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Division / Office	DVRPA/OVRR
Committee Chair	Sudhakar Agnihothram
Clinical Reviewer(s)	Rachel Zhang; Jaya Goswami
Project Manager	Joseph Kulinski; Josephine Resnick
Priority Review	Yes
Reviewer Name	Ye Yang, Mathematical Statistician, DB/VEB
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, DB/VEB
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, DB/VEB
Supervisory Concurrence	John Scott, Director, DB
Applicant	ModernaTX, Inc.
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	SPIKEVAX
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.5 mL doses, four weeks apart
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 18 years of age and older

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GLOSSARY

ADaM	Analysis Data Model
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
FAS	Full Analysis Set
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
MAAE	Medically Attended Adverse Event
mITT	Modified Intent-to-Treat Set
NIH	National Institutes of Health
PPS	Per-Protocol Set
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDTM	Study Data Tabulation Model
VE	Vaccine Efficacy

1. Executive Summary

The Moderna Coronavirus Disease 2019 (COVID-19) Vaccine (mRNA-1273) was authorized under an Emergency Use Authorization (EUA) on December 18, 2020 for active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals ≥ 18 years of age. Moderna initiated a rolling Biologics License Application (BLA), STN 125752/0, to seek licensure of this vaccine in the same population. The submission was completed on August 24, 2021. The BLA is supported by safety, efficacy, and immunogenicity data from three ongoing studies: mRNA-1273-P201 (P201), mRNA-1273-P301 (P301), and 20-0003. This statistical review focuses on the final efficacy analysis and safety data from Study P301 collected up to the March 26, 2021 data cut-off.

Study P301 is an ongoing, randomized, placebo-controlled, observer-blind Phase 3 study being conducted in the United States. A total of 30,415 subjects were randomized 1:1 to receive two doses of mRNA-1273 or placebo 28 days apart. Randomization was stratified by age and health risk (≥ 18 to < 65 years and not at risk, ≥ 18 to < 65 years and at risk, and ≥ 65 years) defined by chronic lung disease, significant cardiac disease, severe obesity (Body Mass Index [BMI] ≥ 40 kg/m²), diabetes, liver disease, or human immunodeficiency virus (HIV) infection.

Study participants were surveilled throughout the study for potential COVID-19. The primary efficacy endpoint was the occurrence of symptomatic, reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 as assessed by an adjudication committee. Two interim analyses of the primary efficacy endpoint were planned at 53 and 106 cases, and a primary analysis at 151 cases. The primary efficacy objective would be met if the point estimate of vaccine efficacy (VE) is $\geq 50\%$ and the null hypothesis of $H_0: VE \leq 30\%$ is rejected at any of the interim or primary analyses, with the Type I error rate controlled at a one-sided 2.5% by the Lan-DeMets approximation of the O'Brien Fleming boundaries.

All subjects were to record local and systemic reactions from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs), medically attended AEs (MAAEs), and serious AEs (SAEs) were collected from Dose 1 up to the March 26, 2021 data cut-off.

The primary efficacy objective was met at the first and only interim analysis with an estimated VE of 94.5% (95% Confidence Interval [CI]: 86.5% - 97.8%) and a one-sided p-value of < 0.001 for testing $H_0: VE \leq 30\%$, when 95 cases were accumulated. The EUA was granted by FDA based on this interim efficacy analysis and a subsequent primary analysis. In addition, a final efficacy analysis during blinded follow-up up to the March 26, 2021 data cut-off was conducted. A VE of 93.2% (95% CI: 91.0% - 94.8%) was observed at the final analysis after a median follow-up of 119 days post Dose 2. Similarly high efficacies were observed against severe COVID-19 (VE=98.2%; 95% CI: 92.8% - 99.6%), COVID-19 defined according to the Centers for Disease Control and Prevention (CDC) criteria (VE=93.4%; 95% CI: 91.4% - 94.9%), COVID-19 starting 14 days after Dose 1 (VE=93.3%; 95% CI: 91.1% - 94.9%), and COVID-19 regardless of evidence of prior SARS-CoV-2 infection (VE=92.8%; 95% CI: 90.6% - 94.5%), while lower

efficacies were observed against asymptomatic SARS-CoV-2 infection (VE=62.9%; 95% CI: 56.4% - 68.5%) and infection regardless of symptomatology (VE=82.2%; 95% CI: 79.7% - 84.3%).

The frequency and severity of local and systemic reactions were generally higher among mRNA-1273 recipients than among placebo recipients after either dose regardless of age group. The most commonly reported adverse reactions were injection site pain, fatigue, headache, and myalgia. There was no notable difference in the frequencies of any unsolicited AE, MAAE, SAE, or death between the mRNA-1273 and placebo groups during blinded follow-up.

Overall, the clinical data support the effectiveness of mRNA-1273. While there is some reactogenicity associated with mRNA-1273, the majority of solicited adverse reactions were mild or moderate in severity and of short duration. I defer to the clinical reviewers, Drs. Rachel Zhang and Jaya Goswami, on the overall safety conclusion for mRNA-1273.

2. Clinical and Regulatory Background

The Moderna COVID-19 Vaccine, mRNA-1273, was authorized under an EUA on December 18, 2020 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥ 18 years of age. Moderna initiated a rolling BLA on May 28, 2021 to seek licensure of the vaccine in this population. The BLA submission was completed on August 24, 2021.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to Bhanu Kannan's Bioresearch Monitoring inspections review memo.

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 IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the final analysis of the P301 efficacy data collected up to participant unblinding and the P301 safety data collected up to the March 26, 2021 data cut-off.

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

The following documents submitted to the BLA are reviewed:

STN 125752/0:

1. Amendment 2 (submitted on 8/24/2021)
 - Module 2. Common Technical Document Summaries
 - Module 5. Clinical Study Reports
2. Amendment 3 (submitted on 9/15/2021)
 - Module 1. Administrative Information and Prescribing Information
3. Amendment 4 (submitted on 9/22/2021)
 - Module 1. Administrative Information and Prescribing Information
4. Amendment 7 (submitted on 9/30/2021)
 - Module 1. Administrative Information and Prescribing Information
5. Amendment 9 (submitted on 10/7/2021)
 - Module 1. Administrative Information and Prescribing Information
6. Amendment 10 (submitted on 10/12/2021)
 - Module 1. Administrative Information and Prescribing Information
 - Module 5. Clinical Study Reports
7. Amendment 16 (submitted on 11/1/2021)
 - Module 1. Administrative Information and Prescribing Information
8. Amendment 18 (submitted on 11/8/2021)
 - Module 1. Administrative Information and Prescribing Information
 - Module 5. Clinical Study Reports
9. Amendment 20 (submitted on 11/10/2021)
 - Module 1. Administrative Information and Prescribing Information
10. Amendment 27 (submitted on 12/1/2021)
 - Module 1. Administrative Information and Prescribing Information
 - Module 5. Clinical Study Reports
11. Amendment 28 (submitted on 12/3/2021)
 - Module 1. Administrative Information and Prescribing Information
12. Amendment 31 (submitted on 12/9/2021)
 - Module 1. Administrative Information and Prescribing Information

5.3 Table of Studies/Clinical Trials

Data from three ongoing clinical studies were used to support licensure of mRNA-1273 and are summarized in Table 1 below. Study P301 is a Phase 3, randomized, double-blinded, placebo-controlled safety, immunogenicity, and efficacy study in adults 18 years of age and older, Study P201 is a Phase 2 safety and immunogenicity study evaluating two dose levels of mRNA-1273, and Study 20-0003 is a Phase 1 dose-ranging study sponsored by the National Institutes of Health (NIH).

Table 1. Clinical Trials Supporting Licensure of mRNA-1273

Study	Description	mRNA-1273 (N)	Placebo (N)	Status
P301	Phase 3, randomized, double-blinded, placebo-controlled safety, immunogenicity, and efficacy study in adults 18 years of age and older	15209 (100-µg)	15206	Ongoing
P201	Phase 2, randomized, double-blinded, placebo-controlled safety and immunogenicity study in adults 18 years of age and older	200 (50-µg) 200 (100-µg)	200	Ongoing
20-0003	Phase 1, open-label, dose-ranging safety and immunogenicity study in adults 18 years of age and older	35 (25-µg) 35 (50-µg) 35 (100-µg) 15 (250-µg)	0	Ongoing

Source: Summarized by the reviewer based on information provided in Clinical Overview.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study P301

6.1.1 Objectives

Primary Efficacy Objective:

- To demonstrate the efficacy of mRNA-1273 to prevent COVID-19.

Primary Safety Objective:

- To evaluate the safety and reactogenicity of two injections of mRNA-1273 given 28 days apart.

Secondary Efficacy Objectives:

- To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.
- To evaluate VE against a secondary definition of COVID-19.
- To evaluate VE to prevent death caused by COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose.
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.
- To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.

6.1.2 Design Overview

Study P301 is an ongoing, randomized, placebo-controlled, observer-blind Phase 3 study being conducted in the United States. A total of 30,415 subjects were randomized 1:1 to receive two doses of mRNA-1273 or placebo 28 days apart. Randomization was stratified by age and health risk (≥ 18 to < 65 years and not at risk, ≥ 18 to < 65 years and at risk, and

≥65 years) defined by chronic lung disease, significant cardiac disease, severe obesity (BMI ≥40 kg/m²), diabetes, liver disease, or HIV infection.

Study participants were surveilled throughout the study for potential COVID-19. Participants who developed COVID-19 symptoms were tested for SARS-CoV-2 infection via RT-PCR in an unscheduled illness visit. Two interim analyses of the primary efficacy endpoint at 53 and 106 cases and a primary analysis at 151 cases were planned. Participants were to be followed for 24 months following the last dose.

All subjects were to record local and systemic reactions from Day 1 through Day 7 after each dose. Unsolicited AEs, MAAEs, and SAEs were collected from Dose 1 up to the March 26, 2021 data cut-off.

Following the EUA issuance in December 2020, eligible participants as determined by the investigators per CDC recommendations were systematically unblinded and offered mRNA-1273 vaccination in a Participant Decision Visit if they had been randomized to placebo.

6.1.3 Population

The P301 study population consisted of adults 18 years of age and older whose locations or circumstances put them at appreciable risk of exposure to the virus.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study interventions were 100-µg of mRNA-1273 and saline placebo.

6.1.6 Sites and Centers

A total of 99 sites across the United States participated in the study.

6.1.7 Surveillance/Monitoring

Please refer to Drs. Rachel Zhang and Jaya Goswami's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

1. First occurrence of COVID-19 starting at 14 days after Dose 2, defined as having at least one nasopharyngeal swab, nasal swab, or saliva sample positive for SARS-CoV-2 by RT-PCR, and at least one of the following:
 - At least two of the following systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
 - At least one of the following respiratory symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiological evidence of pneumonia.

The primary study success criteria required the lower bound of the multiplicity adjusted CI for VE, defined as $VE = 1 - HR$, to be >30% and the point estimate of VE to be ≥50%. The Lan-DeMets approximation of the O'Brien-Fleming boundaries was applied to control the Type I error rate at a one-sided 2.5% at the interim and primary analyses.

Secondary Efficacy Endpoints

1. Severe COVID-19 starting at 14 days after Dose 2, defined as COVID-19 plus one of the following:
 - Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, $SpO_2 \leq 93\%$ on room air at sea level, $PaO_2/FIO_2 < 300$ mm Hg, or
 - Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors), or
 - Significant renal, hepatic, or neurologic dysfunction, admission to an intensive care unit, or death.
2. Secondary (CDC) definition of COVID-19 starting at 14 days after Dose 2, defined as a positive RT-PCR test plus at least one of the following:
 - Fever ($\geq 38^\circ C$), chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea.
3. Asymptomatic SARS-CoV-2 infection starting at 14 days after Dose 2, defined as a positive RT-PCR test or serology based on a ligand-binding assay specific to the nucleocapsid protein at a scheduled visit in the absence of symptoms.
4. SARS-CoV-2 infection regardless of symptomatology or severity starting at 14 days after Dose 2, including symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection.
5. Death due to COVID-19 starting at 14 days after Dose 2.
6. COVID-19 as defined for the primary endpoint starting after Dose 1.
7. COVID-19 as defined for the primary endpoint starting at 14 days after Dose 2 regardless of evidence of prior SARS-CoV-2 infection.

Safety Endpoints

1. Solicited local and systemic reactions within seven days of each dose.
2. AEs, MAAEs, and SAEs from Dose 1 up to the March 26, 2021 data cut-off.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Efficacy

Vaccine efficacy was defined as $VE = 1 - \text{Hazard Ratio (HR)}$, estimated by a Cox proportional hazards model using Efron's method to handle ties and with treatment group as the independent variable, stratified on the same factor used for randomization. The primary objective would be met if the point estimate of VE is $\geq 50\%$ and the null hypothesis of $H_0: VE \leq 30\%$ is rejected at any of the interim or primary analysis, with the Type I error rate controlled at one-sided 2.5% by the Lan-DeMets approximation of the O'Brien Fleming boundaries. A descriptive final efficacy analysis would be performed at the end of the blinded portion of the study.

After demonstrating the primary objective at either the interim or primary analysis, the following secondary endpoints were to be tested sequentially: 1) COVID-19 regardless of evidence of prior infection, 2) SARS-CoV-2 infection regardless of symptomatology or severity, and 3) severe COVID-19, each against $H_0: VE \leq 0\%$ at a one-sided Type I error rate of 2.5%. Additional hypotheses of $H_0: VE \leq 10\%$, $H_0: VE \leq 20\%$, and $H_0: VE \leq 30\%$ were tested sequentially over the three endpoints upon rejection of the previous H_0 for all three endpoints.

Participants who had no documented SARS-CoV-2 infection were censored at the last study assessment date. Participants who discontinued the study, those who died due to cause unrelated to COVID-19, and those infected prior to 14 days post Dose 2 were censored at the respective event date. The documented COVID-19 date was defined as the later date of 1) the earliest systemic and/or respiratory symptoms reported and 2) the positive RT-PCR test, where the two dates must be within 14 days of each other.

The Per-Protocol Set (PPS) was the primary analysis population, consisting of subjects who had no serologic or virologic evidence of SARS-CoV-2 infection prior to Dose 1, received planned doses of the randomized treatment per schedule, and had no major protocol deviations that impact key study data. Efficacy against COVID-19 regardless of evidence of prior infection was estimated based on the Full Analysis Set (FAS), consisting of all subjects who received at least one dose of the investigational product, analyzed according to the treatment group randomized.

Primary analyses of COVID-19 (primary endpoint definition) and severe COVID-19 cases were based on determinations by the adjudication committee. Supportive analyses were performed based on cases derived per Statistical Analysis Plan (SAP) and based on the Modified Intent-to-Treat (mITT) population, consisting of subjects in the FAS with no evidence of prior infection at Dose 1. Subgroup analyses included estimates of VE by randomization stratum, sex, ethnicity, and race.

Safety

Solicited safety analyses were based on subjects who received at least one dose of the study intervention and responded yes or no to the reaction within seven days of each dose. Unsolicited safety analyses were based on the Safety Set, which consisted of all subjects who received at least one dose of the study intervention, analyzed according to the intervention received. Safety endpoints were summarized descriptively by computing the number and percentage of participants within the analysis set who reported at least one event.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 30,415 participants were randomized (Table 2), of whom 99.8% received at least one dose of the investigational product and 93.5% were included in the PPS for efficacy. The percentages of subjects who received each dose were similar between the

intervention groups. A slightly higher percentage of subjects in the placebo group discontinued the study compared to the mRNA-1273 group.

Table 2. Subject Disposition

	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Randomized	15209	15206	30415
Received Dose 1	15180 (99.8)	15166 (99.7)	30346 (99.8)
Received Dose 2	14727 (96.8)	14635 (96.2)	29362 (96.5)
Discontinued from vaccination	453 (3.0)	531 (3.5)	984 (3.2)
Adverse event	47 (0.3)	44 (0.3)	91 (0.3)
Serious adverse event	12 (<0.1)	18 (0.1)	30 (<0.1)
Death	2 (<0.1)	3 (<0.1)	5 (<0.1)
Loss to follow-up	76 (0.5)	73 (0.5)	149 (0.5)
Physician decision	21 (0.1)	18 (0.1)	39 (0.1)
Pregnancy	3 (<0.1)	4 (<0.1)	7 (<0.1)
Protocol deviation	37 (0.2)	37 (0.2)	74 (0.2)
Withdrawal of consent	78 (0.5)	108 (0.7)	186 (0.6)
Due to SARS-CoV-2	81 (0.5)	119 (0.8)	200 (0.7)
Other	94 (0.6)	104 (0.7)	198 (0.7)
Discontinued from the study	440 (2.9)	691 (4.5)	1131 (3.7)
Adverse event	4 (<0.1)	5 (<0.1)	9 (<0.1)
Serious adverse event	5 (<0.1)	3 (<0.1)	8 (<0.1)
Death	16 (0.1)	15 (<0.1)	31 (0.1)
Loss to follow-up	160 (1.1)	191 (1.3)	351 (1.2)
Physician decision	13 (<0.1)	7 (<0.1)	20 (<0.1)
Pregnancy	0	0	0
Protocol deviation	46 (0.3)	160 (1.1)	206 (0.7)
Withdrawal of consent	155 (1.0)	250 (1.6)	405 (1.3)
Due to SARS-CoV-2	0	0	0
Other	41 (0.3)	60 (0.4)	101 (0.3)
Full Analysis Set	15180 (99.8)	15166 (99.7)	30346 (99.8)
Modified Intent-to-Treat Set	14746 (97.0)	14745 (97.0)	29491 (97.0)
Per-Protocol Set	14287 (93.9)	14164 (93.1)	28451 (93.5)
Safety Set	15184 ¹	15162 ¹	30346

¹Number of subjects as treated.

Source: Adapted from Tables 5-1 and 5-2 of P301 Clinical Study Report.

6.1.10.1.1 Demographics

Table 3 presents demographic characteristics for the Safety Set and PPS. Baseline demographics were generally similar between the placebo and mRNA-1273 groups and between the analysis sets with regard to age, sex, race, and ethnicity. Overall, among the study participants in the PPS, 52.5% were male, 79.7% were White, 19.7% were Hispanic or Latino, and 25.3% aged 65 years and above.

Table 3. Demographic Characteristics of the Safety and PPS Populations

	mRNA-1273 Safety Set N=15184 n (%)	Placebo Safety Set N=15162 n (%)	mRNA-1273 PPS N=14287 n (%)	Placebo PPS N=14164 n (%)
Sex	-	-	-	-
Male	7918 (52.1)	8056 (53.1)	7439 (52.1)	7494 (52.9)
Female	7266 (47.9)	7106 (46.9)	6848 (47.9)	6670 (47.1)
Race	-	-	-	-
White	12034 (79.3)	11998 (79.1)	11391 (79.7)	11273 (79.6)
Black/African-American	1567 (10.3)	1531 (10.1)	1395 (9.8)	1352 (9.5)
American Indian/Alaskan Native	113 (0.7)	121 (0.8)	109 (0.8)	113 (0.8)
Asian	656 (4.3)	739 (4.9)	628 (4.4)	700 (4.9)
Native Hawaiian/Other Pacific Islander	36 (0.2)	32 (0.2)	36 (0.3)	31 (0.2)
Multiracial	320 (2.1)	318 (2.1)	300 (2.1)	304 (2.1)
Other	299 (2.0)	294 (1.9)	282 (2.0)	274 (1.9)
Not Reported	97 (0.6)	74 (0.5)	90 (0.6)	65 (0.5)
Unknown	62 (0.4)	55 (0.4)	56 (0.4)	52 (0.4)
Ethnicity	-	-	-	-
Hispanic/Latino	3122 (20.6)	3108 (20.5)	2831 (19.8)	2787 (19.7)
Non-Hispanic/Non-Latino	11920 (78.5)	11918 (78.6)	11322 (79.2)	11249 (79.4)
Not Reported	105 (0.7)	83 (0.5)	99 (0.7)	76 (0.5)
Unknown	37 (0.3)	53 (0.3)	35 (0.2)	52 (0.4)
Randomization Stratum	-	-	-	-
18 to <65 years and not at risk	8890 (58.5)	8880 (58.6)	8271 (57.9)	8242 (58.2)
18 to <65 years and at risk	2530 (16.7)	2535 (16.7)	2395 (16.8)	2331 (16.5)
≥65 years	3764 (24.8)	3747 (24.7)	3621 (25.3)	3591 (25.4)
Age	-	-	-	-
Mean (Standard Deviation)	51.4 (15.5)	51.3 (15.6)	51.6 (15.4)	51.6 (15.6)
Median (Minimum, Maximum)	53 (18, 95)	52 (18, 95)	53 (18, 95)	52 (18, 95)
Baseline SARS-CoV-2 status	-	-	-	-
Negative	14750 (97.1)	14741 (97.2)	14287 (100)	14164 (100)
Positive	347 (2.3)	337 (2.2)	-	-
Missing	87 (0.6)	84 (0.6)	-	-

Source: Adapted from Tables 14.1.3.2.3 and 14.1.3.4.2 of P301 Clinical Study Report.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

Efficacy against COVID-19 starting at 14 days after Dose 2 as assessed by the adjudication committee is presented in Table 4 at each analysis time point. The primary efficacy objective was met at the first and only interim analysis, with 5 COVID-19 cases in the mRNA-1273 group and 90 cases in the placebo group, resulting in an estimated VE of 94.5% (95% CI: 86.5% - 97.8%) and a one-sided p-value of <0.001 for testing H0: VE ≤30%. The final efficacy analysis included 799 adjudicated cases, with 55 cases in the mRNA-1273 group and 744 cases in the placebo group, corresponding to a median blinded follow-up of 119 days from Dose 2 and a VE of 93.2% (95% CI: 91.0% - 94.8%).

Table 4. COVID-19 Per Adjudication Committee Starting at 14 Days Post Dose 2 (PPS)

Analysis (Cut-off Date)	mRNA-1273 Cases/N	Placebo Cases/N	VE (95% CI)
Interim Analysis (Nov 11, 2020)	5/13934	90/13883	94.5 (86.5, 97.8)
Primary Analysis (Nov 25, 2020)	11/14134	185/14073	94.1 (89.3, 96.8)
Final Analysis (Mar 26, 2021)	55/14287	744/14164	93.2 (91.0, 94.8)

N = number of subjects in the PPS at the data cut-off.

Source: Adapted from Tables 6-1 and 6-2 of P301 Clinical Study Report.

6.1.11.2 Analyses of Secondary Endpoints

Table 5 presents VE estimates for each secondary efficacy endpoint. Figure 1 shows the cumulative incidence curve starting at randomization in the mITT Set. There were a total of 108 adjudicated, severe COVID-19 cases starting at 14 days after Dose 2 during blinded follow-up, of which 106 were in the placebo group (VE=98.2%; 95% CI: 92.8% - 99.6%). VE estimates based on the SAP-derived cases for both the primary COVID-19 case definition and severe COVID-19 were consistent with those assessed by the adjudication committee.

Similarly high efficacies were observed against the CDC case definition (VE=93.4%; 95% CI: 91.4% - 94.9%), COVID-19 per adjudication starting at 14 days after Dose 1 (VE=93.3%; 95% CI: 91.1% - 94.9%), and COVID-19 regardless of evidence of prior SARS-CoV-2 infection (VE=92.8%; 95% CI: 90.6% - 94.5%), while lower efficacies were observed against SARS-CoV-2 infection regardless of symptomatology (VE=82.2%; 95% CI: 79.7% - 84.3%) and asymptomatic infection (VE=62.9%; 95% CI: 56.4% - 68.5%).

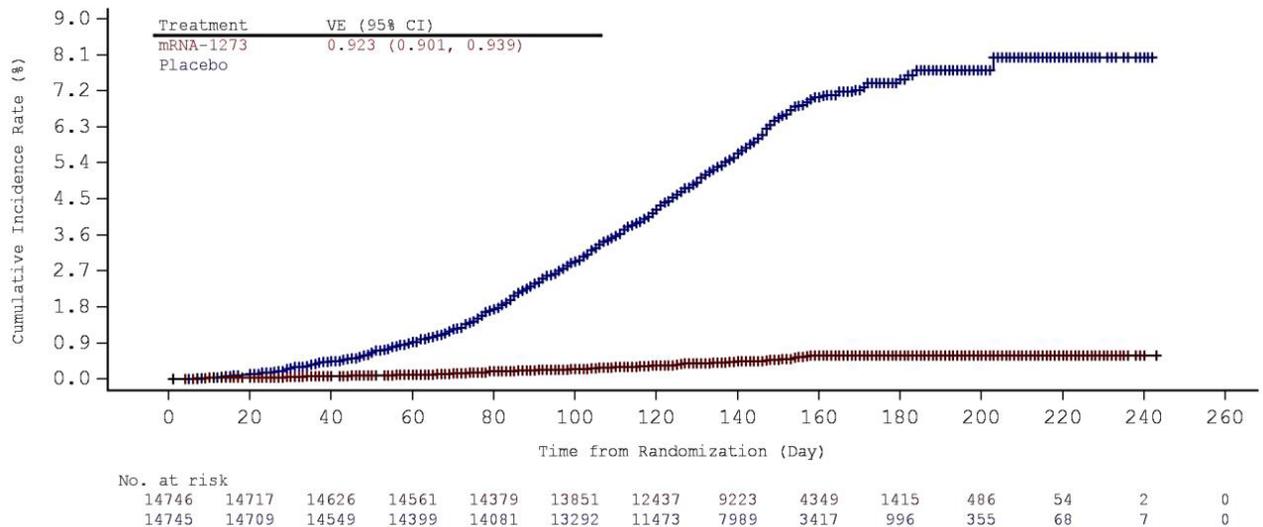
Table 5. Secondary Efficacy Analysis Results Starting at 14 Days Post Dose 2 (PPS and FAS)

Endpoint	mRNA-1273 Cases/N	Placebo Cases/N	VE (95% CI)
COVID-19 per SAP \geq 14 days post Dose 2	55/14287	751/14164	93.2 (91.1, 94.9)
COVID-19 per adjudication \geq 14 days post Dose 1	56/14287	769/14164	93.3 (91.1, 94.9)
COVID-19 per SAP \geq 14 days post Dose 1	58/14287	782/14164	93.1 (91.0, 94.7)
Severe COVID-19 per adjudication \geq 14 days post Dose 2	2/14287	106/14164	98.2 (92.8, 99.6)
Severe COVID-19 per SAP \geq 14 days post Dose 2	3/14287	118/14164	97.6 (92.4, 99.2)
SARS-CoV-2 infection \geq 14 days post Dose 2	275/14287	1327/14164	82.2 (79.7, 84.3)
CDC definition \geq 14 days post Dose 2	58/14287	807/14164	93.4 (91.4, 94.9)
Death due to COVID-19 \geq 14 days post Dose 2	0/14287	3/14164	100 (NE, 100)
Asymptomatic infection \geq 14 days post Dose 2	210/14287	487/14164	62.9 (56.4, 68.5)
COVID-19 per adjudication regardless of prior SARS-CoV-2 infection \geq 14 days post Dose 2	58/15180	754/15166	92.8 (90.6, 94.5)
COVID-19 per SAP regardless of prior SARS-CoV-2 infection \geq 14 days post Dose 2	58/15180	762/15166	92.9 (90.7, 94.6)

NE = not evaluable; *N* = number of subjects in the PPS or FAS.

Source: Table 6 of Clinical Overview and Tables 1-2 and 1-3 of Response to December 6, 2021 Information Request.

Figure 1. Adjudicated COVID-19 Cumulative Incidence Starting After Randomization (mITT)



Source: Figure 6-1 of P301 Clinical Study Report.

Reviewer Comments:

- The efficacy analyses were confirmed based on data submitted in the Standard Data Tabulation Model (SDTM) format, and the results were consistent with those reported by the Applicant.
- Subjects who met the definitions for COVID-19, including severe COVID-19 and CDC-defined COVID-19, but had a positive RT-PCR or serology at a scheduled visit prior to disease onset were censored at the date of the scheduled visit. However, subjects who did not meet the definition of symptomatic COVID-19 but had a positive test at a scheduled visit did not appear to be censored at that visit. Nonetheless, censoring all subjects who reported a positive test at a scheduled visit regardless of subsequent disease status did not yield a major difference in the VE estimates based on my sensitivity analysis.
- Supportive analyses of VE based on the incidence rate ratio and based on the mITT resulted in similar estimates for each efficacy endpoint.
- Of the 806 COVID-19 cases derived based on the SAP starting at 14 days after Dose 2, 11 (10 placebo and 1 mRNA-1273) have not yet been adjudicated and 2 (both placebo) were adjudicated not to be a case. Of the 799 adjudicated cases of COVID-19, 6 (5 placebo and 1 mRNA-1273) did not meet the protocol-specified case definition for symptomatology or virology.
- SARS-CoV-2 infections regardless of symptomatology and asymptomatic infection were derived based on both serology and RT-PCR tests from scheduled visits up to and including the Participant Decision Visit. The original analyses of VE against SARS-CoV-2 infection regardless of symptomatology and asymptomatic infection starting at 14 days after Dose 2 in the P301 Clinical Study Report included infections that occurred outside of blinded follow-up and excluded infections prior to unblinding as a result of mis-labelling the “Visit” of assayed samples. For example, some subjects tested positive using samples labelled “Participant Decision Visit” which were in fact collected on a date after the

actual decision visit, resulting in inappropriate inclusion into the case split. Likewise, some subjects tested positive using samples collected on the same date as the actual Participant Decision Visit, but were not counted as cases since the “Visit” was not labelled as the “Participant Decision Visit.” Several information requests were communicated to the Applicant to clarify and reconcile differences between the data and the results and to rectify the analyses. The VE estimates for these two endpoints in Table 5 reflect the corrected analyses from the Applicant.

- The asymptomatic infection definition excluded SARS-CoV-2-positive subjects who fulfilled the protocol or CDC’s definition of COVID-19 prior to infection, but did not exclude those who later developed COVID-19. As a result, SARS-CoV-2-positive subjects who reported symptoms within days after a positive test were still considered asymptomatic, provided no symptoms were reported at the time of sample collection, since COVID-19 onset was defined as the later date of the first RT-PCR test or symptom (i.e. disease began after infection). Thus, some of the asymptomatic infections may not have been truly symptom-free. CBER requested the Applicant to conduct a sensitivity analysis of VE against asymptomatic infection excluding asymptomatic cases from subjects who reported any protocol or CDC-defined COVID-19 symptom at any time during the study, corrected for the issues noted above. The sensitivity analysis resulted in 399 cases in the placebo group, 180 cases in the mRNA-1273 group, and a VE of 61.0% (95% CI: 53.4% - 67.3%).

6.1.11.3 Subpopulation Analyses

Descriptive subgroup efficacy estimates are presented in Table 6. Overall, efficacy against COVID-19 based on adjudication committee assessments starting at 14 days after Dose 2 were consistent across strata defined by age and presence of risk factors, sex, ethnicity, and race.

Table 6. Efficacy Against COVID-19 per Adjudication by Subgroup (PPS)

	mRNA-1273 Cases/N	Placebo Cases/N	VE (95% CI)
-	-	-	-
Age and presence of risk factors	-	-	-
18 to <65 years and not at risk	35/8464	501/8428	93.5 (90.9, 95.4)
18 to <65 years and at risk	11/2197	143/2141	92.9 (87.0, 96.2)
≥65 years	9/3626	100/3595	91.5 (83.2, 95.7)
Sex	-	-	-
Male	30/7439	378/7494	92.5 (89.1, 94.8)
Female	25/6848	366/6670	93.8 (90.7, 95.9)
Ethnicity	-	-	-
Hispanic or Latino	10/2831	177/2787	94.8 (90.2, 97.3)
Not Hispanic or Latino	45/11322	563/11249	92.6 (89.9, 94.5)
Race	-	-	-
White and Non-Hispanic/Latino	39/9123	488/8998	92.6 (89.8, 94.7)
Others	16/5139	256/5141	94.2 (90.3, 96.5)

N = number of subjects in the PPS.

Source: Adapted from Figure 6-2 of P301 Clinical Study Report.

Reviewer Comment:

- *Some subjects were categorized into a randomization stratum different from their reported age and presence of risk factors, hence the difference in the total number of subjects in each age by risk group between Tables 3 and 6. Nonetheless, this did not notably affect balance between treatment groups with respect to age and risk factors.*

6.1.12 Safety Analyses

Solicited Local and Systemic Reactions

Tables 7 and 8 present the frequency of each solicited local and systemic reaction within seven days of each dose for participants 18 to 64 years of age and participants ≥ 65 years of age, respectively. Incidence of any local and systemic reaction was generally higher among mRNA-1273 recipients than among placebo recipients in both age groups after either dose. In both the younger and older age groups, after Dose 2 of mRNA-1273, pain at the injection site (89.9% and 83.2%, respectively) was the most frequently reported solicited adverse reaction, followed by fatigue (67.8% and 58.4%), headache (63.0% and 46.3%), and myalgia (61.7% and 47.2%).

The frequency and severity of systemic reactions were generally higher in the younger age group and after Dose 2 regardless of age. Among mRNA-1273 recipients, the median duration of pain at the injection site after Dose 2 was 3.0 days (range 1 to 154 days), 2.0 days for erythema (range 1 to 39 days), 2.0 days for swelling (range 1 to 31 days), and 2.0 days (range 1 to 155 days) for axillary swelling/tenderness.

Table 7. Frequency of Solicited Reactions by Dose in Participants 18 to 64 Years of Age

	mRNA-1273 Dose 1 n (%)	Placebo Dose 1 n (%)	mRNA-1273 Dose 2 n (%)	Placebo Dose 2 n (%)
Pain	N=11402	N=11400	N=10999	N=10928
Any	9908 (86.9)	2183 (19.1)	9893 (89.9)	2048 (18.7)
Grade ≥ 3	366 (3.2)	23 (0.2)	506 (4.6)	22 (0.2)
Erythema (redness)	N=11402	N=11400	N=10998	N=10928
Any	354 (3.1)	54 (0.5)	989 (9.0)	53 (0.5)
Grade ≥ 3	34 (0.3)	11 (<0.1)	210 (1.9)	12 (0.1)
Swelling (hardness)	N=11402	N=11400	N=10998	N=10928
Any	766 (6.7)	42 (0.4)	1399 (12.7)	46 (0.4)
Grade ≥ 3	62 (0.5)	3 (<0.1)	183 (1.7)	5 (<0.1)
Axillary swelling/tenderness	N=11402	N=11400	N=10998	N=10928
Any	1322 (11.6)	567 (5.0)	1777 (16.2)	474 (4.3)
Grade ≥ 3	37 (0.3)	13 (0.1)	47 (0.4)	12 (0.1)
Fever	N=11404	N=11400	N=10993	N=10925
Any ($\geq 38.0^\circ\text{C}$)	102 (0.9)	37 (0.3)	1909 (17.4)	38 (0.3)
Grade ≥ 3 ($\geq 39.0^\circ\text{C}$)	14 (0.1)	5 (<0.1)	197 (1.8)	4 (<0.1)
Headache	N=11402	N=11400	N=10998	N=10926
Any	4028 (35.3)	3303 (29.0)	6929 (63.0)	2775 (25.4)
Grade ≥ 3	220 (1.9)	163 (1.4)	559 (5.1)	132 (1.2)

	mRNA-1273 Dose 1 n (%)	Placebo Dose 1 n (%)	mRNA-1273 Dose 2 n (%)	Placebo Dose 2 n (%)
Fatigue	N=11402	N=11400	N=10998	N=10926
Any	4385 (38.5)	3281 (28.8)	7453 (67.8)	2701 (24.7)
Grade ≥3	122 (1.1)	83 (0.7)	1178 (10.7)	88 (0.8)
Myalgia	N=11402	N=11400	N=10998	N=10926
Any	2700 (23.7)	1625 (14.3)	6789 (61.7)	1425 (13.0)
Grade ≥3	74 (0.6)	38 (0.3)	1116 (10.1)	42 (0.4)
Arthralgia	N=11402	N=11400	N=10998	N=10926
Any	1892 (16.6)	1327 (11.6)	5010 (45.6)	1180 (10.8)
Grade ≥3	48 (0.4)	30 (0.3)	650 (5.9)	37 (0.3)
Nausea/Vomiting	N=11402	N=11400	N=10998	N=10926
Any	1068 (9.4)	908 (8.0)	2355 (21.4)	807 (7.4)
Grade ≥3	6 (<0.1)	8 (<0.1)	11 (0.1)	8 (<0.1)
Chills	N=11402	N=11400	N=10998	N=10926
Any	1050 (9.2)	730 (6.4)	5357 (48.7)	662 (6.1)
Grade ≥3	17 (0.1)	8 (<0.1)	164 (1.5)	15 (0.1)

N=number of subjects responding yes or no to the reaction within seven days of injection.

n=number of subjects with the specified reaction.

Source: Adapted from Tables 7-6 and 7-7 of P301 Clinical Study Report.

Table 8. Frequency of Solicited Reactions by Dose in Participants ≥65 Years of Age

	mRNA-1273 Dose 1 n (%)	Placebo Dose 1 n (%)	mRNA-1273 Dose 2 n (%)	Placebo Dose 2 n (%)
Pain	N=3760	N=3747	N=3689	N=3649
Any	2780 (73.9)	482 (12.9)	3071 (83.2)	438 (12.0)
Grade ≥3	50 (1.3)	32 (0.9)	100 (2.7)	19 (0.5)
Erythema (redness)	N=3760	N=3747	N=3689	N=3649
Any	91 (2.4)	23 (0.6)	285 (7.7)	15 (0.4)
Grade ≥3	8 (0.2)	2 (<0.1)	77 (2.1)	3 (<0.1)
Swelling (hardness)	N=3760	N=3747	N=3689	N=3649
Any	169 (4.5)	23 (0.6)	408 (11.1)	14 (0.4)
Grade ≥3	20 (0.5)	3 (<0.1)	72 (2.0)	7 (0.2)
Axillary swelling/tenderness	N=3760	N=3747	N=3689	N=3649
Any	231 (6.1)	155 (4.1)	315 (8.5)	97 (2.7)
Grade ≥3	12 (0.3)	14 (0.4)	21 (0.6)	8 (0.2)
Fever	N=3759	N=3749	N=3689	N=3648
Any (≥38.0°C)	10 (0.3)	7 (0.2)	367 (9.9)	5 (0.1)
Grade ≥3 (≥39.0°C)	1 (<0.1)	3 (<0.1)	19 (0.5)	1 (<0.1)
Headache	N=3760	N=3746	N=3689	N=3649
Any	922 (24.5)	723 (19.3)	1708 (46.3)	652 (17.9)
Grade ≥3	53 (1.4)	34 (0.9)	107 (2.9)	33 (0.9)
Fatigue	N=3760	N=3746	N=3689	N=3649
Any	1251 (33.3)	852 (22.7)	2154 (58.4)	717 (19.6)
Grade ≥3	30 (0.8)	22 (0.6)	255 (6.9)	20 (0.5)
Myalgia	N=3760	N=3746	N=3689	N=3649
Any	742 (19.7)	444 (11.9)	1740 (47.2)	399 (10.9)
Grade ≥3	17 (0.5)	9 (0.2)	205 (5.6)	10 (0.3)
Arthralgia	N=3760	N=3746	N=3689	N=3649

	mRNA-1273 Dose 1 n (%)	Placebo Dose 1 n (%)	mRNA-1273 Dose 2 n (%)	Placebo Dose 2 n (%)
-				
Any	618 (16.4)	457 (12.2)	1293 (25.1)	399 (10.9)
Grade ≥ 3	13 (0.3)	8 (0.2)	125 (3.4)	7 (0.2)
Nausea/Vomiting	N=3760	N=3746	N=3689	N=3649
Any	194 (5.2)	167 (4.5)	439 (11.9)	134 (3.7)
Grade ≥ 3	4 (0.1)	5 (0.1)	11 (0.3)	3 (<0.1)
Chills	N=3760	N=3746	N=3689	N=3649
Any	201 (5.3)	148 (4.0)	1143 (31.0)	151 (4.1)
Grade ≥ 3	7 (0.2)	6 (0.2)	27 (0.7)	2 (<0.1)

N=number of subjects responding yes or no to the reaction within seven days of injection.

n=number of subjects with the specified reaction.

Source: Adapted from Tables 7-6 and 7-7 of P301 Clinical Study Report.

Unsolicited Adverse Events

Tables 9 and 10 present the numbers and percentages of subjects who reported any unsolicited AE, MAAE, SAE, or AE leading to discontinuation of vaccination or study participation after the first dose. These numbers are reported for three separate risk windows: a) Dose 1 to 28 days after any dose, b) Dose 1 to unblinding or data cut-off (whichever is first), and c) unblinding to data cut-off.

The percentages of subjects reporting any unsolicited AE, MAAE, SAE, death, and AE leading to discontinuation of vaccination or study participation were generally similar between arms up to 28 days after any dose and from Dose 1 to unblinding. A higher percentage of mRNA-1273 recipients reported any related AE after Dose 1 than placebo recipients. There was no death up to the data cut-off that was considered by the investigator to be related to the investigational product. SAEs considered related to the investigational product by the investigator were reported by 12 (<0.1%) mRNA-1273 recipients during blinded follow-up compared to four (<0.1%) in the placebo group. In these analyses, the median duration of follow-up was 147 days from Dose 1 to unblinding and 67 days from unblinding to the March 26, 2021 cut-off.

A total of 12,648 subjects who originally received placebo received at least one dose of mRNA-1273 after unblinding. Among these subjects, four (<0.1%) reported an SAE prior to cut-off that were considered related to the study vaccine by the investigator.

Table 9. Number of Subjects Reporting Any AE by Time Period – Blinded Follow-up (Safety Set)

	mRNA-1273 Dose 1 to 28 Days After Any Dose N=15184 n (%)	Placebo Dose 1 to 28 Days After Any Dose N=15162 n (%)	mRNA-1273 Dose 1 to Unblinding or Cut-off N=15184 n (%)	Placebo Dose 1 to Unblinding or Cut-off N=15162 n (%)
-				
Any AE	4752 (31.3)	4338 (28.6)	6310 (41.6)	6513 (43.0)
Serious	98 (0.6)	104 (0.7)	268 (1.8)	292 (1.9)
Fatal	2 (<0.1)	2 (<0.1)	17 (0.1)	16 (0.1)

	mRNA-1273 Dose 1 to 28 Days After Any Dose N=15184 n (%)	Placebo Dose 1 to 28 Days After Any Dose N=15162 n (%)	mRNA-1273 Dose 1 to Unblinding or Cut-off N=15184 n (%)	Placebo Dose 1 to Unblinding or Cut-off N=15162 n (%)
-				
Medically-attended	1819 (12.0)	1940 (12.8)	3468 (22.8)	4131 (27.2)
Discontinued vaccination	61 (0.4)	92 (0.6)	74 (0.5)	109 (0.7)
Discontinued study	9 (<0.1)	6 (<0.1)	26 (0.2)	23 (0.2)
Severe	258 (1.7)	233 (1.5)	461 (3.0)	486 (3.2)
Any related AE	2067 (13.6)	1236 (8.2)	2107 (13.9)	1288 (8.5)
Serious	8 (<0.1)	3 (<0.1)	12 (<0.1)	4 (<0.1)
Fatal	0	0	0	0
Medically-attended	198 (1.3)	95 (0.6)	213 (1.4)	109 (0.7)
Discontinued vaccination	20 (0.1)	14 (<0.1)	20 (0.1)	15 (<0.1)
Discontinued study	1 (<0.1)	0	1 (<0.1)	0
Severe	83 (0.5)	31 (0.2)	88 (0.6)	34 (0.2)

N=number of subjects who received at least one dose of the study intervention.

n=number of subjects reporting at least one event.

Source: Adapted from Tables 7-12 and 7-13 of P301 Clinical Study Report.

Table 10. Number of Subjects Reporting Any AE by Time Period – Open-Label (Safety Set)

	mRNA-1273 Unblinding to Cut-off N=15184 n (%)	Placebo Unblinding to Cut-off N=2514¹ n (%)	Placebo- mRNA-1273 Unblinding to Cut-off N=12648² n (%)
-			
Any AE	1729 (11.4)	41 (1.6)	2446 (19.3)
Serious	141 (0.9)	7 (0.3)	148 (1.2)
Fatal	7 (<0.1)	1 (<0.1)	3 (<0.1)
Medically-attended	1457 (9.6)	37 (1.5)	1509 (11.9)
Discontinued vaccination	2 (<0.1)	0	12 (<0.1)
Discontinued study	7 (<0.1)	1 (<0.1)	4 (<0.1)
Severe	147 (1.0)	4 (0.2)	179 (1.4)
Any related AE	22 (0.1)	0	758 (6.0)
Serious	0	0	4 (<0.1)
Fatal	0	0	0
Medically-attended	9 (<0.1)	0	74 (0.6)
Discontinued vaccination	0	0	4 (<0.1)
Discontinued study	0	0	0
Severe	1 (<0.1)	0	24 (0.2)

N=number of subjects who received at least one dose of the study intervention.

n=number of subjects reporting at least one event.

Source: Table 7-1 of P301 Clinical Study Report Addendum 1.

Reviewer Comments:

- *The safety analyses were confirmed based on data submitted in the SDTM format, and the results were consistent with those reported by the Applicant.*
- *In the P301 Clinical Study Report, the Applicant calculated the duration of solicited reactions as the total number of distinct days an event was reported. As*

this may under-report the reactogenicity duration due to missing e-diary entries in between reports, CBER requested an alternate calculation of duration as one plus the last day minus the first day for which an event was reported, regardless of how many days the event was reported in between. These results are considered in this memo.

- *Questions were raised during the review regarding the safety results:*
 - *Many reactogenicity events reported in the e-diary starting on Day 8 of either dose were not appropriately included in the unsolicited AE frequencies. In my sensitivity analysis of unsolicited AEs up to 28 days of either dose, including all events reported in the e-diary starting on Day 8 of either dose increased the percentages of participants reporting any AE by approximately 1% in both groups, and by approximately 2% in both groups for any related AE. Thus, excluding these reactogenicity events did not appear to have a major impact on the safety results or conclusions.*
 - *Some unsolicited AEs may have been erroneously categorized by the investigator as reactogenicity. However, these AEs appear to be appropriately accounted for in the analyses.*
 - *Solicited AEs may have been documented by some participants as COVID-19 symptoms. The Applicant performed a sensitivity analysis, upon CBER's request, counting symptoms within seven days of injection consistent with reactogenicity from participants who subsequently tested negative by RT-PCR, and the results did not indicate a notable increase in solicited AE frequencies (<1% point difference in each group and event).*

Myocarditis and Pericarditis

No myocarditis was reported in the blinded and open-label portions of the study. Two placebo and two mRNA-1273 recipients (a 59-year-old female at 67 days after Dose 2 and a 65-year-old male at 72 days after Dose 2) reported pericarditis during blinded follow-up. Please refer to Drs. Rachel Zhang and Jaya Goswami's clinical review memo for additional safety analysis.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated analysis of efficacy was performed.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated analysis of safety was performed.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

No major statistical issues affecting study conclusions were identified for the efficacy and safety data. The primary efficacy objective was met at the first and only interim analysis with an estimated VE of 94.5% (95% CI: 86.5% - 97.8%) and a one-sided p-value of <0.001 for testing $H_0: VE \leq 30\%$. Efficacy remained high (VE=93.2%; 95% CI: 91.0% - 94.8%) at the final analysis after a median blinded follow-up of 119 days post Dose 2. Similarly high efficacies were observed against the secondary (CDC) case definition (VE=93.4%; 95% CI: 91.4% - 94.9%), COVID-19 starting 14 days after Dose 1 (VE=93.3%; 95% CI: 91.1% - 94.9%), and COVID-19 regardless of evidence of prior SARS-CoV-2 infection (VE=92.8%; 95% CI: 90.6% - 94.5%), while lower efficacies were observed against asymptomatic SARS-CoV-2 infection (VE=62.9%; 95% CI: 56.4% - 68.5%) and infection regardless of symptomatology (VE=82.2%; 95% CI: 79.7% - 84.3%).

The frequency and severity of local and systemic reactions were generally higher among mRNA-1273 recipients than among placebo recipients after either dose regardless of age. The most commonly reported adverse reactions were injection site pain, fatigue, headache, and myalgia. There was no notable difference in the frequencies of any unsolicited AE, MAAE, SAE, or death between arms during blinded follow-up.

10.2 Conclusions and Recommendations

Overall, the clinical data support the effectiveness of mRNA-1273. While there is some reactogenicity associated with mRNA-1273, the majority of solicited adverse reactions were mild or moderate in severity and of short duration. I defer to Drs. Rachel Zhang and Jaya Goswami on the overall safety conclusion for mRNA-1273.