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| | |
|---|---|
| Application Type | BLA, Original Application |
| STN | 125835/0 |
| CBER Received Date | September 30, 2024 |
| PDUFA Goal Date | May 31, 2025 |
| Committee Chair | Joseph Kulinski |
| Clinical Reviewers | Timothy Brennan, Brittany Shepherd |
| Project Managers | Sylvia Park, Donna Elhindi |
| Priority Review | Yes |
| Reviewer Names | Ross Peterson<br>Mathematical Statistician, VEB, DB, OBPV |
| Review Completion Date/Stamped Date | |
| Concurrence | Ye Yang<br>Lead Mathematical Statistician, VEB, DB, OBPV |
| Supervisory Concurrence | Tsai-Lien Lin<br>Branch Chief, VEB, DB, OBPV |
| Supervisory Concurrence | John Scott<br>Director, DB, OBPV |
| Applicant | ModernaTX, Inc. |
| Established Name | COVID-19 Vaccine, mRNA |
| (Proposed) Trade Name | MNEXSPIKE |
| Dosage Form(s) and Route(s) of Administration | Injectable Suspension, Intramuscular |
| Dosing Regimen | Single dose of 0.2 mL administered at least 3 months after the last dose of COVID-19 vaccine. |
| Indication(s) and Intended Population(s) | 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 who have been previously vaccinated with any COVID-19 vaccine. |

**Table of Contents**

**Glossary**

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| ANCOVA | Analysis of Covariance |
| AR | Adverse Reaction |
| CBER | Center for Biologics Evaluation and Research |
| CDC | Centers for Disease Control and Prevention |
| BLA | Biologics License Application |
| BMI | Body Mass Index |
| CHW | Cui, Hung, and Wang |
| CI | Confidence Interval |
| COVID-19 | Coronavirus Disease 2019 |
| FAS | Full Analysis Set |
| GLSM | Geometric Least Squares Mean |
| GMR | Geometric Mean Titer Ratio |
| HR | Hazard Ratio |
| IA | Interim Analysis |
| IS | Immunogenicity Set |
| ISS | Immunogenicity Subcohort Set |
| LL | Lower Limit |
| LLOQ | Lower Limit of Quantitation |
| MAAE | Medically Attended Adverse Events |
| PPSE | Per-Protocol Set for Efficacy |
| PPIS | Per-Protocol Immunogenicity Set |
| PsVNA | Pseudovirus neutralization assay |
| RT-PCR | Reverse Transcriptase-Polymerase Chain Reaction |
| rVE | Relative Vaccine Efficacy |
| SAE | Serious Adverse Event |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SD | Standard Deviation |
| SRR | Seroresponse Rate |
| SS | Safety Set |
| SSS | Solicited Safety Set |
| ULOQ | Upper Limit of Quantitation |
| YOA | Years of Age |

## 1. Executive Summary

ModernaTX, Inc. submitted a Biologics License Application (BLA) to seek licensure of the mRNA-1283 vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age (YOA) and older who have been previously vaccinated with any COVID-19 vaccine. The BLA was designated as Priority Review.

Two studies were conducted to determine both the number of doses and dose level for mRNA-1283 to be used in the Phase 3 clinical studies, P301 and P301 – Japan. These include the Phase 1 clinical study, P101, which investigated both factors, and the Phase 2 clinical study, P201, which investigated the dose level only. Based on the results of both Studies P101 and P201, a single dose of 10 μg was selected for mRNA-1283 in both Studies P301 and P301 – Japan. The BLA is primarily supported by immunogenicity, efficacy, and safety data from Study P301, as well as both immunogenicity and safety data from Study P301 – Japan, which are the focus of this review.

Study P301 was a randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy (rVE) of mRNA-1283 compared with mRNA-1273 (SPIKEVAX) in previously vaccinated participants aged ≥12 years for the prevention of COVID-19. A total of 20,122 subjects were planned to be randomized in a 1:1 allocation ratio to receive either a single dose of mRNA-1283.222 10 μg or mRNA-1273.222 50 μg, stratified by age category (i.e., 12 to < 18, 18 to < 65, and ≥ 65 years). Both mRNA-1283.222 and mRNA-1273.222 were bivalent vaccines encoded for both ancestral SARS-CoV-2 D614G and Omicron BA.4/5.

The four co-primary immunogenicity endpoints were both geometric mean titer ratios (GMRs) and seroresponse rate (SRR) differences of pseudovirus neutralization assay (PsVNA) titers against both Omicron BA.4/5 and ancestral SARS-CoV-2 D614G at Day 29. SRR was defined as change in PsVNA titer from baseline below the lower limit of quantitation (LLOQ) to ≥4 × LLOQ, or at least a 4-fold rise if baseline was ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline was ≥4 × LLOQ. The co-primary immunogenicity endpoints were planned to be evaluated on a subset of subjects (N = 980). For GMR, the success criterion was that the lower limit (LL) of the 2-sided confidence interval (CI) was > 2/3. For SRR difference, the success criterion was that the LL of the 2-sided CI was > -10%.

If the success criteria for all four co-primary immunogenicity endpoints were met, the primary efficacy endpoint was to be evaluated. The primary efficacy endpoint was the first episode of COVID-19 according to Centers for Disease Control and Prevention (CDC) case definition within the period of 14 days post-injection up to at least 6 months post-injection. The success criterion was that the LL of the 2-sided CI for rVE was > -10%.

For the primary efficacy endpoint, one interim analysis (IA) was pre-specified based on the Lan-DeMets approximation to O'Brien-Fleming stopping boundaries with an information fraction of 0.34 (700 out of a total of 2,087 cases).

At the IA, the success criteria for all four co-primary immunogenicity endpoints and rVE were met. The median follow-up at the IA was 244 days up to the data cutoff of 31 Jan 2024 in both groups.

The adjusted anti-Omicron BA.4/5 GMR was 1.3 with 95% CI = 1.2 to 1.5, while the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.1 to 1.4. Both GMRs were adjusted for SARS-CoV-2 status at baseline (positive or negative), age category, number of prior COVID-19 booster doses (0, 1, 2, or ≥3), and type of last prior COVID-19 vaccine (mRNA bivalent, mRNA monovalent, or non-mRNA vaccine). The anti-Omicron BA.4/5 SRR difference was 14.4% with 95% CI = 9.3% to 19.4%, while the anti-ancestral SARS-CoV-2 D614G SRR difference was 10.7% with 95% CI = 6.0% to 15.4%.

For CDC case definition, 560 and 617 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE with stratification by age category was 9.3% with 99.4% CI = -6.6% to 22.8%. The alpha value of 0.6% for the 2-sided CI was derived from the Lan-DeMets approximation to the O'Brien-Fleming stopping boundary with an information fraction of 0.56 (1,177 out of a total of 2,087 cases).

Supportive efficacy analyses were conducted up to the data cutoff of 23 Feb 2024. The median follow-up was 267 days in both groups. Compared to the IA, for CDC case definition, the estimated rVE with stratification by age category marginally decreased to 7.3% with 95% CI = -3.4% to 17.0%.

Safety analyses were conducted up to the data cutoff of 23 Feb 2024. The median follow-up was 267 days in both groups. Solicited adverse reactions (ARs) were collected through 7 days post-injection. Unsolicited adverse events (AEs) (including medically attended adverse events [MAAEs], adverse events of special interest [AESIs], serious adverse events [SAEs], and AEs leading to study discontinuation) were collected through 28 days post-injection and up to the data cutoff of 23 Feb 2024.

Within 7 days post-injection, rates of solicited local ARs were slightly lower in the mRNA-1283.222 group than the mRNA-1273.222 group. Rates of solicited systemic ARs were generally similar between the mRNA-1283.222 group and the mRNA-1273.222 group. For both groups, injection site pain was the most frequently reported solicited local AR, while fatigue was the most frequently reported solicited systemic AR.

Within 28 days post-injection, regardless of relationship to study vaccination per the investigator, there were similar percentages of unsolicited AEs, SAEs, MAAEs, and AESIs in both groups. One related AESI (possible anaphylaxis) was reported in the mRNA-1283.222 group while none were reported in the mRNA-1273.222 group. One

death reported in the mRNA-1273.222 group was considered to be related per the investigator and occurred on Day 7 post-injection with cause of death reported as unknown. However, the Applicant assessed the death as unrelated given the subject's long term cardiovascular history.

These findings generally held for the unsolicited AEs collected up to the data cutoff of 23 Feb 2024. One event of pericarditis was reported in the mRNA-1273.222 group on Day 136 post-injection while none were reported in the mRNA-1283.222 group, which was not considered to be related per the investigator. No events of myocarditis were reported.

Study P301 – Japan was a randomized, observer-blind, active-controlled Phase 3 study to investigate the safety and immunogenicity of mRNA-1283 compared with mRNA-1273 in participants aged 12 years and older. A total of 692 subjects were planned to be randomized in a 1:1 allocation ratio to receive either a single dose of mRNA-1283.815 10 μg or mRNA-1273.815 50 μg, both encoding for Omicron XBB.1.5, stratified by age category (i.e., 12 to < 18, 18 to < 65, and ≥ 65 years).

The primary and secondary immunogenicity endpoints were the GMR and SRR difference, respectively, for PsVNA titer against Omicron XBB.1.5 at Day 29. Secondary immunogenicity endpoints also included the GMR and SRR difference for PsVNA titer against ancestral SARS-CoV-2 D614G at Day 29. The adjusted anti-Omicron XBB.1.5 GMR met the success criterion that the LL of the 2-sided CI be > 2/3 with a GMR of 1.2 and 95% CI = 1.0 to 1.4. The anti-Omicron XBB.1.5 SRR difference was 5.4% with 95% CI = 0.8% to 10.2%, the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.0 to 1.3, and the anti-ancestral SARS-CoV-2 D614G SRR difference was 8.6% with 95% CI = 2.2% to 15.0% — all three were assessed descriptively. Both GMRs were adjusted for SARS-CoV-2 status at pre-booster (positive or negative), age category, number of prior COVID-19 booster doses (0, 1, 2, or ≥3), and type of last prior COVID-19 vaccine.

Safety analyses were conducted up to the data cutoff of 02 May 2024. The median follow-up was 36 days and 35 days in the mRNA-1283.815 group and mRNA-1273.815 group, respectively. Findings for solicited ARs were similar to Study P301 and no notable differences in unsolicited AEs were found either within 28 days post-injection or up to the data cutoff of 02 May 2024. No SAEs, AEs leading to study discontinuation, AESIs, deaths, myocarditis, or pericarditis were reported.

Overall, the immunogenicity, efficacy, and safety data support licensure of the mRNA-1283 vaccine in individuals 12 YOA and older who have been previously vaccinated with any COVID-19 vaccine.

## 2. Clinical and Regulatory Background

ModernaTX, Inc. submitted a BLA to seek licensure of the mRNA-1283 vaccine intended to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 YOA and older

who previously received COVID-19 vaccination. The BLA was designated as Priority Review.

Compared to mRNA-1273 (SPIKEVAX), the currently licensed COVID-19 vaccine from ModernaTX, Inc., the Applicant stated that mRNA-1283 has an improved shelf-life at refrigerated temperatures and requires a lower dose to elicit an immune response.

Two studies were conducted to determine both the number of doses and dose level for mRNA-1283 to be used in the Phase 3 clinical studies, P301 and P301 – Japan. These include the Phase 1 clinical study, P101, which investigated both factors, and the Phase 2 clinical study, P201, which investigated the dose level only.

Based on the results of both Studies P101 and P201, a single dose of 10 μg mRNA-1283 was selected. The BLA is primarily supported by immunogenicity, efficacy, and safety data from Study P301, as well as both immunogenicity and safety data from Study P301 – Japan.

## 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 Practice 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 memo focuses on the Phase 3 clinical studies, P301 and P301 – Japan, supporting licensure of mRNA-1283 for participants 12 YOA and older. The Phase 1 clinical study, P101, and Phase 2 clinical study, P201, are not included in this review memo.

### 5.2 BLA Documents That Serve as the Basis for the Statistical Review

The following documents submitted to the BLA are reviewed:

STN 125835/0.0 (submitted on 9/30/2024)

1. Module 5. Clinical Study Reports
   - P101 Clinical Study Report
   - P201 Clinical Study Report
   - P301 Clinical Study Report
   - P301 Trial Protocol
   - P301 Statistical Analysis Plan
   - P301 – Japan Clinical Study Report
   - P301 – Japan Trial Protocol
   - P301 – Japan Statistical Analysis Plan

STN 125835/0.7 (submitted on 12/4/2024)

1. Module 1. Information Amendments
   - Response to Information Request (IR) 6

### 5.3 Table of Studies/Clinical Trials

Four clinical studies, P101, P201 (comprising both Parts A and B), P301, and P301 – Japan, were conducted to support licensure of the mRNA-1283 vaccine and are summarized in Table 1.

Table 1: Clinical Studies Supporting the BLA

| Study | N | Age | Description |
|---|---|---|---|
| P101 | 105 | 18 to 55 YOA | Phase 1, randomized, observer-blind, active-controlled, dose-ranging study to evaluate the safety and immunogenicity of different numbers of doses and dose levels of mRNA-1283 (monovalent vaccine encoded for ancestral SARS-CoV-2 D614G) versus two doses of mRNA-1273 (monovalent vaccine encoded for ancestral SARS-CoV-2 D614G) in participants 18 to 55 YOA |
| P201 – Part A | 340 | ≥ 18 YOA | Phase 2, randomized, observer-blind, active-controlled, dose-ranging study to evaluate the safety and immunogenicity of different dose levels of a single dose of mRNA-1283 or mRNA-1283.211 (bivalent vaccine encoded for both ancestral SARS-CoV-2 D614G and Beta) versus a single dose of mRNA-1273 in participants 18 YOA and older |
| P201 – Part B | 200 | ≥ 18 YOA | Phase 2, randomized, open-label, dose-ranging study to evaluate the safety and immunogenicity of different dose levels of a single dose of mRNA-1283.529 (monovalent vaccine encoded for Omicron BA.1) in participants 18 YOA and older |
| P301 | 11454 | ≥ 12 YOA | Phase 3, randomized, observer-blind, active-controlled study to evaluate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283.222 versus a single dose of mRNA-1273.222 in participants 12 YOA and older |
| P301 – Japan | 692 | ≥ 12 YOA | Phase 3, randomized, observer-blind, active-controlled study to evaluate both the safety and immunogenicity of a single dose of mRNA-1283.815 versus a single dose of mRNA-1273.815 in participants 12 YOA and older |

N = number of enrolled subjects.
*Source: Summarized by the reviewer from P101, P201, P301, and P301 – Japan Clinical Study Reports.*

## 6. Discussion of Individual Studies/Clinical Trials

## 6.1 Clinical Study P301

Title of Study: A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ≥12 years for the prevention of COVID-19.

Dates:
1. Study initiation date (First Subject First Visit): 28 Mar 2023.
2. Data cutoff date for interim efficacy analyses: 31 Jan 2024.
3. Data cutoff date for both supportive efficacy analyses and safety analyses: 23 Feb 2024.

### 6.1.1 Objectives

Co-Primary Immunogenicity Objectives:
1. To demonstrate a non-inferior neutralizing antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against Omicron BA.4/5 based on GMR and SRR[a] difference at Day 29.
2. To demonstrate a non-inferior neutralizing antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against ancestral SARS-CoV-2 D614G based on GMR and SRR[a] difference at Day 29.

[a]SRR was defined as change in PsVNA titer from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline was ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline was ≥4 × LLOQ.

Primary Efficacy Objective:
1. To demonstrate non-inferior rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent COVID-19.

Primary Safety Objective:
1. To evaluate the safety and reactogenicity of mRNA-1283.222 10 µg.

Secondary Efficacy Objectives:
1. To assess SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 [variant formulations]).
2. To assess the incidence of severe COVID-19 (mRNA-1283.815 and mRNA-1273.815).

### 6.1.2 Design Overview

The study was divided into two sequential parts: Part 1 and Part 2.

In Part 1, approximately 11,500 subjects were to be randomized in a 1:1 allocation ratio to receive either a single dose of mRNA-1283.222 10 µg or a single dose of mRNA-

1273.222 50 µg, stratified by age category. Both mRNA-1283.222 and mRNA-1273.222 were bivalent vaccines encoded for both ancestral SARS-CoV-2 D614G and Omicron BA.4/5. A subset of approximately 1300 (650 per arm) subjects was selected for evaluation of the co-primary immunogenicity endpoints.

Subjects were to be followed for at least six months post-injection. The primary efficacy analyses were case-driven, with a target total accrual of 2,087 COVID-19 cases according to CDC case definition and one pre-specified IA at an information fraction of 0.34 (700 out of a total of 2,087 cases).

Part 2 was to compare mRNA-1283.815 to mRNA-1273.815, where subjects were to be randomized in a 1:1 allocation ratio to receive either a single dose of mRNA-1283.815 10 µg or a single dose of mRNA-1273.815 50 µg, stratified by age category. Both mRNA-1283.815 and mRNA-1273.815 were monovalent vaccines encoded for Omicron XBB.1.5. The final analysis of the primary efficacy endpoint was to be pooled across both Parts. Part 2 was to be initiated if the IA for the primary efficacy endpoint did not meet the success criterion and if the conditional power was ≥ 0.35, where conditional power was to be calculated assuming the same data trend. As the IA for the primary efficacy endpoint met the success criterion, Part 2 was not initiated.

Supportive efficacy analyses were conducted after the IA up to the data cutoff of 23 Feb 2024. For immunogenicity, blood samples were collected on Day 1 and Day 29. For safety, solicited ARs were collected through 7 days post-injection. Unsolicited AEs (including MAAEs, AESIs, SAEs, and AEs leading to study discontinuation) were collected through 28 days post-injection and up to the data cutoff of 23 Feb 2024.

### 6.1.3 Population

Enrollment included participants 12 YOA and older who previously received a primary series of an authorized/approved COVID-19 vaccine. Participants aged ≥18 years must have received at least 1 booster dose, while there was no requirement for participants 12 to <18 years to have received a booster dose. A heterologous vaccine regimen (mix-and-match) was permitted.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 10 µg mRNA-1283.222 or 50 µg mRNA-1273.222 was administered.

### 6.1.6 Sites and Centers

The study was conducted at 196 sites across the United States (150 sites), United Kingdom (38 sites), and Canada (8 sites).

### 6.1.7 Surveillance/Monitoring

Please refer to the clinical review memo.

### 6.1.8 Endpoints and Study Success Criteria

Co-Primary Immunogenicity Endpoints:

1a. GMR of PsVNA titer between mRNA-1283.222 10 µg recipients and mRNA-1273.222 50 µg recipients at Day 29 after the study injection against Omicron BA.4/5.
- The LL of the 2-sided 95% CI for the GMR is > 2/3.

1b. SRR difference of PsVNA titer between mRNA-1283.222 10 µg recipients and mRNA-1273.222 50 µg recipients at Day 29 after the study injection against Omicron BA.4/5.
- The LL of the 2-sided 95% CI for the SRR difference is > -10%.

2a. GMR of PsVNA titer between mRNA-1283.222 10 µg recipients and mRNA-1273.222 50 µg recipients at Day 29 after the study injection against ancestral SARS-CoV-2 D614G.
- The LL of the 2-sided 95% CI for the GMR is > 2/3.

2b. SRR difference of PsVNA titer between mRNA-1283.222 10 µg recipients and mRNA-1273.222 50 µg recipients at Day 29 after the study injection against ancestral SARS-CoV-2 D614G.
- The LL of the 2-sided 95% CI for the SRR difference is > -10%.

Primary Efficacy Endpoint:

1. rVE of mRNA-1283 compared to mRNA-1273 (variant formulations) to prevent the first event of COVID-19 starting 14 days after study injection according to CDC case definition (primary analysis), protocol-defined case definition (sensitivity analysis), or modified CDC case definition (sensitivity analysis). See Table 2 for case definitions.
   - The LL of the 2-sided CI for the rVE for CDC case definition is > -10%

Primary Safety Endpoints:

- Solicited local and systemic reactogenicity ARs during a 7-day follow-up period.
- Unsolicited AEs during the 28-day follow-up period.
- SAEs, MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study.

Secondary Efficacy Endpoints:

1. SARS-CoV-2 infection (symptomatic or asymptomatic) case definition and asymptomatic SARS-CoV-2 infection case definition. See Table 2 for case definitions.
2. Severe COVID-19 case definition. See Table 2 for case definitions.

*Reviewer's Comment:*

- *For the primary efficacy endpoint, the sensitivity analysis of modified CDC case definition was not pre-specified in the trial protocol and was added as a post-hoc analysis.*

- *Severe COVID-19 was originally pre-specified for Part 2 only for mRNA-1283.815 versus mRNA-1273.815. As Part 2 was not initiated, the Applicant evaluated this endpoint in Part 1.*

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

Missing data were not replaced. Titers < LLOQ were replaced by 0.5 × LLOQ. Titers > upper limit of quantitation (ULOQ) were not replaced by the ULOQ.

GMRs were estimated via an analysis of covariance (ANCOVA) model using Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, age category, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine. The 95% CIs for the SRR differences were estimated via the Miettinen-Nurminen method.

The primary immunogenicity analyses were performed on the Per-Protocol Immunogenicity Set (PPIS), which was a subset of the Immunogenicity Set (IS), which was a subset of the Full Analysis Set (FAS), which was a subset of the Randomization Subset (RS). All four were defined as:

- RS: All participants who were randomized, regardless of the participant's treatment status in the study.
- FAS: Participants in the RS who received study vaccine. Participants were analyzed according to their randomized study arm.
- IS: A random sample of adult participants in the FAS regardless of baseline SARS-CoV-2 status, as well as the first 210 dosed adolescents.
- PPIS: Participants in the IS who received the planned dose of study vaccination, had pre-injection and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data, and had no major protocol deviations that impact key or critical data.

Subgroup analyses were performed by age category, sex, race, ethnicity, country, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine (</≥ median of the dosing interval).

Analysis of Efficacy

For the efficacy analyses, the stratified Cox PH model with vaccine group as a fixed effect and a stratification factor for age category (12 to <18 years, 18 to <65 years, or ≥65 years) was used to estimate the hazard ratio (HR). Efron's method was used to handle ties. rVE was estimated as rVE = 100 * (1 – HR). Case definitions are displayed in Table 2.

Cases were counted from 14 days post-injection up to the data cutoff date (31 Jan 2024 for the IA; 23 Feb 2024 for the supportive efficacy analyses). Participants without a case were censored at the earliest date of off-study COVID-19 vaccine, last date of study participation, death date, or data cutoff date. Participants with a case before 14 days post-injection were censored at the case date. All cases related to the efficacy endpoints were collected, but only the first case from each subject was considered for the efficacy analyses. Missing data were not replaced.

Efficacy analyses were performed on the Per-Protocol Set for Efficacy (PPSE), which was a subset of the FAS. The PPSE was defined as:

- PPSE: Participants in the FAS who received the planned dose of study vaccine and had no major protocol deviations that impact vaccine efficacy data.

For the primary efficacy endpoint based on CDC case definition, subgroup analyses were performed by age category, sex, race, ethnicity, country, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine.

Table 2: Case Definitions

| Case | Definition |
|---|---|
| CDC | Participant must have:<br>- The presence of ≥1 CDC listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); AND<br>- A positive reverse transcriptase-polymerase chain reaction (RT-PCR) test on a respiratory sample. |
| Protocol-defined COVID-19 | Participant must have:<br>- Experienced ≥2 systemic symptoms: Fever (≥38°C/100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); OR<br>- Experienced ≥1 respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND<br>- ≥1 nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. |
| Modified CDC | Participant must have:<br>- The presence of ≥1 CDC listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); AND<br>- A positive RT-PCR test on a respiratory sample OR a positive SARS-CoV-2 antigen test. |
| SARS-CoV-2 infection (symptomatic or asymptomatic) | A combination of COVID-19 and asymptomatic SARS-CoV-2 infection. |
| Asymptomatic SARS-CoV-2 infection | Absence of symptoms and:<br>- A positive RT-PCR test on a respiratory sample; OR<br>- A positive serologic test for anti-nucleocapsid antibody for those participants with negative SARS-CoV-2 status at baseline.[a] |
| Severe COVID-19 | Virologically confirmed SARS-CoV-2 infection with ANY of the following starting 14 days after study injection:<br>- Clinical signs at rest indicative of severe systemic illness: respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or PaO2/FiO2 <300 mmHg; OR<br>- Respiratory failure or acute respiratory distress syndrome (requiring high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic BP <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); OR<br>- Significant acute renal, hepatic, or neurologic dysfunction; OR<br>- Admission to an intensive care unit or death. |

[a]SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1. Negative status is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1.
*Source: Adapted from both Tables 2 and 3 from P301 Trial Protocol.*

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, and the SS was a subset of the RS. Both are defined as:

- SS: Participants in the RS who received study vaccine. Participants were included in the study arm that they actually received.
- SSS: All randomized participants in the SS who contributed any solicited AR data.

For solicited ARs, subgroup analyses were performed by age category, sex, race, ethnicity, country, geographic region, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine. For unsolicited AEs, subgroup analyses were performed by age category only.

Multiplicity Adjustment

The success criterion for Part 1 was that all four null hypotheses corresponding to both the GMRs and SRR differences must be rejected. If all four were rejected, then the null hypothesis corresponding to the primary efficacy endpoint was to be tested (i.e., following a fixed-sequence method).

For the primary efficacy endpoint, one IA was pre-specified based on the Lan-DeMets approximation to O'Brien-Fleming stopping boundaries at an information fraction of 0.34 (700 out of a total of 2,087 cases) and was to be conducted after all subjects in Part 1 were enrolled. If the null hypothesis of the primary efficacy endpoint was not rejected at the IA, then Part 2 — which was to compare mRNA-1283.815 to mRNA-1273.815 — was to be initiated if the conditional power was ≥ 0.35, where conditional power was to be calculated assuming the same data trend. However, the null hypothesis of the primary efficacy endpoint was rejected at the IA. Hence, Part 2 was not initiated.

Of note, CBER communicated to the Applicant that immunobridging between mRNA-1283.222 and mRNA-1273.222 was not appropriate due to structural differences in their spike proteins. Thus, CBER would only grant licensure to mRNA-1283 if the null hypothesis corresponding to the primary efficacy endpoint was rejected.

Sample Size Determination

For Part 1, a sample size of 980 (490:490) subjects was calculated to yield 90% power for each of the four co-primary immunogenicity endpoints. The sample size calculation assumed a true GMR of 1, a standard deviation (SD) of 1.8 for natural log-titers, and a true SRR difference of 0%, where both SRRs in the mRNA-1283.222 and mRNA-1273.222 groups were 70%. All four co-primary immunogenicity endpoints assumed a non-evaluable rate of 10%.

Across both Parts 1 and 2, a sample size of 20,122 (10,061:10,061) subjects was calculated to yield 80% power for the primary efficacy endpoint based on CDC case definition. Part 1 was to enroll 11,500 (5,750:5,750) subjects, while Part 2 was to enroll

8,622 (4,311:4,311) subjects. The sample size calculation assumed an attack rate of 13.5% in the mRNA-1273 group, an rVE of 3%, a dropout rate of 10%, and a target number of 2,087 cases.

If the null hypothesis of the primary efficacy endpoint was not rejected at the IA and the conditional power was ≥ 0.35 and < 0.8, the sample size for Part 2 was to be increased to 22,074 (11,037:11,037) subjects. The sample size increase assumed an attack rate of 13.5% in the mRNA-1273 group, an rVE of 0%, a dropout rate of 10%, and a target number of 3,500 cases.

Control of Type I Error with Different Sample Sizes for Part 2

The IA was to use the conventional Wald test statistic $Z_1$. For the final analysis, if the sample size of Part 2 was to be increased from 8,622 subjects to 22,074 subjects (corresponding to a total number of events expected to be observed from 2,087 to 3,500), the conventional Wald test statistic $Z$ was to be replaced with the CHW test statistic $Z_{CHW}$ to control the type I error rate (Cui, Hung, and Wang 1999; Mehta and Pocock 2011). The formula for $Z_{CHW}$ is given below.

$$Z_{CHW} = \sqrt{\frac{n_1}{n_2}} Z_1 + \sqrt{\frac{n_2 - n_1}{n_2}} Z_2^*$$

$$Z_2^* = \frac{Z - \sqrt{\frac{n_1}{n_3}} Z_1}{\sqrt{\frac{n_3 - n_1}{n_3}}}$$

Where $n_1$ was the pre-specified number of events expected to be observed at the IA, $n_2$ was the pre-specified total number of events expected to be observed at the final analysis if 8,622 subjects were enrolled in Part 2, $n_3$ was the pre-specified total number of events expected to be observed at the final analysis if 22,074 subjects were enrolled in Part 2, $Z_1$ was the test statistic at the IA, and $Z$ was the unadjusted test statistic at the final analysis after enrollment of Part 2. For Study P301, $n_1 = 700, n_2 = 2{,}087$, and $n_3 = 3{,}500$.

References

1. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999 Sep;55(3):853-7.

2. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statist. Med. Dec 2011; 30 (28); 3267-84.

### 6.1.10 Study Population and Disposition

Table 3 displays the sample size in each analysis set for both the mRNA-1283.222 and mRNA-1273.222 groups. Totals of 5,679 (99.1%) and 5,687 (99.3%) participants in the mRNA-1283.222 and mRNA-1273.222 groups, respectively, met the criteria for inclusion in the PPSE. Totals of 621 (10.8%) and 568 (9.9%) participants in the mRNA-1283.222 and mRNA-1273.222 groups, respectively, met the criteria for inclusion in the PPIS.

Table 4 displays the dispositions of the RS for both the mRNA-1283.222 and mRNA-1273.222 groups, where totals of 5,728 and 5,726 participants were randomized and 5,706 (99.6%) and 5,711 (99.7%) participants received a study intervention, respectively.

Table 5 displays the distributions of the demographic characteristics of the SS for both the mRNA-1283.222 and mRNA-1273.222 groups, where totals of 5,706 and 5,711 participants were included, respectively. No meaningful differences in demographic characteristics were observed between the two groups. Demographic characteristics were generally similar in both the PPSE and PPIS.

Table 3: Number of Participants in Each Analysis Set

| - | **mRNA-1283.222** | **mRNA-1273.222** |
|---|---|---|
| **Randomization Set, n** | 5728 | 5726 |
| Full Analysis Set, n (%)[a] | 5706 (99.6) | 5711 (99.7) |
| Per-Protocol Set for Efficacy, n (%)[a] | 5679 (99.1) | 5687 (99.3) |
| Immunogenicity Set, n (%)[a] | 678 (11.8) | 622 (10.9) |
| Per-Protocol Immunogenicity Set, n (%)[a] | 621 (10.8) | 568 (9.9) |
| Safety Set[a] | 5706 (99.6) | 5711 (99.7) |
| Solicited Safety Set, n (%)[a] | 5702 (99.5) | 5706 (99.7) |

[a]Numbers were based on planned vaccination group, and percentages were based on the number of randomized participants.
*Source: Table 10 from P301 Clinical Study Report.*

Table 4: Participant Disposition (RS)

| - | **mRNA-1283.222 N = 5728** | **mRNA-1273.222 N = 5726** |
|---|---|---|
| **Number of Participants who Received Vaccine** | 5706 (99.6) | 5711 (99.7) |
| Ongoing | 5445 (95.1) | 5497 (96.0) |
| Discontinued | 261 (4.6) | 214 (3.7) |
| **Reason For Discontinuation** | - | - |
| Withdrawal of Consent by Participant | 144 (2.5) | 119 (2.1) |
| Lost to Follow-Up | 92 (1.6) | 70 (1.2) |
| Investigator Decision | 11 (0.2) | 10 (0.2) |
| Fatal event | 5 (0.1) | 10 (0.2) |
| Adverse Event | 3 (0.1) | 2 (<0.1) |
| Protocol Deviation | 2 (<0.1) | 1 (<0.1) |
| Pregnancy | 1 (<0.1) | 0 |
| Other | 3 (0.1) | 2 (<0.1) |

*Source: Table 9 from P301 Clinical Study Report.*

Table 5: Baseline Demographics and Characteristics (SS)

| - | **mRNA-1283.222 N = 5706** | **mRNA-1273.222 N = 5711** |
|---|---|---|
| **Age (Years)** | - | - |
| N | 5706 | 5711 |
| Mean (SD) | 51.1 (18.58) | 51.2 (18.32) |
| Median | 56.0 | 55.0 |
| Q1, Q3 | 38.0, 66.0 | 39.0, 66.0 |
| Min, Max | 12, 96 | 12, 90 |
| **Age Group, n (%)** | - | - |
| ≥12 to <18 Years | 497 (8.7) | 495 (8.7) |
| ≥18 Years | 5209 (91.3) | 5216 (91.3) |
| ≥18 to <65 Years | 3575 (62.7) | 3576 (62.6) |
| ≥65 Years | 1634 (28.6) | 1640 (28.7) |
| ≥75 Years | 322 (5.6) | 269 (4.7) |
| **Sex, n (%)** | - | - |
| Male | 2586 (45.3) | 2631 (46.1) |
| Female | 3120 (54.7) | 3080 (53.9) |
| **Race, n (%)** | - | - |
| White | 4670 (81.8) | 4711 (82.5) |
| Black or African American | 640 (11.2) | 635 (11.1) |
| Asian | 225 (3.9) | 183 (3.2) |
| American Indian or Alaska Native | 20 (0.4) | 26 (0.5) |
| Native Hawaiian or Other Pacific Islander | 9 (0.2) | 6 (0.1) |
| Multiple | 81 (1.4) | 94 (1.6) |
| Other | 20 (0.4) | 20 (0.4) |
| Not Reported | 36 (0.6) | 26 (0.5) |
| Unknown | 5 (0.09) | 10 (0.2) |
| **Ethnicity, n (%)** | - | - |
| Hispanic or Latino | 769 (13.5) | 741 (13.0) |
| Not Hispanic or Latino | 4860 (85.2) | 4864 (85.2) |
| Not Reported | 59 (1.0) | 87 (1.5) |
| Unknown | 18 (0.3) | 19 (0.3) |
| **Body Mass Index ($kg/m^2$)** | - | - |
| N | 5644 | 5645 |
| Mean (SD) | 29.45 (7.167) | 29.50 (7.331) |
| Median | 28.30 | 28.30 |
| Q1, Q3 | 24.40, 33.30 | 24.40, 33.30 |
| Min, Max | 14.4, 81.9 | 14.6, 76.7 |
| **Body Mass Index Group, n (%)** | - | - |
| <30 $kg/m^2$ | 3338 (58.5) | 3372 (59.0) |
| ≥30 $kg/m^2$ | 2306 (40.4) | 2273 (39.8) |
| ≥40 $kg/m^2$ | 451 (7.9) | 489 (8.6) |
| Missing | 62 (1.1) | 66 (1.2) |
| **Geographic Region, n (%)** | - | - |
| North America | 4424 (77.5) | 4424 (77.5) |
| Europe | 1282 (22.5) | 1287 (22.5) |
| **Country, n (%)** | - | - |
| United States | 4323 (75.8) | 4312 (75.5) |
| Canada | 101 (1.8) | 112 (2.0) |
| United Kingdom | 1282 (22.5) | 1287 (22.5) |

Table 5: Baseline Demographics and Characteristics (SS) (continued)

| - | **mRNA-1283.222 N = 5706** | **mRNA-1273.222 N = 5711** |
|---|---|---|
| **Baseline SARS-CoV-2 Status, n (%)[a]** | - | - |
| Negative | 1402 (24.6) | 1372 (24.0) |
| Positive | 4211 (73.8) | 4270 (74.8) |
| Missing | 93 (1.6) | 69 (1.2) |
| **Baseline RT-PCR Status, n (%)** | - | - |
| Negative | 5491 (96.2) | 5511 (96.5) |
| Positive | 64 (1.1) | 73 (1.3) |
| Missing | 151 (2.6) | 127 (2.2) |
| **Baseline Anti-nucleocapsid Antibody Status, n (%)** | - | - |
| Negative | 1446 (25.3) | 1413 (24.7) |
| Positive | 4200 (73.6) | 4257 (74.5) |
| Missing | 60 (1.1) | 41 (0.7) |
| **Number of Prior COVID-19 Vaccine Doses, n (%)** | - | - |
| 0 | 1 (0.02) | 0 |
| 1 | 7 (0.1) | 1 (0.02) |
| 2 | 335 (5.9) | 324 (5.7) |
| 3 | 2243 (39.3) | 2253 (39.5) |
| 4 | 2210 (38.7) | 2250 (39.4) |
| 5 | 903 (15.8) | 882 (15.4) |
| ≥6 | 6 (0.1) | 1 (0.02) |
| Missing | 1 (0.02) | 0 |
| **Number of Prior COVID-19 Booster Doses, n (%)** | - | - |
| 0 | 218 (3.8) | 188 (3.3) |
| 1 | 2131 (37.3) | 2139 (37.5) |
| 2 | 1889 (33.1) | 1905 (33.4) |
| ≥3 | 1451 (25.4) | 1472 (25.8) |
| Missing | 17 (0.3) | 7 (0.1) |
| **Type of Last Prior COVID-19 Vaccine, n (%)** | - | - |
| mRNA Original Monovalent | 2605 (45.7) | 2618 (45.8) |
| mRNA Omicron Bivalent[b] | 2882 (50.5) | 2900 (50.8) |
| non-mRNA Vaccine | 204 (3.6) | 181 (3.2) |
| No Prior COVID-19 Vaccine[c] | 1 (0.02) | 0 |
| Unknown | 13 (0.2) | 12 (0.2) |
| Missing | 1 (0.02) | 0 |
| **Dosing Interval from Last Prior Dose COVID-19 Vaccine to Study Vaccine Day (months)[d]** | - | - |
| N | 5704 | 5711 |
| Mean (SD) | 11.92 (5.343) | 11.87 (5.160) |
| Median | 9.79 | 9.82 |
| Q1, Q3 | 7.59, 16.92 | 7.69, 16.72 |
| **Dosing Interval Group from Last Prior Dose COVID-19 Vaccine to Study Vaccine Day (months), n (%)[d]** | - | - |
| < Median | 2859 (50.1) | 2848 (49.9) |
| ≥ Median | 2845 (49.9) | 2863 (50.1) |

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

[b]Participants with last mRNA COVID-19 vaccine dose date as 1 September 2022 or later.

[c]One participant with no prior COVID-19 vaccine was enrolled into the study by error, this was a protocol deviation.
[d]Dosing interval from last prior dose of COVID-19 vaccine to investigational vaccine (months) = (Date of vaccine – date of last prior dose of COVID-19 vaccine +1) / 30.4375. The median (months) is based on the median across all participants (9.82 months).
*Source: Tables 11 and 12 from P301 Clinical Study Report.*

### 6.1.11 Immunogenicity and Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoints

##### 6.1.11.1.1 Primary Immunogenicity Endpoints

Table 6 displays the Day 29 geometric least squares means (GLSMs), GMRs, and SRRs for both Omicron BA.4/5 and ancestral SARS-CoV-2 D614G. The adjusted anti-Omicron BA.4/5 GMR was 1.3 with 95% CI = 1.2 to 1.5, while the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.1 to 1.4. The anti-Omicron BA.4/5 SRR difference was 14.4% with 95% CI = 9.3% to 19.4%, while the anti-ancestral SARS-CoV-2 D614G SRR difference was 10.7% with 95% CI = 6.0% to 15.4%. The co-primary immunogenicity endpoints met their respective success criteria for non-inferiority; thus, $\alpha = 0.05$ was propagated to the evaluation of the primary efficacy endpoint.

Tables 7, 8, and 9 display the Day 29 GLSMs, GMRs, and SRRs for both Omicron BA.4/5 and ancestral SARS-CoV-2 D614G for age categories 12 to < 18 YOA, 18 to < 65 YOA, and ≥ 65 YOA, respectively. For each age category, both the adjusted anti-Omicron BA.4/5 GMR and adjusted anti-ancestral SARS-CoV-2 D614G GMR were ≥ 1. For age category ≥ 65 YOA, both the adjusted anti-Omicron BA.4/5 GMR and adjusted anti-ancestral SARS-CoV-2 D614G GMR were ≥ 1.5. For each age category, both the anti-Omicron BA.4/5 SRR difference and anti-ancestral SARS-CoV-2 D614G SRR difference were > 0%.

*Reviewer's Comment:*

- *The immunogenicity (Sections 6.1.11 and 6.2.11), efficacy (Section 6.1.12), and safety (Sections 6.1.13 and 6.2.12) analyses were verified based on data submitted in the Study Data Tabulation Model format, and the results were consistent with those reported by the Applicant.*

Table 6: Summary of PsVNA Titer against both Omicron BA.4/5 and Ancestral SARS-CoV-2 D614G at Day 29 (PPIS)

| - | **mRNA-1283.222** | **mRNA-1273.222** |
|---|---|---|
| N | 621 | 568 |
| Omicron BA.4/5 | - | - |
| GLSM (95% CI)[a] | 2340.9 (2167.0, 2528.8) | 1753.8 (1618.2, 1900.7) |
| GMR (95% CI)[a] | 1.3 (1.2, 1.5) | - |
| SRR, % (95% CI)[b] | 496/621<br>79.9 (76.5, 83.0) | 372/568<br>65.5 (61.4, 69.4) |
| SRR difference, % (95% CI)[c] | 14.4 (9.3, 19.4) | - |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 10631.9 (9960.2, 11348.9) | 8576.5 (8012.5, 9180.1) |
| GMR (95% CI)[a] | 1.2 (1.1, 1.4) | - |
| SRR, % (95% CI)[b] | 519/621<br>83.6 (80.4, 86.4) | 414/568<br>72.9 (69.0, 76.5) |
| SRR difference, % (95% CI)[c] | 10.7 (6.0, 15.4) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, age category, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from both Tables 22 and 23 from P301 Clinical Study Report.*

*Reviewer's Comment:*

- *For both Omicron BA.4/5 and ancestral SARS-CoV-2 D614G, titers above the ULOQ were not imputed to the ULOQ. At Day 29, for Omicron BA.4/5, 4/621 and 0/568 subjects in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, had titers > ULOQ. At Day 29, for ancestral SARS-CoV-2 D614G, 4/621 and 1/568 subjects in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, had titers > ULOQ. I conducted sensitivity analyses of the GMRs imputing the ULOQ for titers > ULOQ. Compared to no imputation, both the point estimates and 95% CIs of both the adjusted anti-Omicron BA.4/5 GMR and adjusted anti-ancestral SARS-CoV-2 D614G GMR were approximately equal. Therefore, the results of the sensitivity analyses supported the immunobridging conclusions.*

Table 7: Summary of PsVNA Titer against both Omicron BA.4/5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects 12 to < 18 YOA (PPIS)

| - | **mRNA-1283.222** | **mRNA-1273.222** |
|---|---|---|
| N | 91 | 93 |
| Omicron BA.4/5 | - | - |
| GLSM (95% CI)[a] | 3561.4 (3037.5, 4175.7) | 3398.9 (2908.9, 3971.4) |
| GMR (95% CI)[a] | 1.0 (0.8, 1.3) | - |
| SRR, % (95% CI)[b] | 80/91<br>87.9 (79.4, 93.8) | 75/93<br>80.6 (71.1, 88.1) |
| SRR difference, % (95% CI)[c] | 7.3 (-3.4, 18.0) | - |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 13617.7 (12006.3, 15445.3) | 12404.3 (10966.5, 14030.6) |
| GMR (95% CI)[a] | 1.1 (0.9, 1.3) | - |
| SRR, % (95% CI)[b] | 78/91<br>85.7 (76.8, 92.2) | 69/93<br>74.2 (64.1, 82.7) |
| SRR difference, % (95% CI)[c] | 11.5 (-0.1, 23.1) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from Tables 24, 25, and 14.2.1.1.4.3 from P301 Clinical Study Report.*

Table 8: Summary of PsVNA Titer against both Omicron BA.4/5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects 18 to < 65 YOA (PPIS)

| - | **mRNA-1283.222** | **mRNA-1273.222** |
|---|---|---|
| N | 378 | 316 |
| Omicron BA.4/5 | - | - |
| GLSM (95% CI)[a] | 2120.6 (1917.3, 2345.6) | 1661.0 (1487.8, 1854.4) |
| GMR (95% CI)[a] | 1.3 (1.1, 1.5) | - |
| SRR, % (95% CI)[b] | 301/378<br>79.6 (75.2, 83.6) | 201/316<br>63.6 (58.0, 68.9) |
| SRR difference, % (95% CI)[c] | 16.0 (9.3, 22.7) | - |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 9734.8 (8938.8, 10601.7) | 8251.3 (7517.2, 9057.1) |
| GMR (95% CI)[a] | 1.2 (1.0, 1.3) | - |
| SRR, % (95% CI)[b] | 314/378<br>83.1 (78.9, 86.7) | 240/316<br>75.9 (70.8, 80.6) |
| SRR difference, % (95% CI)[c] | 7.1 (1.1, 13.2) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from Tables 24, 25, and 14.2.1.1.4.3 from P301 Clinical Study Report.*

Table 9: Summary of PsVNA Titer against both Omicron BA.4/5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects ≥ 65 YOA (PPIS)

| - | **mRNA-1283.222** | **mRNA-1273.222** |
|---|---|---|
| N | 152 | 159 |
| Omicron BA.4/5 | - | - |
| GLSM (95% CI)[a] | 2339.5 (1984.3, 2758.3) | 1326.8 (1130.0, 1557.7) |
| GMR (95% CI)[a] | 1.8 (1.4, 2.2) | - |
| SRR, % (95% CI)[b] | 115/152<br>75.7 (68.0, 82.2) | 96/159<br>60.4 (52.3, 68.0) |
| SRR difference, % (95% CI)[c] | 15.3 (4.9, 25.3) | - |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 11451.1 (9936.3, 13196.9) | 7463.3 (6499.4, 8570.1) |
| GMR (95% CI)[a] | 1.5 (1.3, 1.9) | - |
| SRR, % (95% CI)[b] | 127/152<br>83.6 (76.7, 89.1) | 105/159<br>66.0 (58.1, 73.4) |
| SRR difference, % (95% CI)[c] | 17.5 (8.0, 26.9) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from Tables 24, 25, and 14.2.1.1.4.3 from P301 Clinical Study Report.*

### 6.1.11.1.2 Primary Efficacy Endpoint

*Interim Analyses*

Table 10 displays the results of the interim analyses for both the primary (including by age category for CDC case definition) and secondary efficacy endpoints up to the data cutoff of 31 Jan 2024. The median follow-up was 244 days in both groups.

For CDC case definition, 560 and 617 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 9.3% with 2-sided 99.4% CI = -6.6% to 22.8%. The alpha value of 0.6% for the 2-sided CI was derived from the Lan-DeMets approximation to the O'Brien-Fleming stopping boundary with an information fraction of 0.56 (1,177 out of a total of 2,087 cases). Because the LL of the 2-sided CI was above -10%, the success criterion for the primary efficacy endpoint was met.

For protocol-defined COVID-19 case definition, 498 and 556 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 10.5% with 2-sided 95% CI = -1.0% to 20.7%.

For the modified CDC case definition, 634 and 693 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 8.6% with 2-sided 95% CI = -1.8% to 17.9%.

*Supportive Analyses*

Table 11 displays the results of the supportive analyses for both the primary (including by age category for CDC case definition) and secondary efficacy endpoints up to the data cutoff of 23 Feb 2024. The median follow-up was 267 days in both groups.

For the primary efficacy endpoint, the results of the supportive analyses were generally similar to the results of the interim analyses.

#### 6.1.11.2 Analyses of Secondary Endpoints

##### 6.1.11.2.1 Secondary Efficacy Endpoints

*Interim Analyses*

For SARS-CoV-2 infection, 894 and 942 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 5.1% with 2-sided 95% CI = -4.0% to 13.4%.

For asymptomatic SARS-CoV-2 infection, 333 and 321 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was -3.8% with 2-sided 95% CI = -21.0% to 11.0%.

For severe COVID-19 case definition, 21 and 34 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 38.1% with 2-sided 95% CI = -6.7% to 64.1%.

*Supportive Analyses*

For the secondary efficacy endpoints, the results of the supportive analyses were generally similar to the results of the interim analyses.

#### 6.1.11.3 Subpopulation Analyses

##### 6.1.11.3.1 Primary Immunogenicity Endpoints

Across the subgroups of sex, race, ethnicity, country, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine, no meaningful differences in adjusted GMRs or SRR differences were observed for either Omicron BA.4/5 or ancestral SARS-CoV-2 D614G (not shown in tables).

##### 6.1.11.3.2 Primary Efficacy Endpoint

*Interim Analyses*

For CDC case definition, rVEs are presented by age category.

For subjects 12 to < 18 YOA, 29 and 23 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was -29.2% with 2-sided 95% CI = -123.3% to 25.3%.

For subjects 18 to < 65 YOA, 382 and 422 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 9.7% with 2-sided 95% CI = -3.8% to 21.3%.

For subjects ≥ 65 YOA, 149 and 172 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE was 13.5% with 2-sided 95% CI = -7.7% to 30.6%.

For CDC case definition, across the other subgroups of sex, race, ethnicity, country, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine, no meaningful differences in rVEs were observed (not shown in tables).

*Supportive Analyses*

For the primary efficacy endpoint, the results of the supportive subgroup analyses were generally similar to the results of the interim subgroup analyses (only age category is shown in Table 11, other subgroup analyses are not shown in tables).

Table 10: rVE Based on HR of mRNA-1283.222 versus mRNA-1273.222 to Prevent First Episode of COVID-19 According to Various Case Definitions: CDC (with Subgroup Analyses by Age Category), Protocol-defined COVID-19, Modified CDC, SARS-CoV-2 Infection, Asymptomatic SARS-CoV-2 Infection, and Severe COVID-19 (PPSE) — Interim Efficacy Analyses

| **Case Definition** | **mRNA-1283.222 N** | **mRNA-1283.222 Cases** | **mRNA-1273.222 N** | **mRNA-1273.222 Cases** | **VE[a] (% CI[b])** |
|---|---|---|---|---|---|
| CDC | 5679 | 560 | 5687 | 617 | 9.3 (-6.6, 22.8) |
| 12 to < 18 YOA | 491 | 29 | 490 | 23 | -29.2 (-123.3, 25.3) |
| 18 to < 65 YOA | 3558 | 382 | 3562 | 422 | 9.7 (-3.8, 21.3) |
| ≥ 65 YOA | 1630 | 149 | 1635 | 172 | 13.5 (-7.7, 30.6) |
| Protocol-defined COVID-19 | 5679 | 498 | 5687 | 556 | 10.5 (-1.0, 20.7) |
| Modified CDC | 5679 | 634 | 5687 | 693 | 8.6 (-1.8, 17.9) |
| SARS-CoV-2 infection | 5679 | 894 | 5687 | 942 | 5.1 (-4.0, 13.4) |
| Asymptomatic SARS-CoV-2 infection | 5679 | 333 | 5687 | 321 | -3.8 (-21.0, 11.0) |
| Severe COVID-19 | 5679 | 21 | 5687 | 34 | 38.1 (-6.7, 64.1) |

[a]VE = 100 * (1 – HR), where HR was estimated from the stratified Cox PH model with vaccine group as a fixed effect. For the overall analyses for each COVID-19 case definition, age category (12 to <18 years, 18 to <65 years, or ≥65 years) was included as a stratification factor. For the subgroup analyses by age category, no stratification factors were included.

[b]For CDC case definition, 99.4% CI where the alpha value of 0.6% was derived from the Lan-DeMets approximation to the O'Brien-Fleming stopping boundary with an information fraction of 0.56 (1,177 out of a total of 2,087 cases). For all other case definitions and subgroup analyses, 95% CI.

*Source: Adapted from Tables 14, 16, 18, 21, and 30 from P301 Clinical Study Report and Table A from Response to IR 6.*

Table 11: rVE based on HR of mRNA-1283.222 versus mRNA-1273.222 to Prevent First Episode of COVID-19 According to Various Case Definitions: CDC (with Subgroup Analyses by Age Category), Protocol-defined COVID-19, Modified CDC, SARS-CoV-2 Infection, Asymptomatic SARS-CoV-2 Infection, and Severe COVID-19 (PPSE) — Supportive Efficacy Analyses

| Case Definition | mRNA-1283.222 N | mRNA-1283.222 Cases | mRNA-1273.222 N | mRNA-1273.222 Cases | VE[a] (95% CI) |
|---|---|---|---|---|---|
| CDC | 5679 | 613 | 5687 | 661 | 7.3 (-3.4, 17.0) |
| 12 to < 18 YOA | 491 | 37 | 490 | 28 | -35.3 (-121.1, 17.2) |
| 18 to < 65 YOA | 3558 | 414 | 3562 | 452 | 8.7 (-4.4, 20.1) |
| ≥ 65 YOA | 1630 | 162 | 1635 | 181 | 10.6 (-10.6, 27.7) |
| Protocol-defined COVID-19 | 5679 | 546 | 5687 | 599 | 8.9 (-2.3, 18.9) |
| Modified CDC | 5679 | 697 | 5687 | 749 | 7.0 (-3.1, 16.1) |
| SARS-CoV-2 infection | 5679 | 959 | 5687 | 997 | 3.8 (-5.1, 12.0) |
| Asymptomatic SARS-CoV-2 infection | 5679 | 345 | 5687 | 333 | -3.7 (-20.5, 10.8) |
| Severe COVID-19 | 5679 | 23 | 5687 | 36 | 35.9 (-8.2, 62.0) |

[a]VE = 100 * (1 – HR), where HR was estimated from the stratified Cox PH model with vaccine group as a fixed effect. For the overall analyses for each COVID-19 case definition, age category (12 to <18 years, 18 to <65 years, or ≥65 years) was included as a stratification factor. For the subgroup analyses by age category, no stratification factors were included.
*Source: Adapted from Tables 15, 17, 14.2.2.1.2.1, 14.2.2.2.2.1, and 14.2.2.5.2.1 from P301 Clinical Study Report and Table A from Response to IR 6.*

### 6.1.12 Safety Analyses

*Solicited ARs*

Table 12 displays both local and systemic ARs by age category within 7 days post-injection in the SSS.

Rates of solicited local ARs were slightly lower in the mRNA-1283.222 group than the mRNA-1273.222 group and slightly lower for participants aged ≥65 years compared to participants aged ≥12 to <18 years and ≥18 to <65 years. Across both vaccines and age categories, injection site pain was the most frequently reported solicited local AR.

Rates of solicited systemic ARs were generally similar between the mRNA-1283.222 group and the mRNA-1273.222 group and slightly lower for participants aged ≥65 years compared to participants aged ≥12 to <18 years and ≥18 to <65 years. Across the vaccines, fatigue was the most frequently reported solicited systemic AR. Across age categories, headache was the most frequently reported solicited systemic AR among participants aged ≥12 to <18 years, while fatigue was the most frequently reported solicited systemic AR among participants aged ≥18 to <65 years and ≥65 years.

One Grade 4 solicited AR was reported, i.e. a solicited systemic AR of Grade 4 fever in the mRNA-1273.222 group.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, rates of local and systemic ARs were generally higher among female participants, white participants, and non-Hispanic or Latino participants. Across the subgroups of country, geographic region, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine, no meaningful differences in the rates of local or systemic ARs were observed in either group (not shown in tables).

*Unsolicited AEs up to 28 days post-injection*

Table 13 displays unsolicited AEs up to 28 days post-injection in the SS.

For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1283.222 group to the mRNA-1273.222 group, there were similar percentages of unsolicited AEs (12.3% and 11.9%, respectively), SAEs (0.2% and 0.3%, respectively), MAAEs (7.4% and 7.4%, respectively), Grade 3 unsolicited AEs (0.2% and 0.3%, respectively), and AESIs (0.1% and 0.1%, respectively). One death and one unsolicited AE leading to study discontinuation (same subject) were reported in the mRNA-1273.222 group while none were reported in the mRNA-1283.222 group. No events of myocarditis or pericarditis were reported.

For unsolicited AEs considered by the investigator to be related to study vaccination, comparing the mRNA-1283.222 group to the mRNA-1273.222 group, there were similar percentages of unsolicited AEs (0.8% and 0.9%, respectively), SAEs (<0.1% and <0.1%, respectively), MAAEs (0.2% and 0.2%, respectively), and Grade 3 unsolicited AEs (0.1% and <0.1%, respectively). One related AESI (possible anaphylaxis) was reported in the mRNA-1283.222 group while none were reported in the mRNA-1273.222 group. The death and unsolicited AE leading to study discontinuation (same subject) reported in the mRNA-1273.222 group were considered to be related and occurred in a subject on Day 7 post-injection with cause of death reported as unknown. Due to temporality, the investigator considered the death to be related. However, the Applicant assessed the death as unrelated given the subject's long term cardiovascular history.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, across the subgroups of age category, no meaningful differences in the rates of unsolicited AEs were observed (not shown in tables).

*Unsolicited AEs up to data cutoff of 23 Feb 2024*

Table 14 displays unsolicited AEs up to the data cutoff of 23 Feb 2024 in the SS. The median follow-up was 267 days in both groups.

For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1283.222 group to the mRNA-1273.222 group, there were similar percentages of unsolicited AEs (36.8% and 35.8%, respectively), SAEs (2.7% and 2.6%, respectively), deaths (0.1% and 0.2%, respectively), MAAEs (33.9% and 33.0%, respectively), unsolicited AEs leading to study discontinuation (0.1% and 0.2%, respectively), Grade 3 unsolicited AEs (2.3% and 2.3%, respectively), and AESIs (1.1% and 1.1%, respectively). One event of pericarditis was reported in the mRNA-1273.222 group on Day 136 post-injection while none were reported in the mRNA-1283.222 group. No events of myocarditis were reported.

For unsolicited AEs considered by the investigator to be related to study vaccination, comparing the mRNA-1283.222 group to the mRNA-1273.222 group, there were similar percentages of unsolicited AEs (0.8% and 0.9%, respectively), SAEs (<0.1% and <0.1%, respectively), MAAEs (0.2% and 0.2%, respectively), and Grade 3 unsolicited AEs (0.1% and <0.1%, respectively). No additional related deaths, related unsolicited AEs leading to study discontinuation, or related AESIs were reported beyond 28 days post-injection. The event of pericarditis reported in the mRNA-1273.222 group was not considered to be related.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, across the subgroups of age category, no meaningful differences in the rates of unsolicited AEs were observed (not shown in tables).

Table 12: Summary of Participants With Solicited Adverse Reactions Within 7 Days Post-Injection by Age Category (SSS)

| **Event** | **mRNA-1283.222 ≥12-<18 years N=497 n (%)** | **mRNA-1273.222 ≥12-<18 years N=495 n (%)** | **mRNA-1283.222 ≥18-<65 years N=3573 n (%)** | **mRNA-1273.222 ≥18-<65 years N=3574 n (%)** | **mRNA-1283.222 ≥65 years N=1632 n (%)** | **mRNA-1273.222 ≥65 years N=1637 n (%)** |
|---|---|---|---|---|---|---|
| Local ARs, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Local ARs, Any Grade | 355 (71.4) | 395 (79.8) | 2732 (76.5) | 2957 (82.8) | 920 (56.4) | 1121 (68.5) |
| Local ARs, Grade 3 | 15 (3.0) | 21 (4.2) | 61 (1.7) | 80 (2.2) | 16 (1.0) | 21 (1.3) |
| Pain, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Pain, Any Grade | 342 (68.8) | 390 (78.8) | 2672 (74.8) | 2920 (81.7) | 891 (54.6) | 1109 (67.7) |
| Pain, Grade 3[a] | 10 (2.0) | 19 (3.8) | 38 (1.1) | 49 (1.4) | 12 (0.7) | 7 (0.4) |
| Erythema (redness), n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Erythema (redness), Any Grade | 6 (1.2) | 13 (2.6) | 85 (2.4) | 152 (4.3) | 32 (2.0) | 60 (3.7) |
| Erythema (redness), Grade 3[b] | 0 | 0 | 9 (0.3) | 17 (0.5) | 2 (0.1) | 7 (0.4) |
| Swelling (hardness), n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Swelling (hardness), Any Grade | 18 (3.6) | 25 (5.1) | 140 (3.9) | 246 (6.9) | 48 (2.9) | 88 (5.4) |
| Swelling (hardness), Grade 3[b] | 4 (0.8) | 2 (0.4) | 11 (0.3) | 19 (0.5) | 1 (0.06) | 11 (0.7) |
| Axillary swelling/tenderness, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Axillary swelling/tenderness, Any Grade | 172 (34.6) | 134 (27.1) | 777 (21.7) | 749 (21.0) | 174 (10.7) | 164 (10.0) |
| Axillary swelling/tenderness, Grade 3[a] | 6 (1.2) | 2 (0.4) | 11 (0.3) | 15 (0.4) | 2 (0.1) | 2 (0.1) |
| Systemic ARs, n | 497 | 495 | 3573 | 3574 | 1632 | 1637 |
| Systemic ARs, Any Grade | 336 (67.6) | 352 (71.1) | 2439 (68.3) | 2416 (67.6) | 897 (55.0) | 896 (54.7) |
| Systemic ARs, Grade 3 | 71 (14.3) | 44 (8.9) | 259 (7.2) | 225 (6.3) | 78 (4.8) | 60 (3.7) |
| Systemic ARs, Grade 4 | 0 | 0 | 0 | 0 | 0 | 1 (0.06) |
| Fever, n | 496 | 494 | 3572 | 3570 | 1629 | 1635 |
| Fever, Any Grade | 49 (9.9) | 46 (9.3) | 193 (5.4) | 138 (3.9) | 75 (4.6) | 70 (4.3) |
| Fever, Grade 3[c] | 4 (0.8) | 2 (0.4) | 27 (0.8) | 17 (0.5) | 2 (0.1) | 9 (0.6) |
| Fever, Grade 4[d] | 0 | 0 | 0 | 0 | 0 | 1 (0.06) |
| Headache, n | 497 | 495 | 3573 | 3573 | 1632 | 1637 |
| Headache, Any Grade | 271 (54.5) | 287 (58.0) | 1708 (47.8) | 1583 (44.3) | 540 (33.1) | 479 (29.3) |
| Headache, Grade 3[a] | 35 (7.0) | 20 (4.0) | 90 (2.5) | 76 (2.1) | 22 (1.3) | 22 (1.3) |
| Fatigue, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Fatigue, Any Grade | 235 (47.3) | 251 (50.7) | 1939 (54.3) | 1876 (52.5) | 702 (43.0) | 671 (41.0) |
| Fatigue, Grade 3[a] | 34 (6.8) | 22 (4.4) | 170 (4.8) | 156 (4.4) | 59 (3.6) | 41 (2.5) |

Table 12: Summary of Participants With Solicited Adverse Reactions Within 7 Days Post-Injection by Age Category (SSS) (continued)

| Event | mRNA-1283.222 ≥12-<18 years N=497 n (%) | mRNA-1273.222 ≥12-<18 years N=495 n (%) | mRNA-1283.222 ≥18-<65 years N=3573 n (%) | mRNA-1273.222 ≥18-<65 years N=3574 n (%) | mRNA-1283.222 ≥65 years N=1632 n (%) | mRNA-1273.222 ≥65 years N=1637 n (%) |
|---|---|---|---|---|---|---|
| Myalgia, n | 497 | 495 | 3573 | 3574 | 1631 | 1637 |
| Myalgia, Any Grade | 195 (39.2) | 178 (36.0) | 1485 (41.6) | 1469 (41.1) | 498 (30.5) | 467 (28.5) |
| Myalgia, Grade 3[a] | 28 (5.6) | 17 (3.4) | 144 (4.0) | 105 (2.9) | 33 (2.0) | 27 (1.6) |
| Arthralgia, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Arthralgia, Any Grade | 119 (23.9) | 117 (23.6) | 1159 (32.4) | 1094 (30.6) | 418 (25.6) | 366 (22.4) |
| Arthralgia, Grade 3[a] | 10 (2.0) | 6 (1.2) | 86 (2.4) | 62 (1.7) | 24 (1.5) | 21 (1.3) |
| Nausea/vomiting, n | 497 | 495 | 3573 | 3574 | 1631 | 1637 |
| Nausea/vomiting, Any Grade | 80 (16.1) | 87 (17.6) | 492 (13.8) | 424 (11.9) | 119 (7.3) | 114 (7.0) |
| Nausea/vomiting, Grade 3[e] | 0 | 2 (0.4) | 4 (0.1) | 3 (0.08) | 2 (0.1) | 5 (0.3) |
| Chills, n | 497 | 495 | 3573 | 3573 | 1631 | 1637 |
| Chills, Any Grade | 157 (31.6) | 158 (31.9) | 867 (24.3) | 760 (21.3) | 269 (16.5) | 209 (12.8) |
| Chills, Grade 3[f] | 6 (1.2) | 1 (0.2) | 26 (0.7) | 22 (0.6) | 10 (0.6) | 8 (0.5) |

[a]Grade 3 pain, axillary swelling/tenderness, headache, fatigue, myalgia, arthralgia: Defined as prevents daily activity.
[b]Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[c]Grade 3 fever: Defined as ≥ 39.0° – ≤ 40.0°C / ≥ 102.1° – ≤ 104.0°F.
[d]Grade 4 fever: Defined as > 40.0°C / > 104.0°F.
[e]Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration
[f]Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
*Source: Table 36 from P301 Clinical Study Report.*

Table 13: Summary of Unsolicited AEs up to 28 Days Post-Injection (SS)

| - | **mRNA-1283.222 N=5706 n (%)** | **mRNA-1273.222 N=5711 n (%)** |
|---|---|---|
| Unsolicited AEs regardless of relationship to study vaccination | - | - |
| All | 701 (12.3) | 680 (11.9) |
| Serious | 13 (0.2) | 18 (0.3) |
| Fatal | 0 | 1 (<0.1) |
| Medically attended | 425 (7.4) | 422 (7.4) |
| Leading to study discontinuation | 0 | 1 (<0.1) |
| Grade 3 | 13 (0.2) | 18 (0.3) |
| AESI | 3 (0.1) | 6 (0.1) |
| Unsolicited AEs related to study vaccination | - | - |
| All | 45 (0.8) | 51 (0.9) |
| Serious | 1 (<0.1) | 1 (<0.1) |
| Fatal | 0 | 1 (<0.1) |
| Medically attended | 9 (0.2) | 12 (0.2) |
| Leading to study discontinuation | 0 | 1 (<0.1) |
| Grade 3 | 3 (0.1) | 2 (<0.1) |
| AESI | 1 (<0.1) | 0 |

*Source: Adapted from both Tables 38 and 42 from P301 Clinical Study Report.*

Table 14: Summary of Unsolicited AEs up to Data Cutoff of 23 Feb 2024 Post-Injection (SS)

| - | **mRNA-1283.222 N=5706 n (%)** | **mRNA-1273.222 N=5711 n (%)** |
|---|---|---|
| Unsolicited AEs regardless of relationship to study vaccination | - | - |
| All | 2100 (36.8) | 2046 (35.8) |
| Serious | 156 (2.7) | 151 (2.6) |
| Fatal | 5 (0.1) | 10 (0.2) |
| Medically attended | 1932 (33.9) | 1883 (33.0) |
| Leading to study discontinuation | 8 (0.1) | 12 (0.2) |
| Grade 3 | 129 (2.3) | 133 (2.3) |
| AESI | 60 (1.1) | 60 (1.1) |
| Unsolicited AEs related to study vaccination | - | - |
| All | 48 (0.8) | 52 (0.9) |
| Serious | 2 (<0.1) | 1 (<0.1) |
| Fatal | 0 | 1 (<0.1) |
| Medically attended | 12 (0.2) | 13 (0.2) |
| Leading to study discontinuation | 0 | 1 (<0.1) |
| Grade 3 | 4 (0.1) | 2 (<0.1) |
| AESI | 1 (<0.1) | 0 |

*Source: Adapted from both Tables 39 and 14.3.1.6.1.2 from P301 Clinical Study Report.*

## 6.2 Clinical Study P301 – Japan

Title of Study: A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety and immunogenicity of mRNA-1283 compared with mRNA-1273 in participants aged 12 years and older for the prevention of COVID-19.

Dates:
1. Study initiation date (First Subject First Visit): 15 Mar 2024.
2. Data cutoff date for both immunogenicity and safety analyses: 02 May 2024.

### 6.2.1 Objectives

Primary Immunogenicity Objective:
1. To demonstrate a non-inferior neutralizing antibody response of mRNA-1283.815 10 µg compared to the antibody response of mRNA-1273.815 50 µg based on GMR at Day 29 after the study injection.

Primary Safety Objective:
1. To evaluate the safety and reactogenicity of mRNA-1283.815 10 µg study injection.

Secondary Immunogenicity Objective:
1. To characterize the neutralizing antibody response against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G (mRNA-1283.815) at Day 29 after the study injection.

### 6.2.2 Design Overview

Approximately 692 subjects were randomized in a 1:1 allocation ratio to receive either a single dose of mRNA-1283.815 10 µg or a single dose of mRNA-1273.815 50 µg, stratified by age category. Both mRNA-1283.815 and mRNA-1273.815 were monovalent vaccines encoded for Omicron XBB.1.5.

For immunogenicity, blood samples were collected on Day 1 and Day 29. For safety, solicited ARs were collected through 7 days post-injection. Unsolicited AEs (including MAAEs, AESIs, SAEs, and AEs leading to study discontinuation) were collected through 28 days post-injection and up to the data cutoff of 02 May 2024.

### 6.2.3 Population

Enrollment included participants 12 YOA and older who previously received a primary series of an authorized/approved COVID-19 vaccine. Participants aged ≥18 years must have received at least 1 booster dose, while there was no requirement for participants 12 to <18 years to have received a booster. A heterologous vaccine regimen (mix-and-match) was permitted.

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 10 µg mRNA-1283.815 or 50 µg mRNA-1273.815 was administered.

### 6.2.6 Sites and Centers

The study was conducted at 12 sites in Japan.

### 6.2.7 Surveillance/Monitoring

Please refer to the clinical review memo.

### 6.2.8 Endpoints and Study Success Criteria

Primary Immunogenicity Endpoint:

1. GMR of PsVNA titer between mRNA-1283.815 10 μg recipients and mRNA-1273.815 50 μg recipients at Day 29 after the study injection against Omicron XBB.1.5.
   - The LL of the 2-sided CI for the GMR is > 2/3.

Primary Safety Endpoints:

- Solicited local and systemic reactogenicity ARs during a 7-day follow-up period.
- Unsolicited AEs during the 28-day follow-up period.
- SAEs, MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study.

Secondary Immunogenicity Endpoint:

1. SRR[a] difference of PsVNA titer between mRNA-1283.815 10 μg recipients and mRNA-1273.815 50 μg recipients at Day 29 after the study injection against Omicron XBB.1.5.
2. GMR and SRR difference of PsVNA titer between mRNA-1283.815 10 μg recipients and mRNA-1273.815 50 μg recipients at Day 29 after the study injection against ancestral SARS-CoV-2 D614G.

[a]SRR was defined as change in PsVNA titer from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline was ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline was ≥4 × LLOQ.

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

Missing data were not replaced. Titers < LLOQ were replaced by 0.5 × LLOQ. Titers > ULOQ were not replaced by the ULOQ.

For the primary immunogenicity endpoint, GMR was estimated via an ANCOVA model using Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, age category, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine. For the secondary immunogenicity endpoint, the 95% CI for the SRR difference was estimated via the Miettinen-Nurminen method.

Both the primary and secondary immunogenicity analyses were performed on the PPIS, which was a subset of the FAS, which was a subset of the RS. All three were defined as:

- RS: All participants who were randomized, regardless of the participant's treatment status in the study.
- FAS: Participants in the RS who received study vaccine. Participants were analyzed according to their randomized study arm.
- PPIS: Participants in the FAS who received the planned dose of study injection, had Baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data against XBB.1.5, and had no major protocol deviations that impact immunogenicity data.

Subgroup analyses were performed by age category, sex, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine (</≥ median of the dosing interval).

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, and the SS was a subset of the RS. Both were defined as:

- SS: Participants in the RS who received study vaccine. Participants were included in the study arm that they actually received.
- SSS: All randomized participants in the SS who contributed any solicited AR data.

For solicited ARs, subgroup analyses were performed by age category, sex, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine. For unsolicited AEs, subgroup analyses were performed by age category only.

Multiplicity Adjustment

Only one endpoint with hypothesis testing was evaluated (i.e., GMR). Thus, no multiplicity adjustment was necessary.

Sample Size Determination

A sample size of 692 (346:346) subjects was calculated to yield 80% power for the primary immunogenicity endpoint. The sample size calculation assumed a true GMR of 1, an SD of 1.8 for natural log-titers, and a dropout rate of 10%.

### 6.2.10 Study Population and Disposition

Table 15 displays the sample size in each analysis set for both the mRNA-1283.815 and mRNA-1273.815 groups. Totals of 334 (97.1%) and 334 (96.0%) participants in the mRNA-1283.815 and mRNA-1273.815 groups, respectively, met the criteria for inclusion in the PPIS.

Table 16 displays the dispositions of the RS for both the mRNA-1283.815 and mRNA-1273.815 groups, where totals of 344 and 348 participants were randomized and 343 (99.7%) and 346 (99.4%) participants received a study intervention, respectively.

Table 17 displays the distributions of the demographic characteristics of the SS for both the mRNA-1283.815 and mRNA-1273.815 groups, where totals of 343 and 346 participants were included, respectively. No meaningful differences in demographic characteristics were observed between the two groups. Demographic characteristics were generally similar in the PPIS.

Table 15: Number of Participants in Each Analysis Set

| - | **mRNA-1283.815** | **mRNA-1273.815** |
|---|---|---|
| **Randomization Set, n** | 344 | 348 |
| Full Analysis Set, n (%)[a] | 343 (99.7) | 346 (99.4) |
| Per-Protocol Immunogenicity Set, n (%)[a] | 334 (97.1) | 334 (96.0) |
| Safety Set[a] | 343 (99.7) | 346 (99.4) |
| Solicited Safety Set, n (%)[a] | 343 (99.7) | 346 (99.4) |

[a]Numbers were based on planned vaccination group, and percentages were based on the number of randomized participants.
*Source: Table 6 from P301 – Japan Clinical Study Report.*

Table 16: Participant Disposition (RS)

| - | **mRNA-1283.815 N = 344** | **mRNA-1273.815 N = 348** |
|---|---|---|
| **Number of Participants who Received Vaccine** | 343 (99.7) | 346 (99.4) |
| Ongoing on Study | 343 (99.7) | 345 (99.1) |
| Discontinued the Study | 0 | 1 (0.3) |
| **Reason For Discontinuation of Study** | - | - |
| Withdrawal of Consent by Participant | 0 | 1 (0.3) |

*Source: Table 5 from P301 – Japan Clinical Study Report.*

Table 17: Baseline Demographics and Characteristics (SS)

| - | **mRNA-1283.815 N = 343** | **mRNA-1273.815 N = 346** |
|---|---|---|
| **Age (Years)** | - | - |
| N | 343 | 346 |
| Mean (SD) | 46.9 (19.58) | 47.0 (19.72) |
| Median | 52.0 | 52.0 |
| Q1, Q3 | 37.0, 62.0 | 30.0, 63.0 |
| Min, Max | 12, 83 | 12, 82 |
| **Age Group, n (%)** | - | - |
| ≥12 to <18 Years | 70 (20.4) | 70 (20.2) |
| ≥18 Years | 273 (79.6) | 276 (79.8) |
| ≥18 to <65 Years | 203 (59.2) | 202 (58.4) |
| ≥65 Years | 70 (20.4) | 74 (21.4) |
| ≥75 Years | 8 (2.3) | 8 (2.3) |
| **Sex, n (%)** | - | - |
| Male | 225 (65.6) | 228 (65.9) |
| Female | 118 (34.4) | 118 (34.1) |
| **Race, n (%)** | | |
| Asian | 343 (100) | 346 (100) |
| **Body Mass Index ($kg/m^2$)** | | |
| n | 343 | 345 |
| Mean (SD) | 23.55 (4.360) | 23.55 (3.913) |
| Median | 23.10 | 23.10 |
| Q1, Q3 | 20.40, 26.00 | 20.80, 25.90 |
| Min, Max | 15.4, 40.7 | 14.5, 37.9 |
| **Body Mass Index Group, n (%)** | - | - |
| <30 $kg/m^2$ | 317 (92.4) | 321 (92.8) |
| ≥30 $kg/m^2$ | 26 (7.6) | 24 (6.9) |
| ≥40 $kg/m^2$ | 1 (0.3) | 0 |
| Missing | 0 | 1 (0.3) |
| **Baseline SARS-CoV-2 Status, n (%)[a]** | - | - |
| Negative | 111 (32.4) | 96 (27.7) |
| Positive | 232 (67.6) | 250 (72.3) |
| **Baseline RT-PCR Status, n (%)** | - | - |
| Negative | 338 (98.5) | 345 (99.7) |
| Positive | 5 (1.5) | 1 (0.3) |
| **Baseline Elecsys Status, n (%)** | - | - |
| Negative | 113 (32.9) | 96 (27.7) |
| Positive | 230 (67.1) | 250 (72.3) |
| **Number of Prior COVID-19 Vaccine Doses, n (%)** | - | - |
| 0 | 0 | 0 |
| 1 | 0 | 0 |
| 2 | 18 (5.2) | 23 (6.6) |
| 3 | 133 (38.8) | 112 (32.4) |
| 4 | 137 (39.9) | 151 (43.6) |
| 5 | 55 (16.0) | 60 (17.3) |
| **Number of Prior COVID-19 Booster Doses, n (%)** | - | - |
| 0 | 18 (5.2) | 23 (6.6) |
| 1 | 133 (38.8) | 111 (32.1) |
| 2 | 137 (39.9) | 150 (43.4) |
| ≥3 | 55 (16.0) | 62 (17.9) |

Table 17: Baseline Demographics and Characteristics (SS) (continued)

| - | **mRNA-1283.815 N = 343** | **mRNA-1273.815 N = 346** |
|---|---|---|
| **Type of Last Prior COVID-19 Vaccine, n (%)[b]** | - | - |
| mRNA Original Monovalent | 117 (34.1) | 110 (31.8) |
| mRNA Omicron Bivalent | 216 (63.0) | 225 (65.0) |
| non-mRNA Vaccine | 3 (0.9) | 2 (0.6) |
| Unknown | 7 (2.0) | 7 (2.0) |
| **Dosing Interval from Last Prior Dose of COVID-19 Vaccine to Study Vaccine (months)[c]** | - | - |
| n | 343 | 346 |
| Mean (SD) | 18.28 (4.216) | 17.91 (4.534) |
| Median | 16.89 | 16.59 |
| Q1, Q3 | 15.54, 21.59 | 15.28, 20.96 |
| **Dosing Interval Group from Last Prior Dose of COVID-19 Vaccine to Study Vaccine (months), n (%)[c]** | - | - |
| < Median | 162 (47.2) | 181 (52.3) |
| ≥ Median | 181 (52.8) | 165 (47.7) |

[a]Baseline SARS-CoV-2 Status: positive was defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1; negative was defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1.
[b]Type of formulation received was presumed based on date of receipt reported by participant and date of approval of the formulation. Participants with last mRNA COVID-19 vaccine dose date prior to September 1, 2022 were presumed to have received the original monovalent. Participants with last mRNA COVID-19 vaccine dose date on or after September 1, 2022, but before September 20, 2023 were presumed to have received the Omicron bivalent. Two participants received the last mRNA COVID-19 vaccine dose on or after September 20, 2023 (i.e, after approval of Omicron XBB.1.5 formulations), however, they had received a non-XBB.1.5 formulation and are not shown in the table.
[c]Dosing interval from last prior dose of COVID-19 vaccine to investigational vaccine (months) = (Date of vaccine – date of last prior dose of COVID-19 vaccine +1) / 30.4375. The median (months) was based on the median across all participants (16.72 months).
*Source: Tables 7 and 8 from P301 – Japan Clinical Study Report.*

### 6.2.11 Immunogenicity Analyses

#### 6.2.11.1 Analyses of Primary Immunogenicity Endpoint

Table 18 displays the Day 29 GLSMs and SRRs for both Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G. For the primary immunogenicity endpoint, the adjusted anti-Omicron XBB.1.5 GMR was 1.2 with 95% CI = 1.0 to 1.4, which met its success criterion for non-inferiority.

#### 6.2.11.2 Analyses of Secondary Immunogenicity Endpoints

For the secondary immunogenicity endpoints, the anti-Omicron XBB.1.5 SRR difference was 5.4% with 95% CI = 0.8% to 10.2%, the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.0 to 1.3, and the anti-ancestral SARS-CoV-2 D614G SRR difference was 8.6% with 95% CI = 2.2% to 15.0%.

#### 6.2.11.3 Subpopulation Analyses

##### 6.2.11.3.1 Primary and Secondary Immunogenicity Endpoints

Tables 19, 20, and 21 display the Day 29 GLSMs and SRRs for both Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G for age categories 12 to < 18 YOA, 18 to < 65 YOA, and ≥ 65 YOA, respectively. For each age category, the adjusted anti-Omicron XBB.1.5 GMR and the anti-Omicron XBB.1.5 SRR difference were > 1 and > 0%, respectively; the adjusted anti-ancestral SARS-CoV-2 D614G GMR and the anti-ancestral SARS-CoV-2 D614G SRR difference were > 1 and > 0%, respectively.

Across the subgroups of sex, baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine, no meaningful differences in adjusted GMRs or SRR differences were observed (not shown in tables).

Table 18: Summary of PsVNA Titer against Omicron XBB.1.5 and Ancestral SARS-CoV-2 D614G at Day 29 (PPIS)

| - | **mRNA-1283.815** | **mRNA-1273.815** |
|---|---|---|
| N | 334 | 334 |
| Omicron XBB.1.5 | - | - |
| GLSM (95% CI)[a] | 1757.2 (1580.1, 1954.3) | 1470.4 (1322.4, 1635.0) |
| GMR (95% CI)[a] | 1.2 (1.0, 1.4) | - |
| SRR, % (95% CI)[b] | 308/334<br>92.2 (88.8, 94.9) | 290/334<br>86.8 (82.7, 90.3) |
| SRR difference, % (95% CI)[c] | 5.4 (0.8, 10.2) | - |
| N | 324 | 321 |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 6758.7 (6142.3, 7437.0) | 5743.6 (5218.2, 6321.9) |
| GMR (95% CI)[a] | 1.2 (1.0, 1.3) | - |
| SRR, % (95% CI)[b] | 267/323<br>82.7 (78.1, 86.6) | 237/320<br>74.1 (68.9, 78.8) |
| SRR difference, % (95% CI)[c] | 8.6 (2.2, 15.0) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, age category, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from Tables 10, 14, 14.2.1.1.1.2, and 14.2.1.1.1.3 from P301 – Japan Clinical Study Report.*

*Reviewer's Comment:*

- *For both Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G, titers above the ULOQ were not imputed to the ULOQ. At Day 29, for Omicron XBB.1.5, 29/334 and 18/334 subjects in the mRNA-1283.815 group and mRNA-1273.815 group, respectively, had titers > ULOQ. At Day 29, for ancestral SARS-CoV-2 D614G, 1/324 and 0/321 subjects in the mRNA-1283.815 group and mRNA-1273.815 group, respectively, had titers > ULOQ. I conducted sensitivity analyses of the GMRs imputing the ULOQ for titers > ULOQ. Compared to no imputation, both the point estimate and 95% CI of both the adjusted anti-Omicron XBB.1.5 GMR and adjusted anti-ancestral SARS-CoV-2 D614G GMR were approximately equal. Therefore, the results of the sensitivity analyses supported the immunobridging conclusions.*

Table 19: Summary of PsVNA Titer against Omicron XBB.1.5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects 12 to < 18 YOA (PPIS)

| - | **mRNA-1283.815** | **mRNA-1273.815** |
|---|---|---|
| N | 70 | 68 |
| Omicron XBB.1.5 | - | - |
| GLSM (95% CI)[a] | 3302.2 (2729.9, 3994.4) | 2753.3 (2269.8, 3339.9) |
| GMR (95% CI)[a] | 1.2 (0.9, 1.6) | - |
| SRR, % (95% CI)[b] | 69/70<br>98.6 (92.3, 100.0) | 64/68<br>94.1 (85.6, 98.4) |
| SRR difference, % (95% CI)[c] | 4.5 (-2.5, 13.0) | - |
| N | 68 | 67 |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 8726.2 (7207.7, 10564.6) | 7114.4 (5867.9, 8625.7) |
| GMR (95% CI)[a] | 1.2 (0.9, 1.6) | - |
| SRR, % (95% CI)[b] | 66/68<br>97.1 (89.8, 99.6) | 52/66<br>78.8 (67.0, 87.9) |
| SRR difference, % (95% CI)[c] | 18.3 (8.1, 30.1) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from both Tables 11, 14.2.1.1.4.2, and 14.2.1.1.4.3 from P301 – Japan Clinical Study Report.*

Table 20: Summary of PsVNA Titer against Omicron XBB.1.5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects 18 to < 65 YOA (PPIS)

| - | **mRNA-1283.815** | **mRNA-1273.815** |
|---|---|---|
| N | 195 | 197 |
| Omicron XBB.1.5 | - | - |
| GLSM (95% CI)[a] | 1513.0 (1313.2, 1743.2) | 1281.3 (1113.8, 1474.0) |
| GMR (95% CI)[a] | 1.2 (1.0, 1.4) | - |
| SRR, % (95% CI)[b] | 179/195<br>91.8 (87.0, 95.2) | 171/197<br>86.8 (81.3, 91.2) |
| SRR difference, % (95% CI)[c] | 5.0 (-1.2, 11.3) | - |
| N | 188 | 188 |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 6247.3 (5510.1, 7083.1) | 5583.5 (4928.1, 6326.1) |
| GMR (95% CI)[a] | 1.1 (0.9, 1.3) | - |
| SRR, % (95% CI)[b] | 147/187<br>78.6 (72.0, 84.3) | 136/188<br>72.3 (65.4, 78.6) |
| SRR difference, % (95% CI)[c] | 6.3 (-2.5, 15.0) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from both Tables 11, 14.2.1.1.4.2, and 14.2.1.1.4.3 from P301 – Japan Clinical Study Report.*

Table 21: Summary of PsVNA Titer against Omicron XBB.1.5 and Ancestral SARS-CoV-2 D614G at Day 29 Among Subjects ≥ 65 YOA (PPIS)

| - | **mRNA-1283.815** | **mRNA-1273.815** |
|---|---|---|
| N | 69 | 69 |
| Omicron XBB.1.5 | - | - |
| GLSM (95% CI)[a] | 1435.9 (1099.3, 1875.8) | 1123.4 (858.3, 1470.3) |
| GMR (95% CI)[a] | 1.3 (0.9, 1.9) | - |
| SRR, % (95% CI)[b] | 60/69<br>87.0 (76.7, 93.9) | 55/69<br>79.7 (68.3, 88.4) |
| SRR difference, % (95% CI)[c] | 7.2 (-5.4, 20.0) | - |
| N | 68 | 66 |
| Ancestral SARS-CoV-2 D614G | - | - |
| GLSM (95% CI)[a] | 6587.9 (5245.5, 8273.8) | 4882.3 (3867.1, 6164.1) |
| GMR (95% CI)[a] | 1.3 (1.0, 1.9) | - |
| SRR, % (95% CI)[b] | 54/68<br>79.4 (67.9, 88.3) | 49/66<br>74.2 (62.0, 84.2) |
| SRR difference, % (95% CI)[c] | 5.2 (-9.3, 19.6) | - |

[a]Based on ANCOVA modeling, which used Day 29 log-titers as the dependent variable. Independent variables included vaccine group, SARS-CoV-2 status at baseline, number of prior COVID-19 booster doses, and type of last prior COVID-19 vaccine.
[b]95% CI is calculated using the Clopper-Pearson method.
[c]95% CI is calculated using the Miettinen-Nurminen (score) method.
*Source: Adapted from both Tables 11, 14.2.1.1.4.2, and 14.2.1.1.4.3 from P301 – Japan Clinical Study Report.*

*Reviewer's Comment:*

- *Unlike Study P301, not all subjects in the PPIS from Study P301 – Japan reported immunogenicity data at Day 29 for ancestral SARS-CoV-2 D614G. Hence, the sample sizes (N) for ancestral SARS-CoV-2 D614G were different than Omicron XBB.1.5 at Day 29 in the PPIS in Tables 18 – 21.*

### 6.2.12 Safety Analyses

*Solicited ARs*

Table 22 displays both local and systemic ARs by age category within 7 days post-injection in the SSS.

Rates of solicited local ARs were generally lower in the mRNA-1283.222 group than the mRNA-1273.222 group and slightly lower for participants aged ≥65 years compared to participants aged ≥12 to <18 years and ≥18 to <65 years. Across both the vaccines and age categories, injection site pain was the most frequently reported solicited local AR.

Rates of solicited systemic ARs were generally lower in the mRNA-1283.222 group than the mRNA-1273.222 group and tended to decrease with older age categories. Across the vaccines, fatigue was the most frequently reported solicited systemic AR. Across age categories, fatigue and headache were the most frequently reported solicited systemic ARs among participants aged ≥12 to <18 years, while fatigue was the most frequently reported solicited systemic AR among participants aged ≥18 to <65 years and ≥65 years.

No Grade 4 solicited ARs were reported.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, rates of local and systemic ARs were generally higher among female participants. Across the subgroups of baseline SARS-CoV-2 status, number of prior COVID-19 vaccine doses, number of prior COVID-19 booster doses, type of last prior COVID-19 vaccination, and dosing interval from last prior dose of COVID-19 vaccine to administration of study vaccine, no meaningful differences in the rates of local or systemic ARs were observed in either group (not shown in tables).

*Unsolicited AEs up to 28 days post-injection*

Table 23 displays unsolicited AEs up to 28 days post-injection in the SS.

For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1283.815 group to the mRNA-1273.815 group, there were similar percentages of unsolicited AEs (7.0% and 6.9%, respectively) and MAAEs (5.0% and 4.0%, respectively). No SAEs, AEs leading to study discontinuation, AESIs, Grade 3 unsolicited AEs, or deaths were reported. No events of myocarditis or pericarditis were reported.

For unsolicited AEs considered by the investigator to be related to study vaccination, comparing the mRNA-1283.815 group to the mRNA-1273.815 group, there were no notable differences in percentages of unsolicited AEs (0.9% and 0.6%, respectively). One related MAAE was reported in the mRNA-1283.815 group while none were reported in the mRNA-1273.815 group.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, across the subgroups of age category, no meaningful differences in the rates of unsolicited AEs were observed (not shown in tables).

*Unsolicited AEs up to data cutoff of 02 May 2024*

Table 24 displays unsolicited AEs up to the data cutoff of 02 May 2024 in the SS. The median follow-up was 36 days and 35 days in the mRNA-1283.815 group and mRNA-1273.815 group, respectively.

For unsolicited AEs regardless of relationship to study vaccination, comparing the mRNA-1283.815 group to the mRNA-1273.815 group, there were no notable differences in percentages of unsolicited AEs (9.0% and 7.8%, respectively) and MAAEs (7.0% and 5.2%, respectively). No SAEs, AEs leading to study discontinuation, AESIs, Grade 3 unsolicited AEs, or deaths were reported. No events of myocarditis or pericarditis were reported. No additional AEs assessed as related to study vaccination per the investigator were reported beyond 28 days post-injection.

Compared to the overall analysis, in both the mRNA-1283.222 group and mRNA-1273.222 group, across the subgroups of age category, no meaningful differences in the rates of unsolicited AEs were observed (not shown in tables).

Table 22: Summary of Participants With Solicited Adverse Reactions Within 7 Days Post-Injection by Age Category (SSS)

| Event | mRNA-1283.222 ≥12-<18 years N=70 n (%) | mRNA-1273.222 ≥12-<18 years N=70 n (%) | mRNA-1283.222 ≥18-<65 years N=203 n (%) | mRNA-1273.222 ≥18-<65 years N=202 n (%) | mRNA-1283.222 ≥65 years N=70 n (%) | mRNA-1273.222 ≥65 years N=74 n (%) |
|---|---|---|---|---|---|---|
| Local ARs, Any Grade | 64 (91.4) | 65 (92.9) | 178 (87.7) | 196 (97.0) | 54 (77.1) | 68 (91.9) |
| Local ARs, Grade 3 | 2 (2.9) | 6 (8.6) | 7 (3.4) | 13 (6.4) | 1 (1.4) | 4 (5.4) |
| Pain, Any Grade | 62 (88.6) | 65 (92.9) | 175 (86.2) | 195 (96.5) | 54 (77.1) | 67 (90.5) |
| Pain, Grade 3[a] | 0 | 5 (7.1) | 4 (2.0) | 6 (3.0) | 0 | 2 (2.7) |
| Erythema (redness), Any Grade | 3 (4.3) | 9 (12.9) | 9 (4.4) | 19 (9.4) | 1 (1.4) | 10 (13.5) |
| Erythema (redness), Grade 3[b] | 0 | 0 | 1 (0.5) | 4 (2.0) | 0 | 1 (1.4) |
| Swelling (hardness), Any Grade | 5 (7.1) | 9 (12.9) | 20 (9.9) | 32 (15.8) | 7 (10.0) | 10 (13.5) |
| Swelling (hardness), Grade 3[b] | 2 (2.9) | 1 (1.4) | 2 (1.0) | 5 (2.5) | 1 (1.4) | 1 (1.4) |
| Axillary swelling/tenderness, Any Grade | 30 (42.9) | 21 (30.0) | 42 (20.7) | 51 (25.2) | 12 (17.1) | 18 (24.3) |
| Axillary swelling/tenderness, Grade 3[a] | 0 | 0 | 1 (0.5) | 1 (0.5) | 0 | 0 |
| Systemic ARs, Any Grade | 52 (74.3) | 56 (80.0) | 118 (58.1) | 166 (82.2) | 35 (50.0) | 44 (59.5) |
| Systemic ARs, Grade 3 | 4 (5.7) | 11 (15.7) | 13 (6.4) | 17 (8.4) | 1 (1.4) | 2 (2.7) |
| Fever, Any Grade | 11 (15.7) | 17 (24.3) | 11 (5.4) | 23 (11.4) | 2 (2.9) | 4 (5.4) |
| Fever, Grade 3[c] | 0 | 4 (5.7) | 2 (1.0) | 2 (1.0) | 0 | 0 |
| Headache, Any Grade | 41 (58.6) | 45 (64.3) | 86 (42.4) | 120 (59.4) | 19 (27.1) | 29 (39.2) |
| Headache, Grade 3[a] | 1 (1.4) | 6 (8.6) | 5 (2.5) | 7 (3.5) | 0 | 1 (1.4) |
| Fatigue, Any Grade | 43 (61.4) | 41 (58.6) | 102 (50.2) | 143 (70.8) | 30 (42.9) | 36 (48.6) |
| Fatigue, Grade 3[a] | 4 (5.7) | 2 (2.9) | 7 (3.4) | 8 (4.0) | 1 (1.4) | 1 (1.4) |
| Myalgia, Any Grade | 25 (35.7) | 23 (32.9) | 74 (36.5) | 90 (44.6) | 21 (30.0) | 25 (33.8) |
| Myalgia, Grade 3[a] | 2 (2.9) | 0 | 3 (1.5) | 7 (3.5) | 1 (1.4) | 0 |
| Arthralgia, Any Grade | 25 (35.7) | 21 (30.0) | 64 (31.5) | 86 (42.6) | 20 (28.6) | 18 (24.3) |
| Arthralgia, Grade 3[a] | 1 (1.4) | 1 (1.4) | 3 (1.5) | 7 (3.5) | 1 (1.4) | 0 |
| Nausea/vomiting, Any Grade | 9 (12.9) | 10 (14.3) | 16 (7.9) | 17 (8.4) | 2 (2.9) | 4 (5.4) |
| Nausea/vomiting, Grade 3[d] | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills, Any Grade | 11 (15.7) | 16 (22.9) | 49 (24.1) | 77 (38.1) | 12 (17.1) | 16 (21.6) |
| Chills, Grade 3[e] | 1 (1.4) | 2 (2.9) | 2 (1.0) | 3 (1.5) | 1 (1.4) | 0 |

[a]Grade 3 pain, axillary swelling/tenderness, headache, fatigue, myalgia, arthralgia: Defined as prevents daily activity.
[b]Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[c]Grade 3 fever: Defined as ≥ 39.0° – ≤ 40.0°C / ≥ 102.1° – ≤ 104.0°F.

[d]Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration
[e]Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
*Source: Adapted from Table 19 from P301 Clinical Study Report.*

*Reviewer's Comment:*

- *Unlike Table 12 for Study P301, all subjects in Study P301 – Japan completed the diary card. Hence, the sample sizes (N) by solicited AR were identical.*

Table 23: Summary of Unsolicited AEs up to 28 Days Post-Injection (SS)

| - | **mRNA-1283.815 N=343 n (%)** | **mRNA-1273.815 N=346 n (%)** |
|---|---|---|
| Unsolicited AEs regardless of relationship to study vaccination | - | - |
| All | 24 (7.0) | 24 (6.9) |
| Medically attended | 17 (5.0) | 14 (4.0) |
| Unsolicited AEs related to study vaccination | - | - |
| All | 3 (0.9) | 2 (0.6) |
| Medically attended | 1 (0.3) | 0 |

*Source: Table 21 from P301 – Japan Clinical Study Report.*

Table 24: Summary of Unsolicited AEs up to Data Cutoff of 02 May 2024 Post-Injection (SS)

| - | **mRNA-1283.815 N=343 n (%)** | **mRNA-1273.815 N=346 n (%)** |
|---|---|---|
| Unsolicited AEs regardless of relationship to study vaccination | - | - |
| All | 31 (9.0) | 27 (7.8) |
| Medically attended | 24 (7.0) | 18 (5.2) |
| Unsolicited AEs related to study vaccination | - | - |
| All | 3 (0.9) | 2 (0.6) |
| Medically attended | 1 (0.3) | 0 |

*Source: Table 14.3.1.2.1.2 from P301 – Japan Clinical Study Report.*

## 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

### 10.1 Statistical Issues and Collective Evidence

The BLA is primarily supported by immunogenicity, efficacy, and safety data from Study P301, as well as both immunogenicity and safety data from Study P301 – Japan.

For Study P301, at the IA, the success criteria for all four co-primary immunogenicity endpoints and rVE were met. The median follow-up at the IA was 244 days up to the data cutoff of 31 Jan 2024 in both groups.

The adjusted anti-Omicron BA.4/5 GMR was 1.3 with 95% CI = 1.2 to 1.5, while the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.1 to 1.4. Both GMRs were adjusted for SARS-CoV-2 status at baseline (positive or negative), age category, number of prior COVID-19 booster doses (0, 1, 2, or ≥3), and type of last prior COVID-19 vaccine (mRNA bivalent, mRNA monovalent, or non-mRNA vaccine). The anti-Omicron BA.4/5 SRR difference was 14.4% with 95% CI = 9.3% to 19.4%, while the anti-ancestral SARS-CoV-2 D614G SRR difference was 10.7% with 95% CI = 6.0% to 15.4%.

For CDC case definition, 560 and 617 cases were reported in the mRNA-1283.222 group and mRNA-1273.222 group, respectively, where the estimated rVE with stratification by age category was 9.3% with 99.4% CI = -6.6% to 22.8%. The alpha value of 0.6% for the 2-sided CI was derived from the Lan-DeMets approximation to the O'Brien-Fleming stopping boundary with an information fraction of 0.56 (1,177 out of a total of 2,087 cases).

Supportive efficacy analyses were conducted up to the data cutoff of 23 Feb 2024. The median follow-up was 267 days in both groups. Compared to the IA, for CDC case definition, the estimated rVE with stratification by age category marginally decreased to 7.3% with 95% CI = -3.4% to 17.0%.

Within 7 days post-injection, rates of solicited local ARs were slightly lower in the mRNA-1283.222 group than the mRNA-1273.222 group. Rates of solicited systemic ARs were generally similar between the mRNA-1283.222 group and the mRNA-1273.222 group. For both groups, injection site pain was the most frequently reported solicited local AR, while fatigue was the most frequently reported solicited systemic AR.

Within 28 days post-injection, regardless of relationship to study vaccination per the investigator, there were similar percentages of unsolicited AEs, SAEs, MAAEs, and AESIs in both groups. One related AESI (possible anaphylaxis) was reported in the mRNA-1283.222 group while none were reported in the mRNA-1273.222 group. One death reported in the mRNA-1273.222 group was considered to be related per the investigator and occurred on Day 7 post-injection with cause of death reported as unknown. However, the Applicant assessed the death as unrelated given the subject's long term cardiovascular history.

These findings generally held for the unsolicited AEs collected up to the data cutoff of 23 Feb 2024. One event of pericarditis was reported in the mRNA-1273.222 group on Day 136 post-injection while none were reported in the mRNA-1283.222 group, which was not considered to be related per the investigator. No events of myocarditis were reported. The median follow-up was 267 days in both groups.

For Study P301 – Japan, the adjusted anti-Omicron XBB.1.5 GMR met the success criterion that the LL of the 2-sided CI be > 2/3 with a GMR of 1.2 and 95% CI = 1.0 to 1.4. The anti-Omicron XBB.1.5 SRR difference was 5.4% with 95% CI = 0.8% to 10.2%,

the adjusted anti-ancestral SARS-CoV-2 D614G GMR was 1.2 with 95% CI = 1.0 to 1.3, and the anti-ancestral SARS-CoV-2 D614G SRR difference was 8.6% with 95% CI = 2.2% to 15.0% — all three were assessed descriptively. Both GMRs were adjusted for SARS-CoV-2 status at pre-booster (positive or negative), age category, number of prior COVID-19 booster doses (0, 1, 2, or ≥3), and type of last prior COVID-19 vaccine.

Findings for solicited ARs were similar to Study P301 and no notable differences in unsolicited AEs were found either within 28 days post-injection or up to the data cutoff of 02 May 2024. No SAEs, AEs leading to study discontinuation, AESIs, deaths, myocarditis, or pericarditis were reported. The median follow-up was 36 days and 35 days in the mRNA-1283.815 group and mRNA-1273.815 group, respectively.

### 10.2 Conclusions and Recommendations

No major statistical issues have been identified. The pre-specified efficacy objective for Study P301 was met and no notable imbalances in safety results were identified. Overall, the immunogenicity, efficacy, and safety data support licensure of the mRNA-1283 vaccine in individuals 12 YOA and older.