicron BA.4/BA.5 GMR was 6.3 with 95% CI = 5.3 to 7.5, while the anti-ancestral strain GMR was 2.0 with 95% CI = 1.7 to 2.3. Adjusting for age category, the anti-Omicron BA.4/BA.5 SRR Difference was 12.1% with 95% CI = 6.9% to 17.3%, while the anti-ancestral strain SRR Difference was 0% with the SRRs in both groups being 100%.

For P203 – Part 3, the immunogenicity analyses comparing adolescents 12 to 17 YOA who received a single dose of 50 µg mRNA-1273.222 to that of young adults 18 to 25 YOA from P301 who received a two-dose, 100 µg mRNA-1273 primary series met the pre-specified immunobridging success criteria for both superiority of anti-Omicron BA.4/BA.5 GMR (GMR =

49.0, 95% CI = 44.2 to 54.2) and non-inferiority of anti-ancestral strain GMR (GMR = 4.2, 95% CI = 3.7 to 4.9).

For adolescents 12 to 17 YOA, comparing the two-dose, 100 µg mRNA-1273 primary series to placebo in P203 – Part 1A, rates of both local and systemic ARs were generally higher in the mRNA-1273 group than the placebo group for both doses. Comparing a single dose of 50 µg mRNA-1273.222 in COVID-19 vaccine-naïve subjects with evidence of prior SARS-CoV-2 infection from P203 – Part 3 to the second dose of a two-dose, 100 µg mRNA-1273 primary series in subjects without evidence of prior infection at baseline from P203 – Part 1A, subjects from P203 – Part 3 had generally fewer local and systemic ARs. Across studies for individuals 12 YOA and older who received some formulation of mRNA-1273, injection site pain was the most frequently reported solicited local AR. Fatigue and headache tended to be the most frequently reported solicited systemic ARs.

In adolescents 12 to 17 YOA, for unsolicited AEs that occurred within 28 days after each dose administration regardless of relationship to study vaccination, comparing a two-dose, 100 µg mRNA-1273 primary series to placebo in P203 – Part 1A, there were similar or slightly higher percentages of unsolicited AEs, MAAEs, and SAEs. In the mRNA-1273 group, there was 1 participant who had an AESI of appendicitis that was not considered related to study vaccination by the investigator. No events of myocarditis, pericarditis, or Multisystem Inflammatory Syndrome in Children (MIS-C) were reported. For unsolicited AEs that occurred within 28 days after each dose administration and were considered related to study vaccination by the investigator, comparing the mRNA-1273 group to the placebo group, there were higher percentages of both related unsolicited AEs and related MAAEs. No related SAEs or related AESIs as determined by the investigator were reported.

Across all studies in individuals 12 YOA and older who received some formulation of mRNA-1273, the percentages of unsolicited AEs, MAAEs, SAEs, and AESIs were generally consistent within 28 days after each dose administration regardless of relationship to study vaccination as well as those considered related to study vaccination by the investigator. No events of myocarditis, pericarditis, or MIS-C were reported. One death was reported in P205 – Part H that was not considered related to study vaccination by the investigator.

Across all studies in individuals 12 YOA and older, up to the data cutoff (with median follow-up ranging from 35 to 131 days), no events of myocarditis, pericarditis, or MIS-C were reported. One additional death was reported in P205 – Part F that was not considered related to study vaccination by the investigator. No related SAEs or related AESIs as determined by the investigator were reported.

In P203 – Part 1B, adolescents 12 to 17 YOA who originally received a two-dose, 100 µg mRNA-1273 primary series in Part 1A were followed for unsolicited AEs over a substantially longer follow-up period (with median follow-up of 312 days) than the other studies. Compared to the other studies for unsolicited AEs regardless of relationship to study vaccination, subjects in P203 – Part 1B had elevated rates of both unsolicited AEs and MAAEs. According to the Applicant, this was primarily due to a higher case rate of COVID-19, which likely reflected the Omicron BA.1 surge that was observed during the months of December 2021 and January 2022

which overlapped with the follow-up period for P203 – Part 1B. The rates of both SAEs and AESIs were generally similar to the other studies. No deaths, events of myocarditis, pericarditis, or MIS-C were reported. For unsolicited AEs considered related to study vaccination by the investigator, the rates of unsolicited AEs, MAAEs, SAEs, and AESIs were similar to the other studies.

Overall, the available immunogenicity, exploratory efficacy, and safety data support the licensure of the monovalent Omicron XBB.1.5 formulation for individuals 12 YOA and older.