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BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125752/0
CBER Received Date	August 24, 2021
PDUFA Goal Date	April 24, 2022
Division / Office	DVRPA / OVRP
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Rachel Zhang, MD CRB1/DVRPA/OVRP Jaya Goswami, MD, MA CRB1/DVRPA/OVRP
Review Completion Date / Stamped Date	January 28, 2022
Supervisory Concurrence	Anuja Rastogi, MD, MHS; Team Lead CRB1/DVRPA/OVRP Maria Allende, MD; Chief CRB1/DVRPA/OVRP
Applicant	Moderna TX, Inc.
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	SPIKEVAX
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.5 mL dose contains 100 mcg modified mRNA encoding SARS-CoV-2 spike glycoprotein, encapsulated in lipid particles
Dosage Form and Route of Administration	Suspension for intramuscular injection (IM)
Dosing Regimen	Two 0.5 mL doses, 1 month 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
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
bAb	binding antibody
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CSR	clinical study report
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CRF	case report form
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
DVRPA	Division of Vaccines and Related Products Applications
DVT	deep vein thrombosis
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICU	intensive care unit
IgG	immunoglobulin
IM	intramuscular
IND	investigational new drug
IP	investigational product
IR	Information Request (by FDA)
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MS	multiple sclerosis
mITT	modified intent-to-treat
NAAT	nucleic acid amplification-based test
nAb	neutralizing antibody
NP	nasopharyngeal
PDUFA	Prescription Drug User Fee Act
PDV	Participant Decision Visit
PMC	postmarketing commitment
PMR	postmarketing requirement
PPRSI	Per-Protocol Random Subcohort for Immunogenicity
PPS	Per-Protocol Set
PREA	Pediatric Research Equity Act
PsvNA	pseudotyped virus neutralization assay
PT	Preferred Term
RR	relative risk
RT-PCR	reverse transcription-polymerase chain reaction

SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STN	Submission Tracking Number
TTS	thrombosis with thrombocytopenia syndrome
U.S.	United States
USPI	U.S. Prescribing Information
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	Variant of Concern
VOI	Variant of Interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink

1. Executive Summary

An original Biologics License Application (BLA) has been submitted by ModernaTX, Inc. for candidate COVID-19 vaccine, mRNA-1273 (trade name SPIKEVAX, also referred to as mRNA-1273 vaccine during clinical development and as Moderna COVID-19 Vaccine under Emergency Use Authorization) with a proposed indication for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The primary immunization series consists of 2 intramuscular (IM) doses (100 mcg each) administered 1 month apart. mRNA-1273 is nucleoside modified mRNA that encodes for the full-length spike protein of SARS-CoV-2 encapsulated in lipid particles. The SARS-CoV-2 spike protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAb) that prevent infection.

Data to support the safety and efficacy of mRNA-1273 vaccine are primarily from Study P301, a Phase 3, randomized, placebo-controlled, observer-blind trial being conducted in the United States (U.S.) in approximately 30,000 participants randomized 1:1 to mRNA-1273 vaccine or placebo. The primary efficacy objective is to evaluate the efficacy of mRNA-1273 vaccine to prevent laboratory-confirmed, symptomatic COVID-19 starting 14 days after Dose 2 in participants without evidence of SARS-CoV-2 infection prior to Dose 1. Vaccine efficacy (VE) against severe COVID-19 is assessed as a secondary endpoint. Participants are followed for solicited local and systemic adverse reactions for 7 days after each dose, for unsolicited adverse events (AEs) for 28 days after each dose, and for medically attended adverse events (MAAEs) and serious adverse events (SAEs) for the planned study duration of 2 years.

Efficacy and safety data from the primary analysis (data cutoff of November 21, 2020 for efficacy and November 25, 2020 for safety) were used to support Emergency Use Authorization (EUA) of Moderna COVID-19 Vaccine on December 18, 2020. Following this EUA, the protocol for Study P301 was amended to permit study participants to request unblinding so that those who received placebo could opt to receive two doses of mRNA-1273 vaccine. All participants in this “crossover group” continued to be followed in an open-label manner after unblinding. The BLA submission included updated efficacy analyses of COVID-19 accrued during the blinded phase of the study, through the data cutoff date of March 26, 2021. The median duration of blinded follow-up for safety and efficacy after Dose 2 was 4 months. In the mRNA-1273 vaccine group (n=15,184), the median follow-up duration after Dose 2, including both blinded and open-label phases, was approximately 6 months. The BLA included updated safety data accumulated in both the blinded and open-label phases.

In the updated efficacy analysis of the blinded phase, among the 28,451 participants (n=14,287 mRNA-1273 vaccine and n=14,164 placebo) in the Per-Protocol Set without evidence of prior SARS-CoV-2 infection, vaccine efficacy to prevent protocol-defined COVID-19 starting 14 days after Dose 2 was 93.2% (95% CI: 91.0, 94.8). Efficacy was similarly high across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19, although interpretation of some subgroup analyses was limited by low number of cases and/or participants. Updated vaccine efficacy against severe COVID-19 starting 14 days after Dose 2 was 98.2% (95% CI 92.8, 99.6). Overall, the updated efficacy analysis results were consistent with the VE results of the primary analysis that was used to support EUA of the Moderna COVID-19 Vaccine.

The majority of COVID-19 cases in the study were identified by sequencing as SARS-CoV-2 variant B.1.2. Additional SARS-CoV-2 variants identified in the study included B.1.427/B.1.429 (Epsilon), P.1 (Gamma), and P.2 (Zeta), though the numbers were too small to allow for variant-specific estimates of VE. The data cutoff for the blinded phase occurred prior to the widespread circulation of the B.1.617.2 (Delta) variant within the U.S. and prior to the emergence of the B.1.1.529 (Omicron) variant. Despite evidence from published observational studies of waning protection following primary vaccination and decreased effectiveness against some SARS-CoV-2 variants (e.g., Omicron), the clinical benefits of primary vaccination with mRNA-1273 vaccine remain clear, especially regarding protection against more severe COVID-19 and its serious sequelae. Additional doses (e.g., 3rd primary series dose for certain immunocompromised adults and booster dose for the general adult population) improve upon the benefits provided by the primary series and are currently available under EUA, with the potential for approval in a future BLA supplement.

The safety population at the March 26, 2021 data cutoff included 15,184 mRNA-1273 vaccine recipients and 15,162 placebo recipients. In participants 18 through 64 years of age (abbreviated 18-64 years of age), the most commonly reported ($\geq 10\%$) adverse reactions were pain at injection site (93.3%), fatigue (71.9%), headache (68.7%), myalgia (64.8%), chills (49.7%), arthralgia (48.6%), nausea/vomiting (25.7%), axillary swelling/tenderness (22.2%), fever (17.3%), swelling at the injection site (15.4%), and erythema at the injection site (10.5%). In participants 65 years of age and older, the most commonly reported ($\geq 10\%$) adverse reactions were pain at injection site (88.3%), fatigue (64.8%), headache (53.3%), myalgia (51.8%), arthralgia (40.2%), chills (32.7%), nausea/vomiting (15.0%), swelling at the injection site (13.0%), and axillary swelling/tenderness (12.7%). Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

In Study P301, numerical imbalances in unsolicited AEs between treatment groups (with greater number in the mRNA-1273 vaccine group compared to placebo) from Dose 1 through 1 month after Dose 2 included lymphadenopathy-related events (264 vs 167), herpes zoster (22 vs 15), and facial paralysis (2 vs 1). In the blinded phase of the study which included a median duration of follow-up of 4 months after Dose 2, facial paralysis was reported in 8 participants in the mRNA-1273 vaccine group and 3 in the placebo group. The imbalance in lymphadenopathy-related events is consistent with the data on solicited axillary swelling/tenderness of the injected arm. For facial paralysis and herpes zoster, available information is insufficient to determine a causal relationship with vaccination. During the 7-day follow-up period after any vaccination, hypersensitivity events of injection site rash or injection site urticaria, likely related to vaccination, were reported by 6 participants in the mRNA-1273 vaccine group and none in the placebo group. Delayed injection site reactions that began >7 days after vaccination, likely related to vaccination, were reported by 219 participants in the mRNA-1273 vaccine group and 100 in the placebo group.

The SAE data from the blinded phase of Study P301 included a median duration follow up of 4 months after Dose 2. Overall, SAEs were reported by a similar proportion of participants after vaccination: 1.8% (401 events in 268 participants) in the vaccine group and 1.9% (439 events in 292 participants) in the placebo group. There were 32 deaths during the blinded phase of the study (Part A): 16 deaths in the vaccine group, and 16 in the placebo group. None of the unsolicited AEs leading to death were considered

vaccine-related. COVID-19 was reported as the event leading to death for 1 participant in the vaccine group and 3 in the placebo group. There were three serious adverse events of angioedema/ facial swelling in the vaccine group in recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1-2 days after the second dose and was likely related to vaccination. There were no other notable patterns or imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273 vaccine. Additionally, SAEs reported during the open-label phase of the study were reviewed and did not raise any new safety concerns.

There were no cases of anaphylaxis within 30 minutes of administration of mRNA-1273 vaccine in the study; however, anaphylaxis has been reported following EUA of Moderna COVID-19 Vaccine (10 cases per million doses, which is similar in magnitude to the risk of anaphylaxis following other approved preventive vaccines and can be managed with standard vaccination practices). The Applicant has proposed enhanced pharmacovigilance to monitor for this event, and anaphylaxis has been included in the Warnings and Precautions and Adverse Reactions sections of the U.S. Prescribing Information (USPI).

Although evaluation of adverse events in the P301 safety database (N=30,346) did not identify cases of postvaccination myocarditis, post-authorization safety surveillance for Moderna COVID-19 Vaccine has identified a risk of myocarditis and pericarditis that is higher in males than females, with greatest risk in males under the age of 40 following the second primary series dose. To address the identified risk of myocarditis/pericarditis, FDA conducted a quantitative, age-stratified benefit-risk analysis in males ≥ 18 years of age, using healthcare claims and Centers for Disease Control and Prevention (CDC) surveillance databases, to evaluate the balance of benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths against the risk of vaccine-related myocarditis/pericarditis cases, hospitalizations, ICU admissions, and deaths under various conditions of COVID-19 incidence and vaccine effectiveness informed by real-world data. The modeling attempted to account for preliminary estimates of Omicron-specific vaccine efficacy. While COVID-19 is known to cause myocarditis, and COVID-19-associated myocarditis may be more severe than vaccine-associated myocarditis, the model does not specifically estimate the number of COVID-19-associated cases of myocarditis that would have resulted in hospitalizations, ICU admission, or deaths in the absence of COVID-19 vaccination. Modeling for individuals ≥ 65 years and for females was not conducted due to limited cases of vaccine-related myocarditis/pericarditis for these populations. However, this evidence indicates a more favorable benefit-risk profile in individuals ≥ 65 years of age and in females as compared with males 18-64 years of age. Based on the current understanding of vaccine-associated myocarditis, the analyses support the benefits of vaccination over the risks of myocarditis/pericarditis for individuals ≥ 18 years of age. Mitigation of the observed risks of myocarditis/pericarditis and associated uncertainties will be accomplished through labeling (including warning statements about the risks of vaccine-associated myocarditis/pericarditis), continued safety surveillance, and postmarketing studies to be conducted by the Applicant, U.S. government agencies (including FDA and CDC), and other healthcare stakeholders.

The clinical data submitted exceed FDA's expectations for data to support licensure of vaccines for prevention of COVID-19 regarding relevant efficacy success criteria,

numbers of vaccinated study participants, safety database (i.e., 6 months of safety follow-up for at least 3,000 vaccinated participants in each age group). The clinical data submitted in this application, together with the quantitative benefit-risk assessment summarized in this review, support approval of a 2-dose primary series of mRNA-1273 vaccine (100 mcg each dose administered 28 days apart) for the indication of active immunization to prevent symptomatic coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older.

Pediatric studies of mRNA-1273 vaccine in children <18 years of age, as required by the Pediatric Research Equity Act, were deferred for this application, and will be completed after approval of mRNA-1273 vaccine for use in individuals 18 years of age and older. The Applicant committed to conduct additional postmarketing safety studies, including the assessment of pregnancy and birth outcomes following immunization with mRNA-1273 vaccine during pregnancy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The table below summarizes demographic representation of study participants who enrolled in Study P301 and were randomized to a two-dose series of mRNA-1273 vaccine or placebo.

Table 1. Randomized Participants by Subgroup, Study P301

Subgroup	mRNA-1273		Total
	vaccine	Placebo	
Age (≥18 years)	15209	15206	30415
18-64 years	11439	11443	22882
≥65 years	3770	3763	7533
Gender			
Male	7933	8080	16013
Female	7276	7126	14402
Ethnicity			
Hispanic/Latino	3126	3126	6252
Non-Hispanic/Non-Latino	11940	11944	23884
Not reported	143	136	279
Race			
White	12046	12031	24077
Black/African American	1574	1537	3111
All others	1589	1638	3227

Source: FDA-generated table.

The 28,451 participants included for the analyses of efficacy were largely White (79.7%), male (52.5%), and of non-Hispanic/non-Latino ethnicity (79.3%). The median age was 53 years and 25.4% of participants were 65 years of age or older. Subgroup analyses of vaccine efficacy did not suggest meaningful differences in efficacy across age, genders, racial and ethnic groups, or in participants with obesity or medical comorbidities associated with high risk of severe COVID-19, although analyses were limited by small numbers of cases in some subgroups.

The Safety Set was 47.4% female, 52.6% male, 20.5% Hispanic/Latino, 79.2% White, 10.2% Black or African American, 4.6% Asian, <3% other racial groups. The median age was 52 years, and 24.8% were older than 65 years. Overall, 22.8% of participants had protocol-defined high-risk conditions for severe COVID-19 and 38.2% of participants were obese. In safety analyses, reported rates of solicited local and systemic ARs and

use of antipyretic/pain medication in the 7 days after receipt of mRNA-1273 vaccine were generally lower among older adults (≥65 years) compared with younger adults (18-64 years). Other differences between the age groups in overall rates and types of unsolicited AEs and SAEs largely reflected differences in underlying medical conditions between the age groups. No clinically meaningful differences in the occurrence of solicited ARs, unsolicited AEs or SAEs were observed by, ethnicity, race, or sex subgroups.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	N/A
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with

SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of January 10, 2022, has caused approximately 306 million cases of COVID-19, including 5.49 million deaths worldwide. In the U.S., more than 60 million cases and 835,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following EUA of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the U.S. declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 leading to the Delta variant-associated peak in September of 2021. Following the report of the first U.S. case of COVID-19 attributed to the Omicron variant on December 1, 2021, daily numbers of new cases in the U.S. increased sharply, rising by about 540% in 6 weeks. Given the current winter season with more indoor activities due to cold weather, there is concern that the trend of increasing cases may continue.

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

The antiviral remdesivir is the only product currently approved by the FDA for use in adults and pediatric patients 12 years of age and older for treatment of COVID-19 requiring hospitalization. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients, and it remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure. Other pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 under EUA are as follows:

Antivirals

On December 22, 2021, FDA authorized Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. On December 23, 2021, FDA authorized the antiviral molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Three products have been authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older (and weighing at least 40 kg) at high risk for progressing to severe COVID-19: sotrovimab and the two combinations bamlanivimab/etesevimab and casirivimab/imdevimab. The latter combination is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in adults and pediatric patients 2 years of age and older who are at high risk for progressing to severe COVID-19. In light of new data showing that these two monoclonal antibody combinations are unlikely to be active against the Omicron variant, the FDA recently revised the authorizations to limit use to cases in which a patient is likely to have been infected with or exposed to a variant that is susceptible to these treatments.

Immune modulators: Baricitinib and tocilizumab are indicated for treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg.

COVID-19 convalescent plasma with high antibody titer is authorized as a treatment for hospitalized patients with COVID-19.

2.3 Safety and Efficacy of Pharmacologically Related Products

Pfizer-BioNTech COVID-19 mRNA vaccine

At present, only one COVID-19 vaccine has been approved by the FDA for prevention of COVID-19. On August 23, 2021, the Pfizer-BioNTech COVID-19 vaccine was approved for use in individuals 16 years of age and older, under the trade name Comirnaty (FDA 2021a). Efficacy for the prevention of COVID-19 occurring at least 7 days after completion of a two-dose primary series was evaluated in an ongoing Phase 3 study in approximately 44,000 participants who were randomized 1:1 to receive two doses of either Comirnaty or placebo, 3 weeks apart. Overall, 60.8% of participants in the Comirnaty group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after the primary series in the blinded placebo-controlled period. The overall VE against COVID-19 in subjects without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8, 93.1). The overall VE against COVID-19 in subjects with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5, 92.8).

Common solicited adverse reactions after vaccination were injection site reactions, fatigue, headache, muscle pain, chills, and joint pain, which were generally mild to moderate and lasted a few days. Among participants 16 through 55 years of age, SAEs were reported by 0.8% of Comirnaty recipients and 0.9% placebo recipients. In participants 56 years of age and older, SAEs were reported by 1.8% of Comirnaty recipients and 1.7% of placebo recipients. There were no notable patterns between treatment groups for specific categories of SAEs (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Comirnaty.

The Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use and is available under the EUA as a two-dose primary series in individuals 5 years of age and older, as a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions, and as a single booster dose in individuals 12 years of age and older. Comirnaty is also authorized for use as a heterologous (“mix and match”)

booster dose following completion of primary vaccination with a different authorized COVID-19 vaccine. Safety and efficacy data supporting these authorizations are detailed in the decision memoranda for the [Comirnaty and Pfizer-BioNTech COVID-19 Vaccine](#) available on the FDA website.

Janssen COVID-19 replication-incompetent human adenovirus serotype 26 (Ad26) vector vaccine

The Janssen COVID-19 Vaccine is available under EUA as a single primary vaccination dose for individuals 18 years of age and older and as a single booster dose (homologous or heterologous) for individuals 18 years of age and older. In an ongoing Phase 3 study that enrolled participants ≥ 18 year of age ($n \sim 20,000$ vaccine, $n \sim 20,000$ placebo), VE was 66.9% to prevent laboratory-confirmed, moderate-to-severe COVID-19 occurring at least 14 days after a single dose. Common solicited adverse reactions were injection site pain, headache, fatigue, and myalgia, which were mostly mild and moderate. In the post-EUA surveillance period, thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome were identified as rare, but serious adverse reactions following vaccination (CDC Advisory Committee on Immunization Practices 2021a). In December 2021, the EUA was amended to include a warning for regarding the increased risk of TTS with onset of symptoms approximately one to two weeks after vaccine administration. Due to the risk for TTS, the CDC's Advisory Committee on Immunization Practices had CDC update its recommendations for COVID-19 vaccines with a preference for individuals to receive an mRNA COVID-19 vaccine in lieu of the Janssen COVID-19 Vaccine.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Clinical trial experience

Adults ≥ 18 years of age

EUA of a 2-dose primary series of the Moderna COVID-19 Vaccine (also referred to as mRNA-1273 vaccine) was based on the safety and efficacy data from an ongoing Phase 3 randomized and placebo-controlled trial in approximately 30,000 participants. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine (data cutoff of November 21, 2020, with a median follow-up of >2 months post-Dose 2) was 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group. For the secondary efficacy endpoint of efficacy against severe COVID-19, there were 30 cases in the placebo group compared to 0 cases in the mRNA-1273 vaccine group.

The most common solicited adverse reactions associated with mRNA-1273 vaccine were injection site pain, fatigue, headache, muscle pain, joint pain, and chills; severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in participants ≥ 65 years of age as compared to younger participants. There was a numerical imbalance in hypersensitivity adverse events across treatment groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. There were three reports of facial paralysis (Bell's palsy) in the mRNA-1273 vaccine group and one in the placebo group. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse

events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273 vaccine (FDA 2020a).

EUA of additional doses

The Moderna COVID-19 Vaccine is also authorized for emergency use as a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions, as a single booster dose in individuals 18 years of age and older, and for use as a heterologous (“mix and match”) booster dose following completion of primary vaccination with a different available COVID-19 vaccine. Safety and efficacy data supporting these authorizations are detailed in the decision memoranda for the [Moderna COVID-19 Vaccine](#) available on the FDA website.

Post-EUA

Since the issuance of the EUA, published observational studies have supported the effectiveness of mRNA-1273 vaccine to prevent COVID-19, including high-level protection against severe disease, hospitalization, and death, although recent evidence suggests some decrease in vaccine effectiveness against mild-to-moderate disease since emergence of the Delta and Omicron variants in the U.S. (CDC Advisory Committee on Immunization Practices 2021b).

During the post-EUA surveillance period, cases of myocarditis and pericarditis were reported after vaccination, as well as rare cases of anaphylaxis (CDC Advisory Committee on Immunization Practices 2021a). Based on these data, myocarditis and pericarditis were added to the Warnings section of the EUA Fact Sheet for Healthcare Providers. Data obtained from some observational analyses of post-marketing data of mRNA COVID-19 vaccines in the U.S. (including analyses in the Vaccine Safety Datalink and CBER Biologics Effectiveness and Safety System) and in other countries have suggested a greater risk of myocarditis associated with the mRNA-1273 vaccine, in particular in younger adult males following the second primary series dose, than associated with the Pfizer-BioNTech COVID-19 Vaccine/Comirnaty. Discussion of these data is available in the [review memorandum addendum](#) published on the FDA website.

Please see Section [4.6](#) and CBER's Pharmacovigilance Memorandum for the Applicant's ongoing post-authorization studies and results of cumulative analysis of post-authorization AE reports received through November 30, 2021.

International use

The MRNA-1273 vaccine is authorized or approved for use in 85 countries. Its safety and efficacy have been evaluated in 35 trials conducted in 9 countries.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

EUA 27073

- November 30, 2020: Submission of EUA request for individuals ≥ 18 years of age
- December 18, 2020: Issuance of EUA for individuals ≥ 18 years of age
- June 9, 2021: Submission of EUA request for individuals (b) (4) years of age – (b) (4)
- June 25, 2021: EUA amended to include warning statement and associated information regarding myocarditis and pericarditis in the Fact Sheet for Vaccination Providers and the Fact Sheet for Recipients and Caregivers

- August 12, 2021: EUA amended for use of third dose of 100 mcg of Moderna COVID-19 Vaccine in solid organ transplant recipients/immunocompromised individuals.
- August 30, 2021: EUA amended to include safety updates regarding myocarditis and pericarditis, syncope, updates to section 6.2 (postmarketing experience) of the Fact Sheet for Vaccination Providers and the Fact Sheet for Recipients and Caregivers.
- September 3, 2021: Submission of EUA request for authorizing a booster dose of 50 mcg Moderna-COVID-19 Vaccine for individuals ≥ 18 years of age;
- October 20, 2021: EUA amended for the following indication:
 - A booster dose (0.25 mL) may be administered intramuscularly at least 6 months after completing a primary series with the Moderna COVID-19 Vaccine to individuals:
 - 65 years of age and older
 - 18 through 64 years of age at high risk of severe COVID-19
 - 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2
 - A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.
- November 12, 2021: Submission of EUA request for use of the use of Moderna COVID-19 Vaccine as a homologous and heterologous booster in individuals ≥ 18 years
- November 19, 2021: EUA amended for the use of Moderna COVID-19 Vaccine as a homologous and heterologous booster in individuals ≥ 18 years.
- January 4, 2022: Submission of EUA request to revise the dosing interval of the Moderna COVID-19 booster from “at least 6 months” to “at least 5 months” after completion of the primary series
- January 7, 2022: EUA amended to revise the authorized dosing interval of the Moderna COVID-19 booster to at least 5 months after completion of the primary series in individuals ≥ 18 years

Major pre-submission BLA-associated regulatory activity

- February 20, 2020: IND 19635, NIAID submitted Phase 1 protocol P20-0003 for dose ranging study of mRNA-1273 vaccine in adults
- April 27, 2020: IND 19745 submission for Phase 2 study mRNA-1273-P201
- May 11, 2020: Fast Track Designation granted for individuals ≥ 18 years of age
- July 1, 2020: Phase 3 protocol mRNA-1273-P301 submitted; study intended to support licensure
- April 28, 2021: Pre-BLA Written Responses Communicated (Clinical and Pharmacovigilance)
- July 1, 2021: Pre-BLA Written Responses Communicated (CMC and Regulatory)

Major post-submission BLA regulatory activity

- October 14, 2021: Priority review granted

2.6 Other Relevant Background Information

Relevant FDA guidance

In June 2020, FDA published guidance on the Development and Licensure of Vaccines to Prevent COVID-19 (FDA 2020b). In October 2020, FDA published guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 (revised February 2021 and May 2021) (FDA 2021b).

Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings

On October 22, 2020, a VRBPAC meeting was held to discuss considerations for development, EUA, and licensure of vaccines to prevent COVID-19. The VRBPAC committee endorsed the principles outlined in the FDA guidance documents regarding safety and effectiveness data to support EUA and licensure and expectations for continued post-authorization and post-approval evaluation of COVID-19 vaccines.

On December 17, 2020, a VRBPAC meeting was held to discuss Moderna's EUA request for their vaccine to prevent COVID-19 in individuals 18 years of age and older. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the vaccine outweighed its risks for use in individuals 18 years of age and older. Discussion topics included (a) Moderna's plan for an unblinding and crossover of placebo recipients and (b) critical data to be obtained in ongoing clinical trials and other studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine.

Committee members were asked to discuss whether the ongoing Phase 3 trial should be continued using a blinded crossover design or an open-label design as proposed by Moderna. Some members stressed the importance of using a blinded crossover design in order to preserve data integrity and to allow an evaluation of waning of immunity and duration of protection. Other members opined that even though a blinded crossover design would be ideal, it would present with logistical challenges, and that high dropout rates can be anticipated because clinical trial participants would obtain a vaccine made available under EUA before a blinded crossover could be implemented. Therefore, open-label unblinded vaccination of placebo recipients, even though not ideal, may be a more realistic option. However, to preserve blinded placebo-controlled follow-up for as long as is practical, some committee members opined that placebo recipients should be offered the vaccine as they become eligible for vaccination according to CDC prioritization groups.

Regarding critical data to be obtained in ongoing trials, committee members discussed the importance of collecting blood specimens obtained from breakthrough cases to evaluate T- and B-cell immunity and to identify correlates of protection, and the importance of collecting respiratory specimens obtained from breakthrough cases to evaluate effect of the vaccine on shedding of infectious virus and to provide information about potential antigenic escape mutants. Members commented that efforts should be made to obtain data on long term safety of the vaccine, waning of immunity, the vaccine's impact on virus transmission, and asymptomatic infection. In addition, they suggested that ongoing studies should collect additional data on vaccine effectiveness in subjects at increased risk for COVID-19, pregnant women, and pediatric populations.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. However, presentation of the submitted safety datasets for Study P301 did not initially align with the data standards outlined in Clinical Data Interchange Standards Consortium (CDISC). The main issues pertained to incorrect safety event duration calculations and improper adverse event categorization. Following CBER's request, the Applicant submitted revised datasets that were considered sufficient to permit full review and verification of available safety data. Please see memoranda by Dr Brenda Baldwin, PhD, Consult Reviewer and Dr. Ye Yang, PhD, Statistical Reviewer.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch Monitoring inspections of nine clinical sites for Study P301 were conducted to support EUA of the Moderna COVID-19 Vaccine in December 2020. Two of the inspections gave concern regarding adequacy of study monitoring; however, this was subsequently addressed by the study-wide compliance information provided by Moderna (as described in the [EUA decision memorandum](#)) (FDA 2020a). Inspection of one additional clinical study site was conducted during the BLA review. FDA did not identify deficiencies that would affect the integrity of the clinical data submitted in this BLA.

3.3 Financial Disclosures

Studies P301 and P201
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Total number of investigators identified: 107 (99 for P301, 8 for P201)
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer identified no issues that would impact the conclusions of the clinical review.

4.2 Assay Validation

Two diagnostic assays were used for the assessment of the Phase 3 clinical study efficacy endpoints. The Roche Elecsys Anti-SARS-CoV-2 assay, done under contract to PPD Global Central Laboratories, was used for the evaluation of SARS-CoV-2 serostatus of study participants before vaccination. The Viracor Eurofins Clinical Diagnostics RT-qPCR assay was used to determine the virus infection status of study participants before vaccination and to confirm COVID-19 cases for the evaluation of efficacy endpoints. Both assays have FDA's authorization for emergency use.

Assays used in the evaluation of secondary immunogenicity endpoints include the S-2P IgG binding antibody ELISA (validated; (b) (4)) and SARS-CoV-2 pseudotyped virus neutralization assay (PsVNA) (validated; Duke University Medical Center).

The information provided in the BLA supported the suitability of the assays for their intended uses. Details are provided in the CBER's review memorandum for this BLA entitled "Clinical Pharmacology Assays".

4.3 Nonclinical Pharmacology/Toxicology

The CBER toxicology reviewer did not identify any safety issues based on the submitted preclinical studies that would impact the conclusions of the clinical review. Intramuscular administration of mRNA-1273 vaccine to female rats prior to mating and during gestation periods did not have any effects on female fertility, fetal/embryonal development, or postnatal developmental. Details are provided in CBER's toxicology review memorandum with the subject "Review of the non-clinical studies for BLA 125752 from Moderna Therapeutics, Inc".

4.5 Statistical

CBER statistical reviewers confirmed the key statistical analyses for safety and efficacy and found no major statistical issues in this application.

4.6 Pharmacovigilance

Post-EUA safety surveillance reports received by FDA and CDC identified two rare but clinically important serious adverse reactions following use of mRNA-1273 vaccine: anaphylaxis and myocarditis/pericarditis. The crude reporting rate for anaphylaxis in the Vaccine Adverse Event Reporting System (VAERS), including unconfirmed reports, has been ~10 cases per million doses. Anaphylaxis has been identified as an important risk and the Applicant proposes enhanced pharmacovigilance, expedited reporting of cases, and further study in current ongoing clinical trials and in postmarketing safety studies. Because the risk of anaphylactic reactions exists for each dose, this safety event should be monitored following all administered doses, including the booster dose. Anaphylaxis has been included in the Warnings and Precautions and Adverse Reactions sections of the USPI for this vaccine.

On June 25, 2021, Moderna EUA Fact Sheets were revised to add myocarditis and pericarditis as a warning. FDA has been performing ongoing safety reviews for this important identified risk. An analysis of observed vs expected events, stratified by age and dose number, indicated that the observed numbers of events exceeded the expected number of events for multiple age groups and genders, based on U.S. population-based background incidence rates prior to the COVID-19 pandemic. The relative risk (RR) was higher in younger age groups than older age groups, and in males than females for almost all age groups. Ongoing monitoring for myocarditis and pericarditis includes the following activities: passive surveillance using VAERS, benefit-risk analyses using different data sources, active surveillance using Vaccine Safety Datalink (VSD), passive and active surveillance by the Applicant that includes completion of ongoing studies, and post-authorization safety studies that include long-term surveillance for safety events of interest. Myocarditis and pericarditis have been

included in the Warnings and Precautions and Adverse Reactions sections of the USPI for this vaccine.

Please see CBER's Pharmacovigilance Memorandum for further details.

4.7 Quantitative Risk-Benefit Assessment

To inform the review of the BLA for use of mRNA-1273 vaccine in individuals ≥ 18 years of age, FDA conducted a quantitative assessment of the benefits and risks per million individuals vaccinated with two primary series doses of mRNA-1273 vaccine. The assessment included modeling scenarios to evaluate the impacts on benefits and risks of uncertainty associated with the changing dynamic of the pandemic, effectiveness of the vaccine against emerging variants, and rates of myocarditis/pericarditis associated with the vaccine. The analysis was conducted for the male population stratified by age (18-25, 26-35, 36-45, 46-55, and 55-64 years) and assessed the benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) visits, and deaths, and the risks of vaccine-related myocarditis/pericarditis cases, hospitalizations, ICU visits and deaths. While COVID-19 is known to cause myocarditis, and COVID-19-associated myocarditis may be more severe than vaccine-associated myocarditis, the model does not specifically estimate the number of COVID-19-associated cases of myocarditis that would have resulted in hospitalizations, ICU admission, or deaths in the absence of COVID-19 vaccination.

The major sources of data included age/sex-specific incidences of COVID-19 cases and hospitalizations as per the CDC COVID Data Tracker and COVID NET for December 2021 (when the Omicron variant was becoming dominant in the U.S.), average COVID ICU and death rates from COVID NET since the start of the pandemic, age-specific myocarditis/pericarditis case rates attributable to the vaccine estimated from the CBER Biologics Effectiveness and Safety System health claims databases, and rates of vaccine-related myocarditis/pericarditis hospitalizations and ICU visits reported through VSD system. The modeling attempted to account for preliminary estimates of Omicron-specific vaccine efficacy.

The results of the modeling assessment predicted that in the population of adults at highest risk of vaccine associated myocarditis/pericarditis (males ages 18-25 years), vaccination of 1 million individuals with two primary series doses of mRNA-1273 vaccine would prevent 76,362 COVID-19 cases, 1,755 hospitalizations, 421 ICU visits and 4 deaths due to COVID-19, but would cause 148 myocarditis/pericarditis cases resulting in 128 hospitalizations, 47 ICU visits, and no deaths. Modeling in females and in individuals ≥ 65 years was not conducted; there were too few events of myocarditis/pericarditis after vaccination in these groups to reliably estimate a rate. However, this evidence indicates a more favorable benefit-risk profile in individuals ≥ 65 years of age and in females as compared with males 18-64 years of age. FDA concludes that the benefits of mRNA-1273 vaccine outweigh the risks of vaccine-associated myocarditis/pericarditis in the population of adults overall. However, the benefit-risk estimates cannot account for all uncertainties associated with the evolving pandemic (e.g., emerging variants and their impact on disease incidence and vaccine effectiveness), and uncertainties in the estimated rates of vaccine-attributed myocarditis/pericarditis. Another limitation of this benefit-risk assessment is that it does not assess the potential long-term adverse effects due to either COVID-19 or vaccine-attributable myocarditis/pericarditis.

For further details on the benefit-risk assessment, please refer to the review memorandum from the Analytics and Benefit-Risk Assessment Team, Office of Biostatistics and Epidemiology, CBER.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary analysis from Study P301 with 2 months median follow-up for safety and efficacy and Day 57 data from studies P201 and 20-0003 were submitted to and reviewed by the FDA for the EUA of the Moderna COVID-19 Vaccine in December 2020 (See the [EUA Memorandum for the Moderna COVID-19 Vaccine](#)).

This BLA contains new clinical data, as follows:

Study P301

- Safety data with a median follow-up of 6 months after Dose 2, including the blinded and open-label periods
- Updated efficacy analysis of the primary endpoint in the blinded phase, through data cutoff of March 26, 2021
- Immunogenicity data in a subset of participants through 1 month after Dose 2

Study P201

- Safety and immunogenicity data through 6 months after Dose 2

Study 20-0003

- Safety and immunogenicity data through 6 months after Dose 2

Because the primary source of pre-licensure study data to support vaccine safety and efficacy is a single study, P301, FDA agreed with the Applicant that integrated summaries of efficacy and safety were not needed for the BLA submission. Given the relatively small sizes of studies P201 and 20-0003, and overall minimal contribution to the safety and effectiveness data for mRNA-1273 vaccine, results from these studies will not be discussed extensively in this BLA review.

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

The primary source of data considered for review of this investigational vaccine were documents submitted to STN 125752/0. The following sections were reviewed in support of this application:

Module 1, all sections: Administrative Information and Prescribing Information
Section 2.2 Introduction
Section 2.5 Clinical Overview
Section 2.7.3 Summary of Clinical Efficacy
Section 2.7.4 Summary of Clinical Safety
Section 2.7.6 Synopses of Individual Studies
Section 5.2 Tabular Listing of All Clinical Studies
Section 5.3.5.1 Clinical Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
Section 5.3.5.2 Clinical Study Reports of Uncontrolled Clinical Studies

During the BLA review period, the Applicant submitted a total of 52 amendments. Only amendments relevant to the clinical review are included in the table below.

Table 2. Amendments to the Original BLA 125752/0 (submitted May 28, 2021)

Amendment Number	Date Submitted	Description
2	August 24, 2021	Final roll of the BLA (Modules 1, 2, 5)
3	September 15, 2021	CBER requested tables
4	September 22, 2021	Response to IR #1 re: pediatric plans Response to IR #2 re: efficacy against severe COVID-19
5	September 23, 2021	Response to IR #1 re: pediatric plans
6	September 28, 2021	Response to IR #1 re: pediatric plans Response to IR #2 re: SMQ analyses
7	September 30, 2021	CBER requested tables batch 2
8	October 4, 2021	Response to IR #2 re: demographics summary for safety imbalances Response to IR #6 re: COVID-19 cases in baseline seropositive participants
9	October 7, 2021	Response to IR #6 re: concordance of COVID-19 cases CRFs not previously submitted
10	October 12, 2021	Response to IR #5 (Group 1) re: dataset issues Final batch of CBER requested tables
12	October 14, 2021	Response to IR #5 (Group 2) re: dataset issues
15	October 25, 2021	Response to IR #5 (Group 3) re: dataset issues
17	November 1, 2021	Response to IR #12 re: sensitivity analyses for solicited ARs and unsolicited AEs
19	November 8, 2021	Summary of telecon regarding dataset issues
20	November 10, 2021	Response to IR #15 re: asymptomatic infection, suspected COVID-19 cases, sequencing data
22	November 17, 2021	Response to IR #19 re: postmarketing reports of herpes zoster
23	November 22, 2021	Response to IR #20 re: analysis dates used for SARS-CoV-2 infection Response to IR #21 re: labeling revisions
26	December 1, 2021	Updated safety dataset based on feedback from telecon and IR #23
27	December 3, 2021	Response to IR #24 re: asymptomatic infection analysis, blinded follow-up duration
30	December 9, 2021	Response to IR #27 re: sensitivity analysis for asymptomatic infection
31	December 13, 2021	Response to IR #23 re: updated duration of solicited ARs
32	December 14, 2021	Response to IR #30 re: Bell's palsy, herpes zoster, hypersensitivity
34	December 15, 2021	Response to IR #33 re: labeling revisions
36	December 16, 2021	Response to IR #31 re: pharmacovigilance plan Response to IR #34 re: labeling revisions
38	December 20, 2021	Response to IR #36 re: lymphadenopathy, vertigo, autoimmune disorders, SMQs
39	December 21, 2021	Response to IR #37 re: revised datasets Response to IR #39 re: dyspnea, syncope, DVTs, pregnancies
42	December 28, 2021	Response to IR #42 re: labeling revisions
43	January 11, 2022	Response to IR #43 re: herpes zoster
44	January 13, 2022	Response to IR #44 re: pregnancies

Amendment Number	Date Submitted	Description
45	January 14, 2022	Response to IR #45 re: chest pain and MI
47	January 26, 2022	Response to IR #47 re: grade 4 AR
50	January 27, 2022	Response to IR #48 re: labeling revisions

Source: FDA-generated table.

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

Supportive information from EUA 27073/0 and clinical study protocols reviewed under IND 19745 and IND 19635 were also referenced during the review cycle.

5.3 Overview of Clinical Studies

Included with the application were data from three ongoing clinical studies summarized in [Table 3](#) below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of this review. Study mRNA-1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and is summarized in Section [6.2](#). Phase 1 Study 20-0003 is an open label, dose-ranging, first-in-human study of mRNA-1273 vaccine and is summarized in Section [6.3](#).

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the mRNA-1273Vaccine

Study Number	Type of Study	Participants Randomized (N)	Study Design, Type of Control	Dose Levels Assessed	Study Status
P301	Efficacy, safety, immunogenicity	30415	Phase 3, randomized, stratified, observer-blind, placebo-controlled study	100 mcg	Ongoing
P201	Safety, immunogenicity	600	Phase 2a randomized, observer-blind, placebo-controlled, dose-confirmation study	50 mcg, 100 mcg	Ongoing
20-0003 ^a	Safety, immunogenicity	120	Phase 1 open-label dose-ranging study	25 mcg, 50 mcg, 100 mcg, 250 mcg	Ongoing

a. Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

5.4 Consultations

For the purpose of informing the design of required postmarketing safety studies and pediatric clinical trials as required by the Pediatric Research Equity Act (PREA), FDA cardiologists from the Center for Drug Evaluation and Research were asked to provide recommendations for diagnostic evaluations and monitoring for myocarditis/pericarditis (including feasibility of routine screening tests for subclinical myocarditis), interpretation of cardiac testing, and follow-up of identified clinical and subclinical cases. These

recommendations were taken into consideration in negotiations with the Applicant on pediatric development plans and postmarketing studies.

In addition, assistance was sought from data analysts within the Office of Computational Science, Center of Drug Evaluation and Research for the review of safety datasets using FDA developed analyses tools.

5.4.1 Advisory Committee Meeting

The most critical issues involving data to support safety and effectiveness of this vaccine were discussed in the October 2020, December 2020, and October 2021 VRBPAC meetings. Information concerning the risk of myocarditis/pericarditis continued to be updated during the BLA review as more data from post-EUA surveillance and observational studies became available. FDA's assessment of this information did not impact the overall benefit/risk considerations to an extent that VRBPAC input was needed to guide a licensure decision for use in individuals ages 18 years and older.

5.5 Literature Reviewed

CDC Advisory Committee on Immunization Practices, 2021a, COVID-19 Vaccine Safety Technical (VaST) Work Group (slide presentation). April 23, 2021.

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04-23/05-COVID-Lee-508.pdf> Accessed August 20, 2021.

CDC Advisory Committee on Immunization Practices, 2021b, Update on Emerging SARS-CoV-2 Variants and COVID-19 vaccines (slide presentation). August 13, 2021.

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/04-COVID-Scobie-508.pdf>. Accessed August 20, 2021.

CDC Advisory Committee on Immunization Practices, 2021c, Update on Emerging SARS-CoV-2 Variants and COVID-19 vaccines (slide presentation). December 16, 2021.

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-12-16/06-COVID-Scobie-508.pdf>. Accessed January 14, 2022.

CDC, 2021a, SARS-CoV-2 Variant Classifications and Definitions.

<https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>. Accessed August 20, 2021.

CDC, 2021b Vaccine Adverse Event Reporting System Standard Operating Procedures for COVID-19. January 29, 2021.

<https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf>. Accessed January 10, 2022.

FDA, 2020a, Emergency Use Authorization Review Memorandum for the Moderna COVID-19 Vaccine/mRNA-1273. December 18, 2020.

<https://www.fda.gov/media/144673/download>.

FDA, 2020b, Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020.

<https://www.fda.gov/media/139638/download>

FDA, 2021a. Vaccine approval package: COMIRNATY (COVID-19 Vaccine, mRNA) (Application No 125742). August 23, 2021.

<https://www.fda.gov/media/151733/download>.

FDA, 2021b, Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. <https://www.fda.gov/media/142749/download>

FDA, 2021c. Emergency Use Authorization Review Memorandum for the Moderna COVID-19 Vaccine/mRNA-1273, EUA 27073 (Amendment 250) (Booster Dose). September 3, 2021. <https://www.fda.gov/media/153912/download>.

FDA, 2021d. EUA amendment to support use of a Moderna COVID-19 Vaccine heterologous booster dose following primary vaccination with other authorized COVID-19 vaccines. October 20, 2021. <https://www.fda.gov/media/153911/download>

FDA, 2021e. CBER Assessment of a booster dose of Moderna COVID-19 Vaccine (0.25 mL) administered following a primary COVID-19 immunization series in individuals 18 years of age and older. November 19, 2021. <https://www.fda.gov/media/154405/download>

FDA, 2022 CBER assessment of a single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) administered at 5 months. January 6, 2022. <https://www.fda.gov/media/155548/download>

Johnson AG, Amin AB, Ali AR, Hoots B, Cadwell BL, Arora S et al. COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults with and Without Booster Doses During Periods of Delta and Omicron Variant Emergence — 25 U.S. Jurisdictions, April 4–December 25, 2021. Morbidity and Mortality Weekly Report (71) January 21, 2022. https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e2.htm?s_cid=mm7104e2_w Accessed January 24, 2022.

Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, et al. Effectiveness of a Third Dose of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022 (71) January 21, 2022. https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e3.htm?s_cid=mm7104e3_w Accessed January 24, 2022.

World Health Organization, 2021, Weekly epidemiological update on COVID-19 - 1 June 2021. <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-june-2021>. Accessed August 20, 2021.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study P301

NCT04470427

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

6.1.1 Objectives

Primary efficacy objective: To demonstrate the efficacy of mRNA-1273 vaccine to prevent COVID-19 starting 14 days after the second dose

Primary safety objective: To evaluate the safety and reactogenicity of 2 doses of the mRNA-1273 vaccine given 28 days apart

Secondary efficacy objectives: To demonstrate the efficacy of mRNA-1273 vaccine to prevent:

- Severe COVID-19 starting 14 days after the second dose
- Serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity
- COVID-19 as defined by a secondary definition
- Death caused by COVID-19
- COVID-19 starting 14 days after the first dose.
- COVID-19 regardless of evidence of prior SARS-CoV-2 infection
- Asymptomatic SARS-CoV-2 infection

Secondary immunogenicity objective: To evaluate the immunogenicity of 2 doses of mRNA-1273 vaccine given 28 days apart

Exploratory objectives:

- To evaluate the effect of mRNA-1273 vaccine on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by reverse transcription-polymerase chain reaction (RT-PCR) and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR
- To assess VE to reduce the duration of symptoms of COVID-19
- To evaluate VE against all-cause mortality
- To assess VE against the burden of disease due to COVID-19
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence
- To conduct additional analyses related to furthering the understanding of SARS-CoV-2 infection and COVID-19, including analyses related to the immunology of this or other vaccines, detection of viral infection, and clinical conduct

6.1.2. Design Overview

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 vaccine administered as two doses 28 days apart to adults 18 years of age and older. The study took place in 99 sites in the U.S. Participants (N=30,415) were randomized 1:1 to receive intramuscular injections of either 100 mcg of mRNA-1273 vaccine (n=15,209) or placebo (n=15,206) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18-64 years of age and not at risk for progression to severe COVID-19, 18-64 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV.

Approximately 25% of study participants were healthcare workers. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during postvaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS-CoV-2 at a central laboratory using a RT-PCR test (Viracor; FDA authorized under EUA) or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the primary efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. After mRNA-1273 vaccine was granted EUA, the protocol was amended and unblinding procedures were initiated to vaccinate the placebo group (see below for further details). Once each individual participant was unblinded, the participant moved from the blinded phase of the study (Part A) to the open-label phase of the study (Part B). A final analysis of efficacy for Part A was planned when at least 90% of the study participants had been unblinded and when a median follow-up of at least 6 months had occurred.

Beginning December 28, 2021, per amended protocol following the issuance of the EUA for the Moderna COVID-19 Vaccine, all participants were asked to schedule a Participant Decision Visit (PDV), at which they were given the option to be unblinded to their original treatment group. Investigators considered local and national public health guidance for administration of COVID-19 vaccines under EUA when determining the scheduling priority of participants, and thus the unblinding process occurred progressively over several months. Participants initially randomized to the placebo group were offered mRNA-1273 vaccine after unblinding. Participants who received only one dose of mRNA-1273 vaccine prior to unblinding were given a second dose in the open-label phase. For participants unblinded to his/her vaccine assignment, follow-up evaluations thereafter were conducted in an open-label manner. The expected duration of study participation is approximately 25 months.

Reviewer Comment: The protocol for this ongoing study has been amended over time with changes to the eligibility criteria, symptom surveillance, case definitions, and planned analyses. The study design as described in this BLA review is based on protocol amendment 7, which was the active version at the time of the March 26, 2021 data cutoff. Since this time, the protocol has been further amended to provide participants with an option to receive a booster dose of mRNA-1273 vaccine (50 mcg dose) as part of the study. The data from the booster phase of this study are outside the scope of this BLA, and therefore not presented in this review.

6.1.3 Population

The study enrolled adults 18 years of age or older who had no known history of SARS-CoV-2 infection, some of whom were healthy and some of whom had stable pre-existing medical conditions. Enrollment targeted individuals at high risk of SARS-CoV-2 exposure

and was stratified to ensure representation of individuals at higher risk of severe COVID-19 (due to age or underlying medical conditions).

6.1.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1273 is nucleoside modified mRNA that encodes for the full-length spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-2P spike protein into a prefusion conformation. In the mRNA-1273 vaccine, mRNA-1273 is encapsulated in lipid particles. The CoV spike protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for nAb that prevent infection. mRNA-1273 vaccine was compared to a placebo containing 0.9% sodium chloride.

6.1.5 Directions for Use

IM injection of mRNA-1273 vaccine containing 100 mcg of mRNA-1273 was administered into the deltoid muscle (preferably the nondominant arm) on a 2-dose schedule (Day 1 and Day 29). The second dose should have been administered in the same arm as the first dose. Placebo was administered as a 0.5 mL IM injection at the same injection site and on an identical schedule as mRNA-1273 vaccine.

6.1.6 Sites and Centers

Study P301 enrolled participants at 99 clinical sites, all within the U.S.

6.1.7 Surveillance/Monitoring

Efficacy

Surveillance for COVID-19 symptoms was conducted via a combination of weekly telephone calls and electronic diary (eDiary) prompts from enrollment through the end of the study. Participants with symptoms of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) returned to the study site or were visited at home for collection of an NP swab sample (for RT-PCR) and a blood sample for immunologic analysis of SARS-CoV-2 infection. NP samples were tested for SARS-CoV-2 at a central laboratory using a RT-PCR test (Viracor; FDA authorized under EUA), or other sufficiently validated NAAT. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the primary efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. After mRNA-1273 vaccine was granted EUA (December 18, 2020), the protocol was amended and unblinding procedures were initiated to vaccinate the placebo group. Once each individual participant was unblinded, the participant moved from the blinded phase of the study (Part A) to the open-label phase of the study (Part B). A final analysis of efficacy for Part A was planned when at least 90% of the study participants had been unblinded and when a median follow-up of at least 6 months had occurred.

The table below shows the efficacy analyses populations.

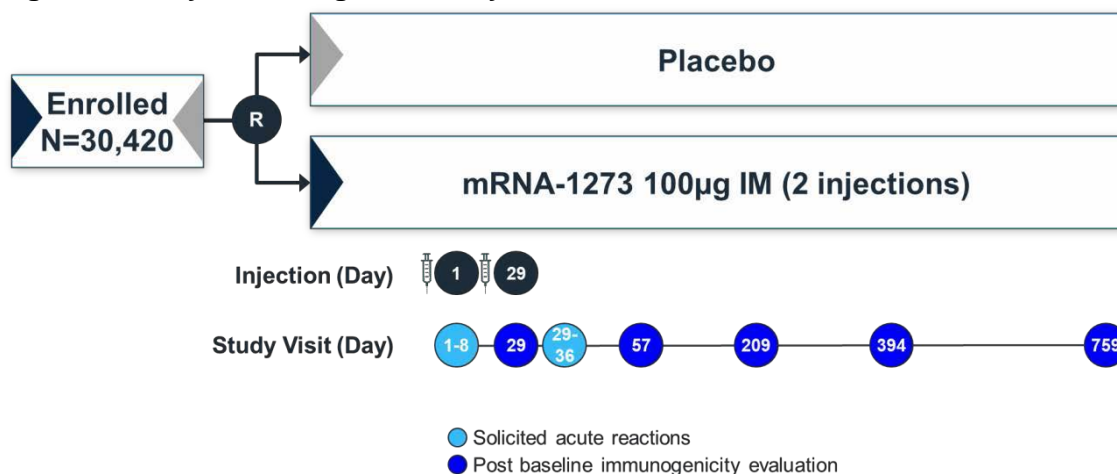
Table 4. Efficacy Populations

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of investigational product (IP).
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab and bAb against SARS-CoV-2 nucleocapsid below limit of detection or lower limit of quantification) at Day 1 before the first dose of IP.
Per-Protocol Set (PPS)	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to database lock and unblinding, that impact critical or key study data.

Safety

The primary safety objective was to evaluate the safety of 2 doses mRNA-1273 vaccine administered 28 days apart. [Figure 1](#) below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically attended adverse events from Day 1 through Day 759 or withdrawal from the study.
- SAEs from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.

- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory valuations were not assessed in Study P301 but were collected in the Phase 1 and Phase 2 studies.

Monitoring for signals of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was specified to be triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited adverse reactions after each dose, unsolicited AEs, MAAEs, and SAEs.

Table 5. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set Dose 1	All randomized participants who received the 1st dose and provided any solicited reaction data.
Solicited Safety Set Dose 2	All randomized participants who received the 2nd dose and provided any solicited reaction data.

Immunogenicity

Blood samples for immunogenicity assessments were collected from all participants at scheduled time points (Days 1, 29, 57, 209, 394, 759, as well as at the PDV). On Day 1 and Day 29, and for crossover participants at the PDV, blood samples were collected prior to administration of investigational product (IP). The following antigens were measured:

- Serum binding antibody (bAb) levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Serum samples were tested for bAb against the nucleocapsid to determine the immunologic status of study participants at baseline and to assess for seroconversion due to infection during the course of the study. Serum from a subset of participants were tested using the other assays for the immunogenicity analysis endpoints.

The table below shows the populations used for the immunogenicity analyses.

Table 6. Immunogenicity Analysis Populations

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of investigational product (IP).
Random Subcohort for Immunogenicity	A stratified, random sample of study participants from the FAS with non-missing key baseline characteristics for the strata, and with serum samples available at both Day 1 and Day 57.
Per-Protocol Random Subcohort for Immunogenicity (PPRSI)	Participants in the Random Subcohort who received both planned doses (i.e., received the treatment as randomized) with Dose 2 received within 21-42 days after Dose 1, and no major protocol deviation that impacted critical or key data.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR along with:

- At least TWO of the following systemic symptoms: Fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vaccine vs placebo) in the hazard of the primary endpoint, i.e., $VE = 1 - \text{Hazard Ratio (HR)}$. 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.

Secondary efficacy endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 vaccine to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19

- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 vaccine to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition (“CDC definition”): a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature $\geq 38^{\circ}\text{C}$), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, HR ≥ 125 beats per minute, SpO₂ $\leq 93\%$ on room air at sea level, or PaO₂/FiO₂ < 300 mm Hg);
- Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Safety endpoints

- Solicited local and systemic ARs through 7 days after each dose of IP
- Unsolicited AEs through 28 days after each dose of IP
- MAAEs or AEs leading to withdrawal through the entire study period
- SAEs throughout the entire study period

Immunogenicity endpoints

- GMT of SARS-CoV-2-specific nAb on Days 1, 29, 57, 209, 394, and 759

- GMFR of SARS-CoV-2-specific nAb relative to Day 1 on Days 29, 57, 209, 394, and 759
- Quantified levels or GMT of S protein-specific bAb on Days 1, 29, 57, 209, 394, and 759
- GMFR of S protein-specific bAb relative to Day 1 on Days 29, 57, 209, 394, and 759

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Per-Protocol Set (PPS) was the primary efficacy analysis population and consisted of all 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 which would impact key study data. Efficacy against COVID-19 regardless of evidence of prior infection was estimated based on the FAS, consisting of all subjects who received at least one dose of the investigational product, analyzed according to the treatment group randomized. Supportive efficacy analyses were performed on the modified Intent-to-Treat (mITT) Set, consisting of subjects in the FAS with no evidence of prior infection prior to Dose 1.

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. Two interim analyses of the primary efficacy endpoint at 53 and 106 cases and a primary analysis at 151 cases were planned. 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.

Reviewer Comment: As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases per the primary endpoint, where the null hypothesis of $H_0: VE \leq 30\%$ was evaluated at a one-sided alpha of 0.0047. The results from this interim analysis (data cutoff of November 7, 2020) and the primary analysis (196 adjudicated COVID-19 cases based on data cutoff of November 21, 2020) supported the EUA of mRNA-1273 vaccine in December 2020. The data submitted to the BLA contains the protocol specified descriptive final efficacy analysis 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 discontinue the study, die 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.

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 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

Following the issuance of the EUA (December 18, 2020), the study protocol was revised to allow participants who originally received placebo the opportunity to receive mRNA-1273 vaccine following local or national recommendations. Hence, for each trial participant, there are 2 periods in the study: enrollment until the date of the PDV for treatment unblinding and the PDV until the end of study participation. Participants originally randomized to mRNA-1273 vaccine continued to be followed for safety as specified in the protocol. The safety data for participants who received placebo prior to disclosure of vaccine assignment include blinded data that contribute to controlled assessment of safety compared to individuals who were randomly assigned to mRNA-1273 vaccine. After treatment unblinding and the administration of mRNA-1273 vaccine, safety data from the placebo recipients was no longer used for direct comparison with participants randomized to mRNA-1273 vaccine. Even though individuals were unblinded on different days after December 28, 2020, the difference in the total blinded follow-up duration is minor between the treatment arms. Thus, the analyses for both the observer-blinded and the open-label portions of the study were conducted using frequencies, i.e., the number of participants within the analysis set reporting at least one event in each category.

Safety data presented for P301, based on the data cutoff date of March 26, 2021, include:

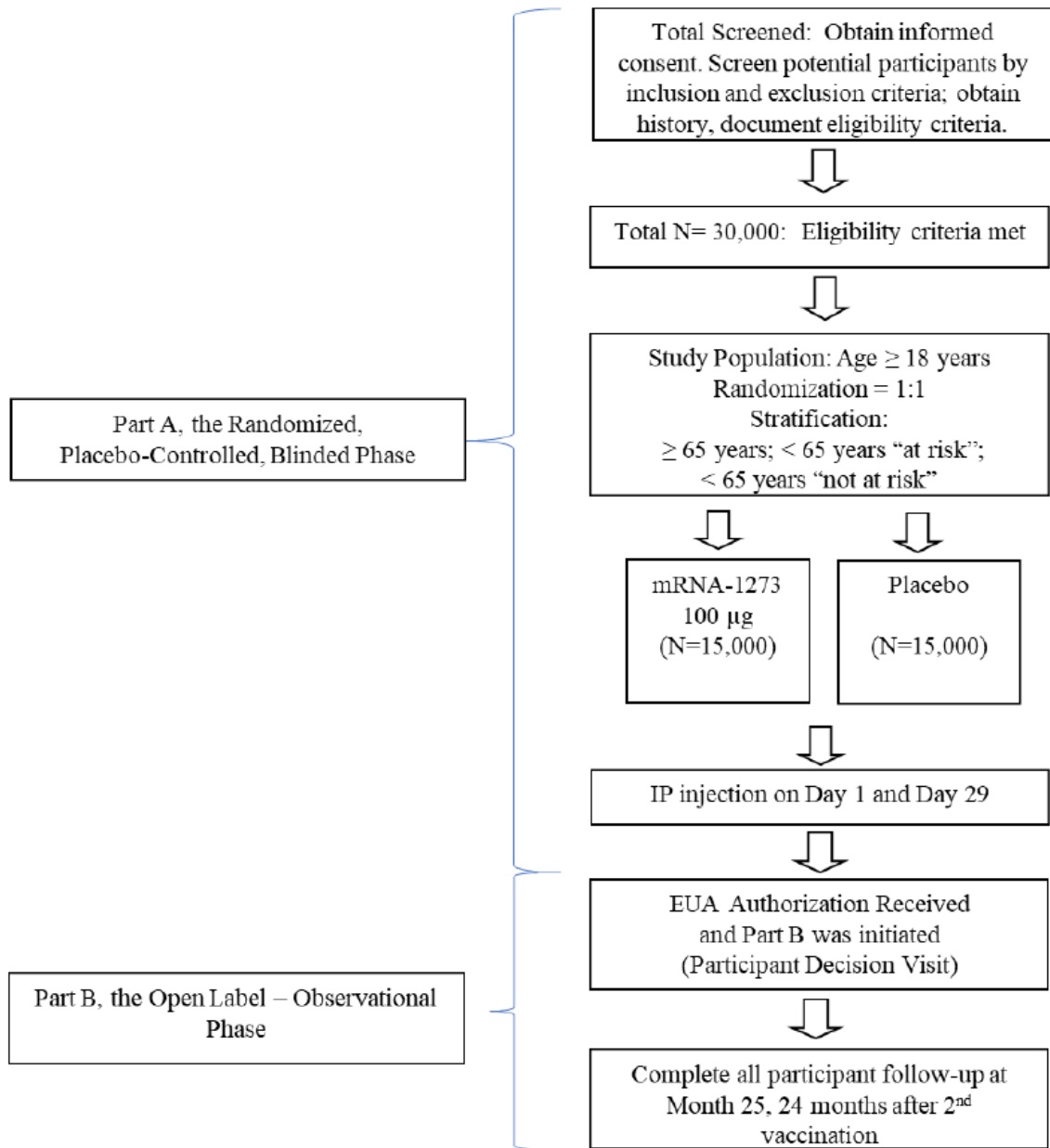
1. Blinded placebo-controlled period (Part A): Dose 1 to PDV/unblinding date:
 - Participants with up to ~6 months after Dose 2 (N= 30,346; mRNA-1273 vaccine group N=15,184 and placebo group N=15,162).
 - Solicited local and systemic ARs were assessed during this time period from a subset of participants.
2. Open-label observational period (Part B): Safety data accrued during Part B was from time of unblinding to data cutoff date. Part B therefore included safety data for unblinded participants who were aware of their vaccination group assignment as follows:
 - Participants originally randomized to mRNA-1273 vaccine in Part A (N=14,618)
 - Participants originally randomized to placebo who then received mRNA-1273 vaccine in Part B (N=12,648)
 - Participants originally randomized to placebo who remained in the placebo group in Part B (N=1,698)

- Only unsolicited AEs (AEs, SAEs and adverse events of special interest [AESIs]) were assessed during this time period.
3. Cumulative follow-up from Dose 1 to at least 6 months after Dose 2:
- Participants originally randomized to mRNA-1273 vaccine (inclusive of blinded data and open-label data through the March 26, 2021 data cutoff) (N=7,499)

Reviewer Comment: The BLA safety database exceeded FDA expectations for at least 3,000 vaccine recipients in each age group with at least 6 months of total safety follow-up.

A graphic of these different time periods taken into consideration for the evaluation of the safety data is displayed in [Figure 2](#), below.

Figure 2. Study Flow Diagram: Part A (Randomized Blinded Phase) and Part B (Open-Label Observational Phase)



Source: Clinical Study Report mRNA-1273-P301, p. 62.

The dates for the different analysis cutoffs for the blinded phase of the study (Part A) are displayed in [Table 7](#).

Table 7. Analyses Used to Support Efficacy and Safety, Study 301, Part A

Analysis Name	Efficacy Data Cutoff Date	Safety Data Cutoff Date
Interim Analysis	Nov 7, 2020	Nov 11, 2020
Primary Analysis	Nov 21, 2020	Nov 25, 2020
Final Analysis	Mar 26, 2021 ^a	Mar 26, 2021 ^a

a. Part A represents the randomized, placebo-controlled, blinded phase of the study and includes available participant level data up to early unblinding, study discontinuation, the Part B Participant Decision Visits (PDV) or data cutoff date (Mar 26, 2021), whichever was earlier. The results of the Elecsys and RT-PCR assay for asymptomatic SARS-CoV-2 infection (obtained at the PDV) are included in the final analysis.

Note: Safety analyses presented in this review are based on a data cutoff of March 26, 2021; however, deaths and pregnancies were monitored until the database lock date of May 4, 2021

The demographics and dispositions shown in the sections below are based on the March 26, 2021 data cutoff, used in the updated analyses of efficacy and safety.

6.1.10.2 Demographics

The Per-Protocol Set was used for the analyses of vaccine efficacy and consisted of a total of 28,451 participants, with 14,287 in the mRNA-1273 vaccine group and 14,164 in the placebo group (Table 8). In the Per-Protocol Set, 47.5% of participants were female, and 25.4% of participants were 65 years of age or older. There were 36.1% of participants considered as representing communities of color, with 9.7% Black or African American, 4.7% Asian, and <3% from other racial groups; 19.7% of participants were Hispanic or Latino. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.8% of participants; 38.0% of participants were obese (body mass index ≥ 30 kg/m²). The demographics were balanced between the treatment groups.

Table 8. Demographics and Other Baseline Characteristics, Per-Protocol Set

Characteristic	mRNA-1273 N=14287 n (%)	Placebo N=14164 n (%)	Total N=28451 n (%)
Sex			
Female	6848 (47.9)	6670 (47.1)	13518 (47.5)
Male	7439 (52.1)	7494 (52.9)	14933 (52.5)
Age (years)			
Mean [SD]	51.6 [15.44]	51.6 [15.55]	51.6 [15.49]
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age subgroups			
18-64 years	10661 (74.6)	10569 (74.6)	21230 (74.6)
≥ 65 years	3626 (25.4)	3595 (25.4)	7221 (25.4)
Race			
American Indian or Alaska Native	109 (0.8)	113 (0.8)	222 (0.8)
Asian	628 (4.4)	700 (4.9)	1328 (4.7)
Black or African American	1395 (9.8)	1352 (9.5)	2747 (9.7)
Native Hawaiian or other Pacific Islander	36 (0.3)	31 (0.2)	67 (0.2)
White	11391 (79.7)	11273 (79.6)	22664 (79.7)
Multiracial	300 (2.1)	304 (2.1)	604 (2.1)
Other	282 (2.0)	274 (1.9)	556 (2.0)
Not reported	90 (0.6)	65 (0.5)	155 (0.5)
Unknown	56 (0.4)	52 (0.4)	108 (0.4)

Characteristic	mRNA-1273 N=14287 n (%)	Placebo N=14164 n (%)	Total N=28451 n (%)
Ethnicity			
Hispanic or Latino	2831 (19.8)	2787 (19.7)	5618 (19.7)
Not Hispanic or Latino	11322 (79.2)	11249 (79.4)	22571 (79.3)
Not reported	99 (0.7)	76 (0.5)	175 (0.6)
Unknown	35 (0.2)	52 (0.4)	87 (0.3)
Race and ethnicity group			
White	9123 (63.9)	8998 (63.5)	18121 (63.7)
Communities of color	5139 (36.0)	5141 (36.3)	10280 (36.1)
Missing	25 (0.2)	25 (0.2)	50 (0.2)
Occupational risk			
Healthcare worker	3631 (25.4)	3621 (25.6)	7252 (25.5)
High-risk conditions			
No high-risk condition	11004 (77.0)	10952 (77.3)	21956 (77.2)
With any protocol risk for severe COVID-19	3283 (23.0)	3212 (22.7)	6495 (22.8)
Chronic lung disease	675 (4.7)	692 (4.9)	1367 (4.8)
Significant cardiac disease	726 (5.1)	696 (4.9)	1422 (5.0)
Severe obesity (BMI >40 kg/m ²)	1009 (7.1)	980 (6.9)	1989 (7.0)
Diabetes	1402 (9.8)	1363 (9.6)	2765 (9.7)
Liver disease	100 (0.7)	90 (0.6)	190 (0.7)
HIV infection	85 (0.6)	82 (0.6)	167 (0.6)
BMI: <30 kg/m ²	8741 (61.2)	8719 (61.6)	17460 (61.4)
BMI: ≥30 kg/m ²	5460 (38.2)	5365 (37.9)	10825 (38.0)
Age and health risk for severe COVID-19^a			
18-64 years and not at risk	8271 (57.9)	8242 (58.2)	16513 (58.0)
18-64 years and at risk	2395 (16.8)	2331 (16.5)	4726 (16.6)
≥65 years	3621 (25.3)	3591 (25.4)	7212 (25.3)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.1.3.4.3.

Abbreviations: BMI=body mass index; N=number of participants in the per-protocol set; n=number of participants in the category; SD=standard deviation

a. Based on stratification factor from IRT, participants who are <65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening.

The Safety Set included 30,346 participants 18 years of age and older (15,184 in the mRNA-1273 vaccine group and 15,162 in the placebo group) ([Table 9](#)). The demographic characteristics among vaccine and placebo participants in the Safety Set were similar. Except for baseline SARS-CoV-2 status, which is negative by definition for the entire Per-Protocol Set, the Safety Set and Per-Protocol Set were similar in terms of demographic and other baseline characteristics.

Table 9. Demographics and Other Baseline Characteristics, Safety Set

Characteristic	mRNA-1273 N=15184 n (%)	Placebo N=15162 n (%)	Total N=30346 n (%)
Sex			
Female	7266 (47.9)	7106 (46.9)	14372 (47.4)
Male	7918 (52.1)	8056 (53.1)	15974 (52.6)
Age (years)			
Mean [SD]	51.4 [15.51]	51.3 [15.60]	51.4 [15.55]
Median	53.0	52.0	52.0
Min, Max	18, 95	18, 95	18, 95

Characteristic	mRNA-1273 N=15184 n (%)	Placebo N=15162 n (%)	Total N=30346 n (%)
Age subgroups (years)			
18-64	11415 (75.2)	11411 (75.3)	22826 (75.2)
≥65 and older	3769 (24.8)	3751 (24.7)	7520 (24.8)
≥75 and older	657 (4.3)	741 (4.9)	1398 (4.6)
Race			
American Indian or Alaska Native	113 (0.7)	121 (0.8)	234 (0.8)
Asian	656 (4.3)	739 (4.9)	1395 (4.6)
Black or African American	1567 (10.3)	1531 (10.1)	3098 (10.2)
Native Hawaiian or other Pacific Islander	36 (0.2)	32 (0.2)	68 (0.2)
White	12034 (79.3)	11998 (79.1)	24032 (79.2)
Multiracial	320 (2.1)	318 (2.1)	638 (2.1)
Other	299 (2.0)	294 (1.9)	593 (2.0)
Not reported	97 (0.6)	74 (0.5)	171 (0.6)
Unknown	62 (0.4)	55 (0.4)	117 (0.4)
Ethnicity			
Hispanic or Latino	3122 (20.6)	3108 (20.5)	6230 (20.5)
Not Hispanic or Latino	11920 (78.5)	11918 (78.6)	23838 (78.6)
Not reported	105 (0.7)	83 (0.5)	188 (0.6)
Unknown	37 (0.2)	53 (0.3)	90 (0.3)
Occupational risk			
Healthcare worker	3809 (25.1)	3840 (25.3)	7649 (25.2)
High-risk conditions			
No high-risk condition	11736 (77.3)	11705 (77.2)	23441 (77.2)
With any protocol risk for severe COVID-19	3448 (22.7)	3457 (22.8)	6905 (22.8)
Chronic lung disease	712 (4.7)	749 (4.9)	1461 (4.8)
Significant cardiac disease	762 (5.0)	742 (4.9)	1504 (5.0)
Severe obesity	1070 (7.0)	1058 (7.0)	2128 (7.0)
Diabetes	1460 (9.6)	1457 (9.6)	2917 (9.6)
Liver disease	104 (0.7)	96 (0.6)	200 (0.7)
HIV infection	94 (0.6)	91 (0.6)	185 (0.6)
BMI: <30 kg/m ²	9276 (61.1)	9300 (61.3)	18576 (61.2)
BMI: ≥30 kg/m ²	5820 (38.3)	5777 (38.1)	11597 (38.2)
Age and health risk for severe COVID-19^a			
18-64 years and not at risk	8890 (58.5)	8880 (58.6)	17770 (58.6)
18-64 years and at risk	2530 (16.7)	2535 (16.7)	5065 (16.7)
≥65 years	3764 (24.8)	3747 (24.7)	7511 (24.8)
Baseline SARS-CoV-2 status^b			
Negative	14750 (97.1)	14741 (97.2)	29491 (97.2)
Positive	347 (2.3)	337 (2.2)	684 (2.3)
Missing	87 (0.6)	84 (0.6)	171 (0.6)

Source: Adapted from STN 125752.1_P301 Clinical Study Report, Table 14.1.3.2.3.

Abbreviations: BMI=body mass index; N=number of participants in the per-protocol set; n=number of participants in the category; SD=standard deviation

a. Based on stratification factor from IRT, participants who are <65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening.

b. Baseline SARS-CoV-2 status: positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

6.1.10.3 Subject Disposition

Study disposition tables for the blinded phase of the study are presented below in [Table 10](#) (efficacy and immunogenicity populations) and [Table 11](#) (Safety Set).

The proportion of participants who were excluded from the Per-Protocol Set was comparable between the placebo and mRNA-1273 vaccine groups (3.8% and 3.0%, respectively). Most participants were excluded from the Per-Protocol Set because they discontinued vaccination prior to receiving the second dose or they received the second dose out of the predefined window. Among participants selected for the Random Subcohort for Immunogenicity, a greater proportion of placebo recipients than mRNA-1273 vaccine recipients (18.8% compared to 5.7%, respectively) were excluded from this subcohort. The majority of these cases were due to participants not receiving Dose 2 per schedule.

Table 10. Disposition, Blinded Phase, Efficacy and Immunogenicity Analyses Populations

Disposition	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Randomized	N=15209	N=15206	N=30415
Full Analysis Set	N=15180	N=15166	N=30346
Modified Intent-To-Treat (mITT) Set	N=14746	N=14745	N=29491
PP Set^a	N=14297	N=14164	N=28451
Excluded from PP Set	459 (3.0)	581 (3.8)	1040 (3.4)
Reason for exclusion ^b			
Received incorrect study vaccination	6 (<0.1)	7 (<0.1)	13 (<0.1)
Discontinued study or study vaccination before receiving second dose	334 (2.2)	425 (2.8)	759 (2.5)
Received second dose out of window for PP Set	102 (0.7)	119 (0.8)	221 (0.7)
Did not receive second dose and passed the window for PP Set	0	0	0
Other major protocol deviation impacting critical data	17 (0.1)	30 (0.2)	47 (0.2)
Per-Protocol Random Subcohort for Immunogenicity (PPRSI)^a	N=1185	N=272	N=1457
Selected for the Random Subcohort for Immunogenicity but excluded from PPRSI	71 (5.7)	63 (18.8)	134 (8.4)
Reason for exclusion ^b			
Received incorrect vaccination	0	1 (0.3)	1 (<0.1)
Received Dose 2 out of window for PP Set	5 (0.4)	3 (0.9)	8 (0.5)
Did not receive Dose 2 per schedule	44 (3.5)	52 (15.5)	96 (6.0)
Human immunodeficiency virus infection	21 (1.7)	4 (1.2)	25 (1.6)
Had other major protocol deviations	1 (<0.1)	3 (0.9)	4 (0.3)

Source: Adapted from STN 125752.1_P301 Clinical Study Report, Table 14.1.2.3, Table 14.1 2.4, Table 14.1.2.5.
Abbreviations: IP=investigational product; N=number of participants in the analysis set; PP=per-protocol.

a. Percentages are based on the number of participants in the analysis set.

b. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.

Among the Safety Set, during the blinded phase, discontinuations from study vaccine between Dose 1 and Dose 2 were balanced between the treatment groups. A greater proportion of placebo recipients (4.5%) than mRNA-1273 vaccine recipients (2.9%) discontinued/withdrew from the study, mostly related to seeking a COVID-19 vaccine under EUA outside of the study.

Table 11. Disposition, Blinded Phase, Safety Set

Disposition	mRNA-1273 N=15184 n (%)	Placebo N=15162 n (%)	Total N=30346 n (%)
Safety Set	N=15184	N=15162	N=30346
Completed 1 dose	15184 (100)	15162 (100)	30346 (100)
Completed 2 doses	14731 (97.0)	14631 (96.5)	29362 (96.8)
Solicited Safety Set	15179 (>99.0)	15159 (>99.9)	30338 (>99.9)
First dose	15166 (99.9)	15151 (>99.9)	30317 (>99.9)
Second dose	14691 (96.8)	14578 (96.1)	29269 (96.5)
Discontinued from study vaccine (after Dose 1 and before Dose 2)	453 (3.0)	531 (3.5)	984 (3.2)
Reason for discontinuation			
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 by participant	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/withdrawn from study	440 (2.9)	691 (4.5)	1131 (3.7)
Reason for withdrawal from study			
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)
Lost to follow-up	160 (1.1)	191 (1.3)	351 (1.2)
Physician decision	13 (<0.1)	7 (<0.1)	20 (<0.1)
Protocol deviation	46 (0.3)	160 (1.1)	206 (0.7)
Withdrawal of consent by participant	155 (1.0)	250 (1.6)	405 (1.3)
Other	41 (0.3)	60 (0.3)	101 (0.3)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.1.2.1, Table 14.1.1.1.1.2.2

After issuance of the EUA in December 2020, study participants were unblinded to their study treatment over the course of several months, and participants who received placebo during the blinded phase were offered mRNA-1273 vaccine during the open-label phase of the study. As of the data cutoff date, 12,648 of the 15,162 participants in the original placebo group had been unblinded and crossed over to receive mRNA-1273 vaccine; 93% of these participants completed both doses of mRNA-1273 vaccine in the open-label phase. Discontinuation from study among individuals who crossed over from placebo to mRNA-1273 vaccine was infrequent (0.4%) as compared with discontinuation among those originally randomized to placebo (54.0%) or mRNA-1273 vaccine (1.9%). Similar to the blinded phase, the majority of discontinuations in the placebo group in the open-label phase were related to seeking COVID-19 vaccine under EUA outside of the study ([Table 12](#)).

Table 12. Disposition, Open-Label Phase, Safety Set

Disposition	mRNA-1273^a N=15184 n (%)	Crossover mRNA-1273^b N=12648 n (%)	Placebo N=2514^c n (%)
Continued in open-label phase ^d	14618 (96.3)	12648 (100)	1698 (67.5)
Discontinued from study during open-label phase	290 (1.9)	51 (0.4)	1357 (54.0)
Reason for discontinuation			
Adverse event	1 (<0.1)	0	0
Serious adverse event	0	1 (<0.1)	0
Death	8 (<0.1)	3 (<0.1)	1 (<0.1)
Lost to follow-up	11 (<0.1)	3 (<0.1)	7 (0.3)
Physician decision	5 (<0.1)	3 (<0.1)	7 (0.3)
Pregnancy	1 (<0.1)	0	1 (<0.1)
Protocol deviation	106 (0.7)	11 (<0.1)	493 (19.6)
Withdrawal of consent	124 (0.8)	23 (0.2)	175 (7.0)
Other	34 (0.2)	7 (<0.1)	673 (26.8)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Addendum 1 (Part B), Table 14.1.1.1.5.5.

a. Includes all participants who received at least one dose of mRNA-1273 vaccine in Part A (includes mRNA-1273 participants who were unblinded and those who chose to remain blinded)

b. Crossover mRNA-1273: participants originally randomized to placebo group in Part A, who then received mRNA-1273 vaccine in Part B following unblinding.

c. Includes all participants who received placebo in Part A and who did not receive mRNA-1273 vaccine in Part B (includes placebo participants who were unblinded and chose to remain in placebo and placebo participants who chose to remain blinded).

d. Subjects who had participant decision visit and were unblinded and contributed to Part B analyses

Durations of follow-up after Dose 2 during the blinded and open-label phases of the study are displayed in [Table 13](#). Due to study unblinding after issuance of EUA, only a small number of participants had at least 6 months of blinded follow-up after Dose 2. The median duration of blinded follow-up after Dose 2 was 4 months and similar between the Safety Set and Per-Protocol Set (not displayed). Blinded follow-up duration was also similar between the treatment groups and age cohorts. In the mRNA-1273 vaccine group, median total follow-up duration after Dose 2, including both blinded and open-label phases, was approximately 6 months. For the original placebo participants who received mRNA-1273 vaccine in the open-label phase, the median duration of follow-up after Dose 2 of mRNA-1273 vaccine was 38 days.

Table 13. Duration of Follow-Up After Dose 2, Safety Set

Follow-up	mRNA-1273 N=15184	Placebo^a N=15162	Total N=30346
Blinded phase			
Median blinded follow-up post Dose 2, days			
All participants	118	114	116
18-64 years	118	114	116
≥65 years	118	115	116
Between 2 to <4 months follow-up post Dose 2, n (%)	7819 (51.5)	8342 (55.0)	16161 (53.3)
Between 4 to <6 months follow-up post Dose 2, n (%)	6370 (42.0)	5670 (37.4)	12040 (39.7)
At least 6 months blinded follow-up post Dose 2, n (%)	153 (1.0)	158 (1.0)	311 (1.0)

Follow-up	mRNA-1273 N=15184	Placebo^a N=15162	Total N=30346
Blinded and open-label phases			
Median total follow-up after Dose 2 of originally assigned treatment, days			
All participants	183	–	–
≥18-65 years	183	–	–
≥65 years	185	–	–
At least 6 months total follow up (blinded + unblinded) after Dose 2 of originally assigned treatment, n (%)	7499 (49.4)	–	–

Source: Adapted from mRNA-1273-P301 P301 Clinical Study Report Table 14.1.6.2.1, Table 14.1.6.2.3; mRNA-1273-P301 Clinical Study Report Addendum 1 (Part B), Table 14.1.1.1.5.5.

Abbreviations: N=number of participants in analysis set.

Notes: 1 month=30.4375 days. Percentages are based on the number of safety participants. Study duration from Dose 2 is 0 days for participants who did not receive Dose 2.

a. Duration of open-label follow-up not calculated for original placebo recipients as the majority (12,648 of 15,162) of these participants crossed over to receive mRNA-1273 vaccine during the open-label phase.

Table 14. Duration of Follow-Up, Participants Who Crossed Over From Placebo to mRNA-1273 Vaccine

Follow-up	Crossover^b N=12648
Received 2 doses of mRNA-1273, n (%)	11757 (93.0)
Median follow-up post dose 4 ^a (2 doses of mRNA-1273), days	
All participants	38
18-64 years	37
≥65 years	43
At least 2 months follow-up post dose 4, n/N (%)	
All participants	39/11757 (0.3)
18-64 years	31/8448 (0.4)
≥65 years	8/3309 (0.2)

Source: Adapted from mRNA-1273-P301 P301 Clinical Study Report Table 14.1.6.2.1, Table 14.1.6.2.3; mRNA-1273-P301 Clinical Study Report Addendum 1 (Part B), Table 14.1.1.1.5.5.

Abbreviations: N=number of participants in analysis set.

Notes: 1 month=30.4375 days. Percentages are based on the number of safety participants. Study duration from Dose 2 is 0 days for participants who did not receive Dose 2.

a. Follow-up post dose 4 is calculated as earlier date of discontinuation from study or 26 Mar 2021 – date of dose 4 + 1.

b. Participants who crossed over from placebo to mRNA-1273 vaccine.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Protocol-specified, event-driven primary efficacy analysis

The primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received two doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was VE in preventing protocol-defined COVID-19 occurring at least 14 days after Dose 2. Cases were adjudicated by a blinded committee. The follow-up period for the primary analysis was from July 27, 2020 (date first participant was dosed) to the primary efficacy data cutoff date of November 21, 2020.

The primary efficacy analysis demonstrated a VE against COVID-19 occurring at least 14 days after the second dose of vaccine of 94.1% (95% CI: 89.3%, 96.8%), which met the pre-specified success criterion. The case split was 11 COVID-19 cases in the mRNA-1273 vaccine group and 185 cases in the placebo group. This protocol-specified, event-driven primary efficacy analysis was the basis for issuance of the EUA for the Moderna COVID-19 Vaccine on December 18, 2020. Please refer to the [EUA Review Memo for the Moderna COVID-19 Vaccine](#) for additional details regarding the primary analysis.

Updated efficacy analyses

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up phase of the study (Part A) through the data cutoff of March 26, 2021, with a median follow-up duration of approximately 4 months after Dose 2 for participants in the efficacy population. All of the following updated primary and secondary VE analyses are from Part A of the study, unless otherwise noted.

In the updated analysis of the primary endpoint of vaccine efficacy to prevent protocol-defined COVID-19 based on adjudication committee assessment starting 14 days after Dose 2, there were 55 cases in the mRNA-1273 vaccine group vs 744 cases in the placebo group, for a VE of 93.2% (95% CI: 91.0, 94.8) ([Table 15](#)).

Table 15. Final Analysis of Vaccine Efficacy in the Blinded Phase (Part A) to Prevent COVID-19 Starting 14 Days After Dose 2, Per-Protocol Set, Data Cutoff March 26, 2021

Pre-Specified Age Group	mRNA-1273	Placebo	Vaccine Efficacy % (95% CI) ^b
	Cases/N (%)	Cases/N (%)	
	Incidence rate per 1,000 person-years ^a	Incidence rate per 1,000 person-years ^a	
All participants	55/14287 (0.4) 9.6	744/14164 (5.3) 136.6	93.2 (91.0, 94.8)
18-64 years	46/10661 (0.4) 10.7	644/10569 (6.1) 159.0	93.4 (91.1, 95.1)
≥65 years	9/3626 (0.2) 6.2	100/3595 (2.8) 71.7	91.5 (83.2, 95.7)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.2.2.1.3.1.1, 14.2.2.1.3.6.1.1.

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; N=number of participants in the per-protocol set; n=number participants in the subgroup.

a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.

b. Vaccine efficacy (VE), defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor

Reviewer Comment: The results from the updated efficacy analysis were similar to those of the primary analysis. At the primary analysis, a lower VE point estimate was observed among participants ≥65 years of age than among those 18-64 years of age, although the 95% confidence intervals were overlapping. Following the accrual of more COVID-19 cases, the updated efficacy analysis had VE point estimates that were comparable between age groups. Given the data cutoff date of March 26, 2021, which occurred before the widespread circulation of Delta variant within the U.S. and prior to the emergence of the Omicron variant, this study was not able to capture COVID-19 cases caused by these variants to assess for VE against these variants.

At the time of the database lock, there were an additional 13 cases (12 in placebo group, 1 in mRNA-1273 vaccine group) that met the protocol definition of COVID-19 but had not been adjudicated to be primary endpoint cases. Of these cases, 11 were pending adjudication and 2 were not classified as cases based on inadequate symptoms at the time of committee review. Relative to the number of cases included in the updated VE analysis, these additional cases would not be expected to impact efficacy conclusions.

6.1.11.2 Subpopulation Analyses

Subgroup analyses of the updated vaccine efficacy endpoint included VE by age, sex, race and ethnicity, and risk for severe COVID-19 and provide additional information on the applicability of these results across the general population. The results are displayed below in [Table 16](#).

Similar to the results obtained in the primary analysis, in the updated efficacy analysis, VE point estimates were consistent across subgroups and were comparable to the VE seen in the overall study population. The VE point estimate for the subgroup of individuals ≥ 65 and at risk of severe COVID-19 was slightly lower than those seen in the younger subgroups and the older but not-at-risk subgroup; however, the confidence interval is wide and overlaps with those of the other subgroups. The small numbers of participants and cases in some subgroups, such as participants ≥ 75 years of age and participants in certain racial subgroups, limit the interpretability of the individual VE results, but are displayed for completeness.

Table 16. Updated Subgroup Analyses of Vaccine Efficacy to Prevent COVID-19 Starting 14 Days After Dose 2, Per-Protocol Set, Data Cutoff March 26, 2021

Subgroup	mRNA-1273	Placebo	Vaccine Efficacy (%) (95% CI)
	Cases/N (%) Incidence rate per 1,000 person-years	Cases/N (%) Incidence rate per 1,000 person-years	
Age group			
18-64 years	46/10661 (0.4) 10.7	644/10569 (6.1) 159.0	93.4 (91.1, 95.1)
65 to <75 years	9/2990 (0.3) 7.5	81/2898 (2.8) 72.0	89.7 (79.6, 94.8)
≥ 75 years	0/636	19/697 (2.7) 70.8	100 (NE, 100)
Age and health risk for severe COVID-19			
18-64 and not at risk	35/8464 (0.4) 10.3	501/8428 (5.9) 155.6	93.5 (90.9, 95.4)
18-64 and at risk	11/2197 (0.5) 12.3	143/2141 (6.7) 172.0	93.0 (87.0, 96.2)
≥ 65 and not at risk	4/2540 (0.2) 4.0	66/2524 (2.6) 67.6	94.3 (84.3, 97.9)
≥ 65 and at risk	5/1086 (0.5) 11.4	34/1071 (3.2) 81.4	86.4 (65.3, 94.7)
Sex			
Male	30/7439 (0.4) 10.1	378/7494 (5.0) 131.7	92.5 (89.1, 94.8)
Female	25/6848 (0.4) 9.1	366/6670 (5.5) 142.2	93.8 (90.7, 95.9)

Subgroup	mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years	Placebo Cases/N (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (%) (95% CI)
Race			
White	48/11391 (0.4) 10.3	631/11273 (5.6) 143.2	93.0 (90.6, 94.7)
Black or African American	4/1395 (0.3) 7.5	41/1352 (3.0) 82.5	91.1 (75.2, 96.8)
Asian	1/628 (0.2) 4.3	29/700 (4.1) 118.0	96.5 (74.2, 99.5)
American Indian or Alaska Native	0/109	5/113 (4.4) 122.2	100 (NE, 100)
Native Hawaiian or Other Pacific Islander	0/36	0/31	NE
Multiple	1/300 (0.3) 9.0	8/304 (2.6) 73.7	88.1 (4.6, 98.5)
Other	1/282 (0.4) 9.7	19/274 (6.9) 203.8	95.8 (68.6, 99.4)
Ethnicity			
Hispanic or Latino	10/2831 (0.4) 9.2	177/2787 (6.4) 174.8	94.8 (90.2, 97.3)
Not Hispanic or Latino	45/11322 (0.4) 9.8	563/11249 (5.0) 128.4	92.6 (89.9, 94.5)
Race and ethnicity			
White	39/9123 (0.4) 10.4	488/8998 (5.4) 136.6	92.6 (89.8, 94.7)
Communities of color	16/5139 (0.3) 8.2	256/5141 (5.0) 137.3	94.2 (90.3, 96.5)
Baseline SARS-CoV-2 Status^a			
Negative	58/14746 (0.4) 9.9	751/14745 (5.1) 134.0	92.8% (90.6, 94.5)
Positive	0/347	2/337 (<0.1) 15.5	100% (NE, 100)
Missing	0/87	3/81 (3.6) 86.7	100% (NE, 100)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.2.2.1.3.6.2.1, 14.2.2.1.3.6.4.1, 14.2.2.1.3.6.11.1, 14.2.2.2.3.6.5.1, 14.2.2.2.3.6.6.1; Sponsor response to IR dated September 28, 2021.

Abbreviations CI=confidence interval; N=number of participants in the per-protocol set; n=number participants in the subgroup.

Notes: Incidence rate is defined as the number of participants with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years. Vaccine efficacy (VE), defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable.

a. based on FAS; case split in baseline positive participants based on sensitivity analysis conducted in Sponsor's response to IR dated Sept 28, 2021

Regarding assessment of VE in individuals previously infected with COVID-19, results were inconclusive due to the small number of participants in the study with evidence of prior SARS-CoV-2 infection at baseline (347 and 337 in the mRNA-1273 vaccine and placebo groups, respectively). There were two COVID-19 cases among study in participants with baseline SARS-CoV-2 status, both in the placebo group. Neither case was assessed as severe.

Results of an evaluation of vaccine efficacy by risk factor for severe COVID-19 are presented in [Table 17](#). Efficacy was similar between participants with and without risk

factors for severe COVID-19. The VE point estimates by individual risk factor were generally consistent with the efficacy observed in the overall study population, though some groups such as those with liver disease or HIV had too few participants to allow for a precise estimate of the VE.

Table 17. Updated Subgroup Analyses of Vaccine Efficacy to Prevent COVID-19 Starting 14 Days After Dose 2, by Risk Factor for Severe COVID-19, Per-Protocol Set, Data Cutoff March 26, 2021

Subgroup	mRNA-1273 Cases/N (%) Incidence rate per 1,000 person-years^a	Placebo Cases/N (%) Incidence rate per 1,000 person-years^a	Vaccine Efficacy (%) (95% CI)^b
Risk for severe COVID-19			
No	39/11004 (0.4) 8.9	567/10952 (5.2) 135.1	93.6 (91.2, 95.4)
Yes	16/3283 (0.5) 12.0	177/3212 (5.5) 141.7	91.7 (86.2, 95.0)
One risk factor	14/2660 (0.5) 13.0	143/2610 (5.5) 141.4	91.1 (84.5, 94.8)
At least 2 risk factors	2/623 (0.3) 8.0	34/602 (5.6) 143.0	94.5 (77.1, 98.7)
Risk factor			
Chronic Lung Disease	4/675 (0.6) 14.4	30/692 (4.3) 109.2	87.2 (63.8, 95.5)
Significant Cardiac Disease	4/726 (0.6) 13.7	30/696 (4.3) 110.0	88.0 (65.9, 95.8)
Severe Obesity	7/1009 (0.7) 17.0	75/980 (7.7) 196.9	91.4 (81.4, 96.0)
Diabetes	3/1402 (0.2) 5.3	72/1363 (5.3) 135.7	96.2 (87.9, 98.8)
Liver Disease	1/100 (1.0) 24.7	5/90 (5.6) 143.2	81.0 (-64.8, 97.8)
HIV	0/85	4/82 (4.9) 145.4	100 (NE, 100)
Obesity (BMI ≥30 kg/m²)			
Yes	29/5460 (0.5) 13.1	326/5365 (6.1) 156.5	91.8 (88.1, 94.4)
No	26/8741 (0.3) 7.5	415/8719 (4.8) 124.6	94.2 (91.3, 96.1)
Age group and obesity (BMI ≥30 kg/m²) status			
16-64 and not obese	24/6415 (0.4) 9.4	358/6379 (5.6) 147.4	93.8% (90.6, 95.9)
16-64 and obese	22/4188 (0.5) 12.9	284/4134 (6.9) 177.5	92.9% (89.1, 95.4)
≥65 and not obese	2/2327 (0.1) 2.2	57/2340 (2.4) 63.2	96.7% (86.4, 99.2)
≥65 and obese	7/1271 (0.6) 13.7	42/1231 (3.4) 86.9	84.3% (65.1, 93.0)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.2.2.1.3.6.7.1 and Table 14.2.2.1.3.6.12.1.; Table 5-1 in rsp-fda-cmts-clin-28sep2021-ir6.pdf
Abbreviations: BMI=body mass index; CI=confidence interval; N=number of participants in per-protocol set; n=number participants in the subgroup

Notes: Censoring rules are applied as for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a participant had positive RT-PCR at pre-Dose 2 visit (Day 29) without eligible symptoms within 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the participant is censored at the date with positive RT-PCR or Elecsys.

a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of participants with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.

b. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years. Vaccine efficacy (VE), defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable.

The demographic characteristics of the participants with confirmed COVID-19 cases contributing to the updated vaccine efficacy analysis were generally representative of those in the overall study population and largely similar between the mRNA-1273 vaccine and placebo groups and are displayed below in [Table 18](#).

Table 18. Demographic Characteristics of Participants With COVID-19 Starting 14 Days After Dose 2, Per-Protocol Set, Data Cutoff March 26, 2021

Characteristic	mRNA-1273 N=55 n (%)	Placebo N=744 n (%)	Total N=799 n (%)
Age			
18-64 years	46 (83.6)	644 (86.6)	690 (86.4)
≥65 to <75 years	9 (16.4)	81 (10.9)	90 (11.3)
≥75 to <85 years	0	15 (2.0)	15 (1.9)
≥85 years	0	4 (0.5)	4 (0.5)
Age and risk for severe COVID-19^a			
18-64 years and not at risk	35 (63.6)	501 (67.3)	536 (67.1)
18-64 years and at risk	11 (20.0)	143 (19.2)	154 (19.3)
≥65 years and not at risk	4 (7.3)	66 (8.9)	70 (8.8)
≥65 years and at risk	5 (9.1)	34 (4.6)	39 (4.9)
Sex			
Female	25 (45.5)	366 (49.2)	391 (48.9)
Male	30 (54.5)	378 (50.8)	408 (51.1)
Race			
American Indian or Alaska Native	0	5 (0.7)	5 (0.6)
Asian	1 (1.8)	29 (3.9)	30 (3.8)
Black or African American	4 (7.3)	41 (5.5)	45 (5.6)
Native Hawaiian or other Pacific Islander	0	0	0
White	48 (87.3)	631 (84.8)	679 (85.0)
Multiracial	1 (1.8)	8 (1.1)	9 (1.1)
Other	1 (1.8)	19 (2.6)	20 (2.5)
Not reported	0	5 (0.7)	5 (0.6)
Unknown	0	6 (0.8)	6 (0.8)
Ethnicity			
Hispanic or Latino	10 (18.2)	177 (23.8)	187 (23.4)
Not Hispanic or Latino	45 (81.8)	563 (75.7)	608 (76.1)
Not reported	0	2 (0.3)	2 (0.3)
Unknown	0	2 (0.3)	2 (0.3)
High risk condition			
Yes	16 (29.1)	177 (23.8)	193 (24.2)
No	39 (70.9)	567 (76.2)	606 (75.8)

Characteristic	mRNA-1273 N=55 n (%)	Placebo N=744 n (%)	Total N=799 n (%)
BMI ≥30	29 (52.7)	326 (43.8)	355 (44.4)
BMI <30	26 (47.3)	415 (55.8)	441 (55.2)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.1.3.4.4.

Abbreviations: BMI=body mass index; N=number of participants in the per-protocol set who had COVID-19 starting 14 days after Dose 2; n=number participants in the subgroup.

* with the censoring rules for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a participant had positive RT-PCR at pre-Dose 2 visit (Day 29) without eligible symptoms with 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the participant is censored at the date with positive RT-PCR or Elecsys.

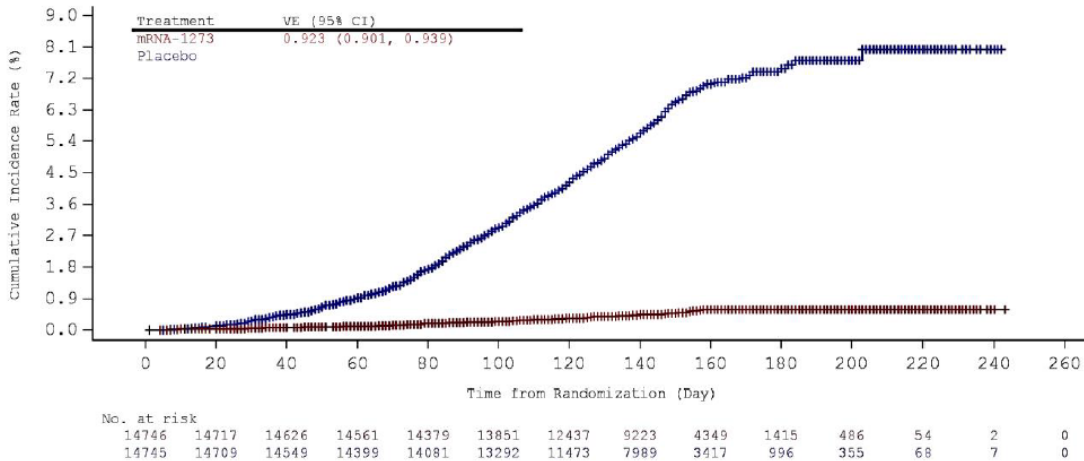
Percentages are based on the number of participants in Per-Protocol Set with COVID-19 based on adjudication committee assessments starting 14 days after second dose.

a. Age and health risk for severe COVID-19 are derived from age and risk factors collected on case report form (CRF).

Cumulative incidence curves

Regarding the cumulative incidence curves for the mITT Set, (Figure 3), the rate of adjudicated COVID-19 cases occurring at any time following randomization appears to be similarly low in both the mRNA-1273 vaccine and placebo groups until approximately 3 weeks after Dose 1, at which time the curves start to diverge.

Figure 3. Updated Cumulative Incidence Rates of COVID-19 Starting After Randomization, Modified Intent-To-Treat Set, Data Cutoff March 26, 2021



Source: Adapted from STN 125752.0 Study 301 Part A CSR Figure 6-1.

The Applicant conducted an updated analysis of vaccine efficacy starting after Dose 1 in the mITT Set, which consisted of participants with negative baseline SARS-CoV-2 status who received at least one dose of IP. The VE estimate for the prevention of COVID-19 after Dose 1 in the mITT Set was 92.1% (Table 19). As most participants received a second dose of IP and the analysis of VE after Dose 1 includes the time points after Dose 2, interpretation of this result is limited.

Reviewer Comment: Based on the number of cases of COVID-19 that accumulated between Dose 1 and Dose 2 in the two treatment groups, there does appear to be some protection against COVID-19 following one dose. However, the data do not provide information about longer-term protection more than 28 days after a single dose.

VE estimates for various time intervals following vaccination appear consistent with the VE point estimate overall in the updated analysis, including the interval of ≥4 months after Dose 2. However, because the median follow-up time for the blinded phase was 4 months after Dose 2, follow-up data after this time point were not sufficient to support assessment of potentially waning efficacy.

Table 19. Updated Vaccine Efficacy Against COVID-19 Following Dose 1, by Time Period, Modified Intent-To-Treat Set, Data Cutoff March 26, 2021

Time Period	mRNA-1273	Placebo	Vaccine Efficacy % (95% CI) ^b
	n/N(%) Incidence rate per 1,000 person-years ^a	n/N (%) Incidence rate per 1,000 person-years ^a	
Any time after Dose 1	69/14746 (0.5) 11.8	834/14745 (5.7) 148.8	92.1% (89.9, 93.9)
Any time after Dose 1 to before Dose 2	10/14746 (0.1) 8.5	59/14745 (0.4) 49.7	83.0% (66.5, 92.2)
Any time after Dose 2	59/14412 (0.4) 12.8	775/14317 (5.4) 177.9	92.8% (90.6, 94.6)
14 days after Dose 2 to <2 months after Dose 2	20/14403 (0.1) 12.1	230/14279 (1.6) 141.9	91.4% (86.5, 94.9)
2 months after Dose 2 to <4 months after Dose 2	30/14102 (0.2) 15.8	437/13684 (3.2) 246.5	93.6% (90.7, 95.7)
≥4 months after Dose 2	8/8482 (0.1) 15.3	84/7261 (1.2) 203.0	92.5% (84.4, 96.8)

Source: Adapted from STN 125752.0, cber-req-tables-mrna-1273.pdf Table 17

Abbreviations: BLA=biologics license application; CI=confidence interval; COVID-19=coronavirus disease 2019;

N=number of participants in analysis set; n=number of participants in the subgroup.

a. Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group within a given time period. Person-years for each time period is defined as the total years from the start of each time period to the date of COVID-19, the end of each time period, last date of study participation, efficacy data cutoff date, end date of the blinded phase, whichever is the earliest.

b. Vaccine efficacy (VE) is defined as 1 - ratio of incidence rates (mRNA-1273 vaccine vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years. 1 month = 28 days.

6.1.11.3 Analyses of Secondary Endpoints

The Applicant conducted updated analyses of the secondary efficacy endpoint of prevention of severe COVID-19 with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 26, 2021 ([Table 20](#)). In the updated analysis, the estimated VE against severe COVID-19 disease occurring at least 14 days after Dose 2 was 98.2% (95% CI: 92.8, 99.6) with 2 severe COVID-19 cases in the mRNA-1273 vaccine group and 106 severe COVID-19 cases in the placebo group. The VE estimate was similarly high among participants ≥65 years of age as those 18-64 years of age.

Table 20. Updated Vaccine Efficacy to Prevent Severe COVID-19 Starting 14 Days After Dose 2, Per-Protocol Set, Data Cutoff March 26, 2021

Age Group	mRNA-1273	Placebo	Vaccine Efficacy % (95% CI) ^b
	Cases/N (%) Incidence rate per 1,000 person-years ^a	Cases/N (%) Incidence rate per 1,000 person-years ^a	
All participants	2/14287 (<0.1) 0.3	106/14164 (0.7) 19.1	98.2 (92.8, 99.6)
18-64 years	1/10661 (<0.1) 0.2	76/10569 (0.7) 18.4	98.7 (91.0, 99.8)
≥65 years	1/3626 (<0.1) 0.7	30/3595 (0.8) 21.4	96.9 (77.1, 99.6)

Source: Adapted from STN 125752.0, CSR Table 6-4, Table 14.2.2.2.3.6.1

N = number of participants in the specified group.

a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.

b. Vaccine efficacy (VE), defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

Of the two mRNA-1273 vaccine recipients who met the severe COVID-19 endpoint, one was in a participant <65 years of age with no comorbidities who met the case definition based on oxygen saturation ≤93% on room air only and who did not require medical intervention. The other severe COVID-19 case was in an mRNA-1273 vaccine recipient >65 years of age with comorbidities who was hospitalized for respiratory failure due to COVID-19 requiring supplemental oxygen (without need for mechanical ventilation). Of the placebo recipients with severe COVID-19, 28.3% were ≥65 years of age, 41.5% had one or more protocol-defined high-risk condition, and 56.6% were obese.

One case of severe COVID-19 in the mRNA-1273 vaccine group (discussed above) and 23 cases in the placebo group required hospitalization, admission to the ICU, intubation or mechanical ventilation, or resulted in death. One additional placebo recipient died from COVID-19, but the case had not yet been adjudicated by the committee and was not included in the analysis.

Updated vaccine efficacy to prevent severe COVID-19 by interval after vaccination in the mITT Set is displayed in [Table 21](#). Starting any time after Dose 1, there were 4 participants in the mRNA-1273 vaccine group compared to 114 participants in the placebo group who had severe COVID-19 per adjudication committee assessment. VE against severe COVID-19 remained high across the different time intervals

Table 21. Updated Vaccine Efficacy to Prevent Severe COVID-19 Starting After Dose 1, Modified Intent-To-Treat Set, Data Cutoff March 26, 2021

Time Point	mRNA-1273	Placebo	Vaccine Efficacy % (95% CI) ^b
	n/N (%) Incidence rate per 1,000 person- years ^a	n/N (%) Incidence rate per 1,000 person- years ^a	
Any time after Dose 1	4/14746 (<0.1) 0.7	114/14745 (0.8) 19.9	96.6% (91.0, 99.1)
Any time after Dose 1 to before Dose 2	2/14746 (<0.1) 1.7	6/14745 (<0.1) 5.1	66.6% (-86.8, 96.7)

Time Point	mRNA-1273 n/N (%) Incidence rate per 1,000 person- years^a	Placebo n/N (%) Incidence rate per 1,000 person- years^a	Vaccine Efficacy % (95% CI)^b
Any time after Dose 2	2/14412 (<0.1) 0.4	108/14320 (0.8) 24.2	98.2% (93.4, 99.8)
14 days after Dose 2 to <2 months after Dose 2	0/14405	33/14306 (0.2) 20.2	100% (88.3, NE)
2 months after Dose 2 to <4 months after Dose 2	2/14123 (<0.1) 1.0	61/13907 (0.4) 33.4	96.9% (88.2, 99.6)
≥4 months after Dose 2	0/8517	13/7669 (0.2) 29.0	100% (72.0, NE)

Source: Adapted from STN 125752.0, cber-req-tables-mma-1273.pdf Table 17

Abbreviations: BLA=biologics license application; CI=confidence interval; COVID-19=coronavirus disease 2019;

N=number of participants in analysis set; n=number of participants in the subgroup.

a. Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group within a given time period. Person-years for each time period is defined as the total years from the start of each time period to the date of COVID-19, the end of each time period, last date of study participation, efficacy data cutoff date, end date of the blinded phase, whichever is the earliest.

b. Vaccine efficacy (VE) is defined as 1 - ratio of incidence rates (mRNA-1273 vaccine vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years. 1 month = 28 days.

Deaths caused by COVID-19

During the blinded phase of the study, there were 4 deaths from COVID-19. Three were among placebo recipients between the ages of 50 to 65 years, all with underlying medical risk factors for severe COVID-19. One death was in an mRNA-1273 vaccine recipient >70 years of age with multiple comorbidities who received only one dose of the vaccine and had onset of COVID-19 starting 126 days after Dose 1. This participant was reported to have refused the second dose due to adverse reactions after the first dose (nausea and fatigue).

Secondary definition of COVID-19

Analysis of updated vaccine efficacy using the more broad, secondary definition (“CDC definition”) of COVID-19 resulted in similar results (VE 93.4% with 95% CI: 91.4, 94.9) as the updated vaccine efficacy based on the protocol COVID-19 case definition.

Asymptomatic infection

Asymptomatic SARS-CoV-2 cases were identified by absence of symptomatic COVID-19 (based on either the primary efficacy endpoint definition or the secondary definition of COVID-19) and either seroconversion as measured by binding antibody specific to SARS-CoV-2 nucleocapsid (N-serology) at scheduled visits (Months 1, 2, 7, 13, 25, PDV) or positive SARS-CoV-2 RT-PCR at scheduled visits (D29, PDV). The protocol-specified asymptomatic infection endpoint was infection starting 14 days after Dose 2, which required a positive PCR and/or positive N-serology at the Day 57 (Month 2) visit or later. The results from the tests collected at the PDV (occurring at or before the data cutoff date of March 26, 2021) were included in this analysis. Due to study unblinding after EUA, few participants reached Month 7 of blinded follow-up, and no participant reached Month 13 or Month 25, and thus the majority of cases as determined by positive N-serology came from the Month 2 or PDV. The date of the asymptomatic infection is the earlier date of seroconversion or positive RT-PCR, with absence of symptoms. Participants who had symptomatic infection prior to an asymptomatic infection were censored at the time of the symptomatic infection.

Table 22. Vaccine Efficacy to Prevent Asymptomatic SARS-CoV-2 Infection Starting 14 Days After Dose 2, Including the Participant Decision Visit, Using the Competing Risk Method, Per-Protocol Set, Data Cutoff March 26, 2021

Subgroup	mRNA-1273 n/N (%) Incidence rate per 1,000 person-years^a	Placebo n/N (%) Incidence rate per 1,000 person-years^a	Vaccine Efficacy % (95% CI)^b
All participants	214/14287 (1.5) 37.178	498/14164 (3.5) 91.508	63.0% (56.6, 68.5)
18-64 years	167/10661 (1.6) 38.834	414/10569 (3.9) 102.349	65.3% (58.4, 71.0)
≥65 years	47/3626 (1.3) 32.285	84/3595 (2.3) 60.122	51.6% (30.9, 66.1)
Based on N-serology only	61/14287 (0.4) 10.6	339/14164 (2.4) 62.3	84.6% (79.7, 88.3)
Based on positive RT-PCR only	160/14287 (1.1) 27.8	272/14164 (1.9) 50.0	49.4% (38.5, 58.4)

Source: Adapted from P301 CSR Table 14.2.2.6.2.1.1.2; cber-req-tables-mrna-1273.pdf Table 14

Abbreviations: CI=confidence interval; N=number of participants in analysis set; RT-PCR=reverse-transcription polymerase chain reaction.

Notes: Censoring rules are applied as for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a participant had positive RT-PCR at pre-Dose 2 visit (Day 29) without eligible symptoms within 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the participant is censored at the date with positive RT-PCR or Elecsys. Severe COVID-19 case is defined based on COVID-19 case. For asymptomatic infection, RT-PCR test and Elecsys anti-SARS-CoV-2 assay results at post-baseline scheduled visits are considered in case definition. Disease cases (COVID-19 or secondary definition of COVID-19) are considered as competing events for asymptomatic SARS-CoV-2 infection.

a. Person-years is defined as the total years from randomization date to the date of relevant event (severe COVID-19, COVID-19 secondary definition, SARS-CoV-2 infection, death caused by COVID-19, or asymptomatic infection), the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of participants with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

b. Vaccine efficacy, defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable.

As asymptomatic cases were defined in the protocol as those without COVID-19 symptoms prior to a positive test, it was possible for participants to be counted as an asymptomatic case but then have documented COVID-19 symptoms at a later timepoint. It was also possible for participants to be included in the asymptomatic infection endpoint if they reported COVID-19 symptoms at an earlier timepoint but did not have an accompanying positive RT-PCR (and thus did not meet the protocol-specified criteria for a COVID-19 or secondary COVID-19 case). Following an information request by CBER, the Applicant conducted a sensitivity analysis excluding participants with any documented, protocol-defined COVID-19 symptoms reported at any time during the study. The sensitivity analysis (displayed in [Table 23](#)) revealed similar VE as the analysis done using asymptomatic cases derived per protocol.

Table 23. Sensitivity Analysis of VE Against Asymptomatic SARS-CoV-2 Infection Starting 14 Days After Dose 2 in the Blinded Phase, Per-Protocol Set

	mRNA-1273 N=14287 n	Placebo N=14164 n	VE ^a (1-Hazard Ratio) (95% CI)
	Incidence rate/1000 person-years (95% CI)	Incidence rate/1000 person-years (95% CI)	
All Participants	180 31.3 (26.9, 36.2)	399 73.3 (66.3, 80.9)	61.0% (53.4, 67.3)

Source: Sponsor response to IR dated December 6, 2021

Abbreviations: IR = incidence rate; 1-IRR = 1-incidence rate ratio; 1-HR= 1-hazard ratio; n=number of asymptomatic cases of COVID-19 defined as positive SARS-CoV-2 serology or PCR in the absence of protocol-defined COVID-19 symptoms reported at any time during the study.

a. VE = 1- hazard ratio and 95% CI were estimated using Fine and Gray's sub-distribution hazard model with COVID-19 disease cases as competing events and with the treatment group as a covariate, adjusting for stratification factor.

Reviewer Comment: There are many limitations to the evaluation of asymptomatic infection in this study, the primary being the infrequent assessments for N-serology (3 collections) and RT-PCR (1 collection) at fixed timepoints. Thus, it is unlikely that all cases of asymptomatic SARS-CoV-2 infection that occurred during the study were captured. There was a lower VE observed when only considering asymptomatic cases identified by RT-PCR compared to cases identified by N-serology. It is possible that mRNA-1273 vaccine is more efficacious in preventing seroconversion than preventing colonization by the virus. However, sampling limitations of PCR testing (one collection timepoint, only able to assess current infection) compared to serology testing (more collection timepoints, can assess for past infection) may also have contributed to the differences observed. This exploratory analysis has been included in the Clinical Studies section of the USPI.

SARS-CoV-2 infection regardless of symptomatology and severity

The endpoint of SARS-CoV-2 infection regardless of symptomatology and severity includes all participants in the Per-Protocol Set with positive RT-PCR tests and/or positive N-serology, with or without reported COVID-19 symptoms. The results from the tests collected at the PDV (occurring on or before March 26, 2021) are included in this analysis. VE against SARS-CoV-2 infection, regardless of symptoms, is shown in [Table 24](#) below.

Table 24. Vaccine Efficacy to Prevent SARS-CoV-2 Infection, Regardless of Symptoms, Starting 14 Days After Dose 2, Including the Participant Decision Visit, Per-Protocol Set, Data Cutoff March 26, 2021

	mRNA-1273 N=14287 Cases (%)	Placebo N=14164 Cases (%)	Vaccine Efficacy % (95% CI) ^b
	Incidence rate per 1,000 person-years ^a	Incidence rate per 1,000 person-years ^a	
All participants	280 (2.0) 48.7	1339 (9.5) 246.0	82.0% (79.5, 84.2)

Source: CSR Table 14.2.2.3.1.1.2

a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.

b. Vaccine efficacy (VE), defined as 1-hazard ratio (mRNA-1273 vaccine vs placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

6.1.11.4 Dropouts and/or Discontinuations

The number of participants who dropped out and/or discontinued from the study was small and did not affect the interpretation of the vaccine efficacy outcomes. Refer to Section [6.1.12.5](#) for details regarding dropouts and/or discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

All-cause mortality

There were 12 deaths in each of the mRNA-1273 vaccine and placebo groups, for an estimated VE against all-cause mortality of 7.2% (95% CI: -107, 58.3). There was one additional death in the mRNA-1273 group for which the onset of the event was in Part A but the day of the death occurred in Part B. That participant was not included in this all-cause mortality analysis for Part A.

Reviewer Comment: While based on a small number of deaths, this result, with a 95% confidence interval that includes zero, supports the expectation that vaccination with mRNA-1273 vaccine would not impact mortality due to non-COVID-related causes.

Suspected COVID-19 cases

There were 21 participants in the mRNA-1273 vaccine group and 39 participants in the placebo group who had suspected COVID-19 and met criteria for illness visit and NP swab collection, starting 14 days post Dose 2, but for whom no PCR results were available. Of these cases, there were 3 participants in the placebo group and none in the mRNA-1273 vaccine group who would have met severe COVID-19 criteria. The most common reason for no PCR results were sample not collected at illness visit (10 [47.6%] and 9 [23.1%] in the mRNA-1273 vaccine and placebo groups, respectively) and no illness visit completed and/or COVID-19 case occurred outside of study clinic (9 [42.9%] and 22 [56.4%] in the mRNA-1273 vaccine and placebo groups, respectively).

Reviewer Comment: The number of participants who had COVID-19 symptoms but were not counted as a confirmed case because the PCR results were unavailable was small (n=60). It is unknown how many of these cases would have been COVID-19 cases if PCR results were available. Given this small number and the case split with a higher number in the placebo group compared to the mRNA-1273 vaccine group (39 vs 21, respectively), inclusion of these suspected cases would be expected to have minimal impact on the VE results.

COVID-19 symptoms

To explore possible effects of the vaccine on duration and severity of symptoms, participants who experienced COVID-19 symptoms and subsequently tested positive for SARS-CoV-2 RT-PCR were monitored daily for symptoms for a 14-day period after diagnosis or until symptoms resolved, whichever was later. Among participants with COVID-19 starting 14 days after Dose 2, the median number of days with at least one COVID-19 symptom was 6 days in the mRNA-1273 vaccine group compared to 11 days in the placebo group. Across all symptoms (both respiratory and systemic) included in the primary endpoint COVID-19 case definition, the most common symptom reported by placebo recipients was cough (84.9%), and the most common symptom reported by mRNA-1273 vaccine recipients was headache (85.5%). Clinical evidence of pneumonia was found to be present in 2.4% of placebo participants, and radiographic evidence of

pneumonia was found to be present in 2.2% of placebo participants, compared to none for either reported in the mRNA-1273 vaccine group. In the placebo group, 84.9% of participants reported cough compared to 63.6% of participants in the mRNA-1273 vaccine group. Systemic symptoms reported more frequently in the placebo group compared to the mRNA-1273 vaccine group included new loss of taste (55.9% vs 25.5%), new loss of smell (59.8% vs 32.7%), chills (50.8% vs 30.9%), body aches (62.4% vs 43.6%), and fever (23.5% vs 9.1%). Systemic symptoms reported more frequently in the mRNA-1273 vaccine group compared to the placebo group included sore throat (61.8% vs 51.9%), headache (85.5% vs 78.4%), and rhinorrhea (70.9% vs 65.7%).

Reviewer Comment: These results suggest that in participants who experienced breakthrough infection after vaccination, symptoms of COVID-19 may potentially be milder and be of shorter duration compared to those in individuals who were not vaccinated and then developed COVID-19. However, these analyses were mainly based on self-reported symptoms during the illness period and participants may not have been compliant with daily documentation of symptoms, especially if they had a more severe illness course.

Sequencing data from centrally confirmed COVID-19 cases

During the study period (July 27, 2020 through the cutoff date of March 26, 2021), new SARS-CoV-2 variants emerged globally and in the U.S. In a post hoc analysis, genomic sequencing was performed on all SARS-CoV-2 RT-PCR positive NP samples from the COVID-19 cases with onset starting 14 days after Dose 2 (cases that contributed to the updated efficacy analysis of the primary endpoint). Sequencing was performed by a team blinded to treatment group assignments; however, there was unequal representation of sequenced cases across treatment groups. Successful sequencing was performed more frequently in samples from placebo recipients (70% of cases) than in samples from vaccine recipients (30% of cases), possibly due to lower viral load in samples from vaccine recipients.

[Table 25](#) below displays the sequence analysis summary for all SARS-CoV-2 lineages associated with the RT-PCR positive NP samples in the mRNA-1273 vaccine and placebo groups, including variants with >10 cases and any designated as Variants of Concern (VOCs) or Variants of Interest (VOIs). Variants being monitored based on World Health Organization and CDC SARS-CoV-2 variant classifications/definitions (World Health Organization 2021; CDC 2021a) were also evaluated, while all other remaining variants were classified as "Other." SARS-CoV-2 sequences from the majority of cases in both study groups were from the B.1.2 lineage, and no VOCs or VOIs were found in the study. Variants being monitored identified during the study included B.1.427/B.1.429 (Epsilon), P.1 (Gamma), and P.2 (Zeta); however, the number of cases were too small to allow for precise estimation of vaccine efficacy against these variants.

Table 25. Summary of COVID-19 Starting 14 Days After Dose 2, by Variant Lineage, Per-Protocol Set

	mRNA-1273 N^b=55 n (%)	Placebo N^b=744 n (%)
SARS-CoV-2 Lineage^a		
B.1.2	13 (23.6)	380 (51.1)
B.1.243	1 (1.8)	23 (3.1)
B.1.596	0	13 (1.7)
B.1.427 (Epsilon)	0	6 (0.8)
B.1.429 (Epsilon)	3 (5.5)	9 (1.2)
P.1 (Gamma)	0	1 (0.1)
P.2 (Zeta)	0	2 (0.2)
Wild Type	0	1 (0.1)
Other	0	92 (12.4)
No sequencing data available	38 (69.1)	217 (29.2)

Source: Table IR15.B-14.2.1.1.2.1.4.1

a. Only lineages with >10 cases, the wild type virus, and variants classified as variant of concern or interest or variant being monitored by CDC are listed. All others are grouped together under "other".

b. N = subjects with COVID-19 based on adjudication committee assessments starting 14 days after Dose 2. This value is the denominator for the percentage calculations.

Reviewer Comment: As the study was conducted entirely in the U.S., and the data cutoff was March 26, 2021, cases that were attributable to SARS-CoV-2 variants of concern, including Alpha (B.1.1.7), Beta (B.1.351) or Delta (B.1.617.2) variants, were not identified. As mentioned above, the imbalance across treatment groups in available sequencing data (30% cases in vaccine group vs 70% of cases from placebo group) makes evaluation of VE against different variants difficult.

Part B analysis

After unblinding, participants who remained in the study were followed as part of the open-label phase of the study (Part B). The median duration of follow-up from the PDV (unblinding) to data cutoff was 67 days. Participants continued to be monitored for symptomatic COVID-19. [Table 26](#) shows the number of COVID-19 cases in each of the three groups in the open-label phase: the original mRNA-1273 vaccine group (mRNA-1273 vaccine group), the original placebo group participants who did not cross over (placebo group), and the original placebo group participants who crossed over to receive mRNA-1273 vaccine (crossover group). During the open-label phase, most COVID-19 cases occurred in participants in the crossover group. However, of the 56 COVID-19 cases in this group, 17 occurred prior to the first dose of mRNA-1273 vaccine and 37 occurred between the first and second doses of mRNA-1273 vaccine.

Table 26. COVID-19 Cases in the Open-Label Phase (Part B), Per-Protocol Set

	mRNA-1273 N ^a =13704 Cases (%)	Placebo N ^a =1175 Cases (%)	Crossover ^b N ^a =11234 Cases (%)
Number of subjects with COVID-19 n (%)	19 (0.1)	3 (0.3)	56 (0.5)
Before first dose of mRNA-1273 vaccine in open-label phase	--	--	17 (0.2)
Between first and second doses of mRNA-1273 vaccine in open-label phase	--	--	37 (0.3)
From second dose up to 14 days after second dose of mRNA-1273 vaccine in open-label phase	--	--	1 (<0.1)
≥14 days after second dose of mRNA-1273 vaccine in open-label phase	--	--	1 (<0.1)
Incidence rate per 1000 person-years (95% CI)	8.0 (4.8, 12.4)	77.3 (16.0, 226.1)	--

Source: CSR addendum 1 Table 14.2.2.1.3.8.1

a. Number of subjects at risk: subjects who started the open-label phase before or on the efficacy data cutoff date, had no prior SARS-CoV-2 infection and were not a COVID-19 case up to Participant Decision Visit or unblinding date, whichever is earlier.

b. Participants who crossed over from placebo to mRNA-1273 vaccine.

Reviewer Comment: For participants in the crossover group, there could be an interval of days to weeks between unblinding to the original treatment group and receipt of the first dose of mRNA-1273 vaccine. The number of cases that occurred in this group during this short interval and between Dose 1 and Dose 2 of mRNA-1273 vaccine may reflect the high community circulation of SARS-CoV-2 at the time of this phase of the study (December 2020 to March 2021).

In the analysis of severe COVID-19 cases in Part B, there was 1 severe case in each of the original mRNA-1273 vaccine and placebo groups and 8 severe cases in the crossover group. Of the 8 cases in the crossover group, 4 occurred prior to the first dose of mRNA-1273 vaccine and 4 occurred between the first and second doses of mRNA-1273 vaccine. The one severe case in the original mRNA-1273 vaccine group was in a participant <65 years with no risk factors who had onset of COVID-19 84 days after Dose 2 and met the severe criteria based on oxygen saturation <93%, but who did not require medical intervention. At the time of data cutoff, there were no deaths related to COVID-19 reported during the open-label phase.

Immunogenicity

A total of 1591 participants were included in the Random Subcohort for Immunogenicity, of which 1457 participants (272 placebo recipients and 1185 mRNA-1273 vaccine recipients) were included in the Per-Protocol Random Subcohort for Immunogenicity (PPRSI). The PPRSI was used for the analyses of immunogenicity postvaccination. Immunogenicity assessments included neutralizing antibody levels against SARS-CoV-2 as measured with an ID50 assay using a pseudovirus expressing the SARS-CoV-2 spike protein (USA_WA1/2020 isolate carrying the D614G mutation). The pseudovirus neutralizing antibody assay (Duke University Medical Center) used in this study has been validated.

Summaries of immune response after vaccination, as measured by pseudovirus neutralizing antibody titers, are displayed in [Table 27](#) (participants SARS-CoV-2 negative at baseline) and [Table 28](#) (participants SARS-CoV-2 positive at baseline)

participants. Immunogenicity assessments also included serum binding antibody levels against SARS-CoV-2 as measured by a validated ELISA specific to the SARS-CoV-2 spike protein (b) (4) but these results are not discussed in the review as the overall trend was similar as that measured by neutralizing antibody titers.

In participants with negative SARS-CoV-2 status at baseline, there was a rise in neutralizing antibody titers observed 1 month after Dose 1, with an even more robust response observed 1 month after Dose 2. On Day 57, GMTs were lower in the ≥65 years age group than in the younger age group.

Table 27. Summary of Pseudovirus Neutralizing Antibody (ID50) Titers by Age Group, Baseline SARS-CoV-2 Status Negative, Per-Protocol Subcohort for Immunogenicity

	18-64 Years Placebo N=94	18-64 Years mRNA-1273 N=700	≥65 Years Placebo N=48	≥65 Years mRNA-1273 N=355
Timepoint	n=94	n=699	n=48	n=353
Baseline (Day 1)	n=94	n=699	n=48	n=353
GM titer	9.3	9.8	9.3	9.3
(95% CI) ^a	(NE, NE)	(9.4, 10.2)	(NE, NE)	(9.2, 9.5)
Day 29	n=94	n=700	n=48	n=355
GM titer	9.3	66.8	10.1	37.2
(95% CI) ^a	(NE, NE)	(61.1, 73.0)	(8.5, 11.9)	(33.0, 41.9)
GM fold-rise	1.0	6.8	1.1	4.0
(95% CI) ^a	(NE, NE)	(6.3, 7.5)	(0.9, 1.3)	(3.5, 4.5)
Day 57	n=94	n=698	n=48	n=355
GM titer	9.8	1206.6	10.1	871.2
(95% CI) ^a	(8.7, 11.1)	(1125.7, 1293.3)	(8.5, 11.9)	(785.5, 966.3)
GM fold-rise	1.1	123.6	1.1	93.0
(95% CI) ^a	(0.9, 1.2)	(114.3, 133.5)	(0.9, 1.3)	(83.6, 103.5)

Source: Table 14.2.4.2.1.3.1.

N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint.

n= Number of subjects with non-missing data at the corresponding timepoint.

(LLOQ: 18.5, ULOQ: 4404)

Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.

a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.

As expected, compared to participants with negative baseline SARS-CoV-2 status, participants who had evidence of prior SARS-CoV-2 infection at baseline had higher baseline GMTs. On Day 29, baseline positive participants had a much higher fold-rise in titers than the baseline negative group, and the GMT were comparable to the Day 57 levels in the baseline negative group. Further increase in titers is observed on Day 57. GMTs were similar between participants 18-64 years and those 65 years or older.

Table 28. Summary of Pseudovirus Neutralizing Antibody (ID50) Titers by Age Group, Baseline SARS-CoV-2 Status Positive, Per-Protocol Subcohort for Immunogenicity

Timepoint	18-64 Years	18-64 Years	≥65 Years	≥65 Years
	Placebo	mRNA-1273	Placebo	mRNA-1273
Baseline (Day 1)	n=110	n=107	n=19	n=23
GM titer	83.8	69.6	75.5	61.7
(95% CI) ^a	(58.5, 120.1)	(49.2, 98.4)	(31.2, 182.7)	(28.6, 133.3)
Day 29	n=110	n=107	n=19	n=23
GM titer	53.2	1722.8	49.9	727.1
(95% CI) ^a	(38.7, 73.3)	(1235.2, 2402.9)	(23.8, 104.6)	(269.1, 1964.7)
GM fold-rise	0.6	24.8	0.7	11.8
(95% CI) ^a	(0.6, 0.7)	(17.9, 34.2)	(0.5, 1.0)	(5.3, 26.2)
Day 57	n=110	n=107	n=20	n=23
GM titer	47.2	3108.9	50.8	3324.1
(95% CI) ^a	(34.4, 64.7)	(2432.9, 3972.7)	(20.0, 129.1)	(2142.6, 5156.9)
GM fold-rise	0.6	44.7	0.7	53.8
(95% CI) ^a	(0.5, 0.7)	(31.7, 63.0)	(0.4, 1.4)	(27.4, 105.6)

Source: Table 14.2.4.2.1.4.1.

N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint.

n= Number of subjects with non-missing data at the corresponding timepoint.

(LLOQ: 18.5, ULOQ: 4404)

Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.

a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.

Reviewer Comment: In participants who were positive at baseline, the first dose of mRNA-1273 vaccine elicited an immune response comparable to that observed after the second mRNA-1273 vaccine dose in participants negative at baseline. However, as these baseline positive participants all went on to receive a second mRNA-1273 vaccine dose, it is unknown whether the level of immune response after a single dose would have been sustained at later timepoints and remained similar to the immune response levels in baseline negative participants who received 2 mRNA-1273 vaccine doses, or if it would have declined more rapidly.

Immunogenicity against variants

To assess for the immune response of mRNA-1273 vaccine against current variants of concern, the Applicant submitted to the IND summaries of several small immunogenicity studies. The data from these studies have not been independently confirmed by the FDA.

Immune response against B.1.617.2 (Delta) was assessed using serum samples from 59 participants from Study P301 using a non-validated pseudovirus neutralization assay (psVNA) against Delta at Duke University. These samples were selected based on their known geometric mean ID50 titers against D614G (prototype strain) that were acquired during the formal analysis of Phase 3 samples. The samples were collected 2 weeks after either the first or second dose of vaccine, but as Duke laboratory remains blinded to the study day, it was unknown how many of these samples were post first or second dose. Overall, the ID50 titers from the serum samples were 2.1-fold lower against Delta compared to D614G. Data are also available from an analysis of psVNA against Delta using a non-validated assay in a different subgroup of participants in P301 (n=580) at 28 days after Dose 2. The data from this group was used as a comparator for analysis of a booster dose and results of this analysis are discussed in the [EUA review memo for Moderna booster dose](#) (FDA 2021c). Although there was no direct comparison of titers

against Delta vs D614G done in this analysis. The GMTs at 28 days post Dose 2 against Delta in this subgroup appeared to be approximately 3-fold lower compared to those against D614G observed in a different subgroup from P301 (n=1053). Limitations of these studies include the use of a non-validated assay, the non-random sample, and different assay characteristics used for the different groups which may impact interpretability.

Immune response against the newly emerged B.1.1.529 (Omicron) variant was assessed using serum samples from 30 participants from P301 which were tested for neutralization against Omicron using a non-validated lentivirus-based pseudovirus assay in 2 independent laboratories—the Vaccine Research Center and Duke University. At one month after Dose 2, serum neutralizing titers to Omicron were 49-84 times lower compared to titers against D614G. The study further tested neutralization titers in a small group of participants who received a booster dose of mRNA-1273 vaccine 4 to 9 months after completing 2 doses of mRNA-1273 vaccine, either as part of a clinical study or under EUA. At 2 weeks post-booster, serum neutralizing titers to Omicron were 4.2 to 6.5 times lower compared to neutralization titers against D614G. Limitations of this study include the small sample size, the non-random sampling, the use of a non-validated assay for the assessment of Omicron-specific antibody titers, and the different booster intervals of the participants who contributed samples.

Reviewer Comment: These results show a lower immune response against the Omicron variant compared to the prototype strain after 2 doses of mRNA-1273 vaccine. Although not analyzed in the same study, the fold-reduction in neutralization titers against Omicron was much greater compared to what was observed against Delta suggesting more marked decreased vaccine effectiveness against Omicron, which is consistent with the available observational data during the current Omicron surge (Johnson et al. 2022). Although the data indicates decreased vaccine effectiveness against infection and mild symptomatic disease attributable to Omicron, effectiveness against COVID-related hospitalizations and deaths appears to remain high. Early observational data shared by the Applicant also suggests that vaccine efficacy against Omicron after the 2-dose primary series may not be as durable and wanes more quickly compared to against the ancestral strains.

After a booster dose, the immune response against Omicron is improved, with a less notable fold-reduction compared to D614G, consistent with the improved vaccine effectiveness against Omicron after a booster noted observed in surveillance data (Thompson et al. 2022). However, the durability of this immune response cannot be determined from this evaluation with a single post-booster assessment timepoint.

6.1.12 Safety Analyses

Phase 3 safety data were presented for two study periods: the blinded placebo-controlled phase (Part A) and the open-label observational phase (Part B). The data cutoff date for safety was March 26, 2021, except for deaths and pregnancies which were monitored through the database lock date of May 4, 2021.

Blinded phase (Part A)

Safety data accrued during the blinded phase (Part A) for the relevant safety populations ([Table 5](#)) as outlined below:

- mRNA-1273 vaccine and placebo recipients in Part A who did not receive mRNA-1273 vaccine in Part B: safety data for Part A was accrued from administration of Dose 1 to the earlier date of: study discontinuation, study completion, death, data cutoff for safety, PDV/unblinding.
- For participants who received mRNA-1273 vaccine in Part B: safety data was accrued from administration of Dose 1 to receipt of mRNA-1273 vaccine in Part B or to the data cutoff, whichever date was earlier.

Reviewer Comment: For the participants in the placebo group in Part A who chose to crossover to receive mRNA-1273 vaccine in Part B, there could sometimes be a period of days to weeks between the PDV or treatment unblinding date and the date of receipt of Dose 1 of mRNA-1273 vaccine. Adverse events which occurred after unblinding but before receipt of mRNA-1273 vaccine were still counted in the Part A analysis for the placebo group, although participants were unblinded at the time of the event. An analysis of the dataset found 77 such events, and none occurred within the 28 days postvaccination period. Given the small number of these events, which occurred in the placebo group, and since none were within 28 days postvaccination, these events did not impact the interpretation of the safety data.

The Safety Set included 15,184 mRNA-1273 vaccine recipients and 15,162 placebo recipients. The median duration of blinded follow-up after Dose 1 was 148 days (4.8 months) in Part A. Solicited local and systemic adverse reactions were assessed during this period in a subset of participants.

Open-label phase (Part B)

Safety data accrued during the open-label phase (Part B) was from the time of unblinding to the data cutoff date. Part B therefore included safety data for unblinded participants who were aware of their vaccination group assignment as follows:

- Participants originally randomized to mRNA-1273 vaccine (N=14,618) in Part A
- Participants originally randomized to placebo in Part A who then received mRNA-1273 vaccine (N=12,648) in Part B (crossover group)
- Participants originally randomized to placebo in Part A and who remained in the placebo group in Part B (N=1,698).

Only unsolicited AEs (AEs, SAEs and AESIs) were collected during this period.

Reviewer Comment: Interpretation of safety data from mRNA-1273 vaccine recipients during the open-label phase of the study was limited by the absence of a placebo group comparator.

6.1.12.1 Methods

Please see Section [6.1.7](#).

6.1.12.2 Overview of Adverse Events

Overview of adverse events

[Table 29](#) below summarizes solicited local and systemic reactions including immediate (within 30 minutes) adverse reactions in the Safety Set in the blinded phase of the study. The most frequently reported solicited local and systemic adverse reactions across all age groups included injection site pain, fatigue, headache, and muscle pain. Frequently

reported unsolicited adverse events in the mRNA-1273 vaccine group within 28 days of vaccination were consistent with solicited reactions reported within the 7 days following vaccination.

Table 29. Safety Overview, Part A, Safety Set and Solicited Safety Set

Event Type	mRNA-1273 n/N(%)	Placebo n/N(%)
Solicited AR within 30 minutes after vaccination		
Dose 1	74/15184 (0.5)	68/15162 (0.4)
Dose 2	47/14631 (0.3)	41/14631 (0.3)
Solicited local AR within 7 days		
Dose 1	12765/15162 (84.2)	3009/15147 (19.9)
Dose 2	13029/14688 (88.7)	2757/14577 (18.9)
Grade 3 or 4 solicited local AR (any dose)	1420/15179 (9.4)	148/15158 (1.0)
Solicited systemic AR within 7 days		
Dose 1	8316/15166 (54.8)	6397/15151 (42.2)
Dose 2	11678/14690 (79.5)	5343/14577 (36.7)
Grade 3 or 4 systemic AR (any dose)	2640/15178 (17.4)	571/15159 (3.8)
Unsolicited AE		
Unsolicited AE up to 28 days after any dose	4752/15184 (31.3)	4338/15162 (28.6)
Non-serious unsolicited AE	4716/15184 (31.1)	4294/15162 (28.3)
Related non-serious unsolicited AE	2062/15184 (13.6)	1234/15162 (8.1)
Severe non-serious unsolicited AE	225/15184 (1.5)	186/15162 (1.2)
Related severe non-serious unsolicited AE	82/15184 (0.5)	30/15162 (0.2)
MAAE up to 28 days after any dose	1819/15184 (12.0)	1940/15162 (12.8)
Related MAAE	198/15184 (1.3)	95/15162 (0.6)
SAEs during Pa=rt A	268/15184 (1.8)	292/15162 (1.9)
SAEs up to 28 days after any dose	98/15184 (0.6)	104/15162 (0.7)
Related SAE up to 28 days after any dose	8/15184 (<0.1)	3/15162 (<0.1)
Deaths during Part A	16/15184 (0.1)	16/15162 (0.1)
Deaths up to 28 days after any dose	2/15184 (<0.1)	2/15162 (<0.1)
AE leading to discontinuation of the vaccine up to 28 days after any dose	61/15184 (0.4)	92/15162 (0.6)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1.1.1, Table 14.3.1.1.1.2, Table 14.3.1.1.1.3, Table 14.3.1.7.1.1, Table 14.3.1.19.5.1, Table 14.3.1.19.5.2, Table 14.3.1.23.1.1.

Abbreviations: AE=adverse event; AR=adverse reaction; IP=investigational product; MAAE=medically attended adverse events; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Notes: The Safety Set consists of all randomized participants who received at least 1 dose of IP. Percentages for unsolicited AEs are based on the number of safety participants (N) who received the first injection (Dose 1), second injection (Dose 2), or any injection (any injection).

The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, i.e., had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1).

[Table 30](#) summarizes safety by baseline SARS-CoV-2 status. Approximately 98% of participants were seronegative at baseline (N=29,491). Overall, rates of adverse events based on baseline serostatus were generally similar.

Table 30. Subjects Reporting at Least One Safety Event, by Baseline SARS-CoV-2 Status, Part A, Safety Set and Solicited Safety Set

Event Type and Timing	Baseline SARS-CoV-2 Negative mRNA-1273 n/N1 (%)	Baseline SARS-CoV-2 Negative Placebo n/N1 (%)	Baseline SARS-CoV-2 Positive mRNA-1273 n/N1 (%)	Baseline SARS-CoV-2 Positive Placebo n/N1 (%)
Solicited AR within 30 minutes after vaccination				
Dose 1	1538/14733 (10.4)	1558/14730 (10.6)	27/346 (7.8)	27/337 (8.0)
Dose 2	1435/14378 (10.0)	1535/14267 (10.8)	15/232 (6.5)	22/233 (9.4)
Solicited local AR within 7 days				
Dose 1	12442/14729 (84.5)	2934/14726 (19.9)	250/346 (72.3)	60/337 (17.8)
Dose 2	12783/14375 (88.9)	2699/14267 (18.9)	172/232 (74.1)	42/232 (18.1)
Grade 3 or 4 solicited local AR (any dose)	1385/14745 (9.4)	143/14737 (1.0)	23/347 (6.6)	5/337 (1.5)
Solicited systemic AR within 7 days				
Dose 1	8053/14733 (54.7)	6239/14730 (42.4)	214/346 (61.8)	122/337 (36.2)
Dose 2	11459/14377 (79.9)	5241/14266 (36.7)	152/232 (65.5)	73/233 (31.3)
Grade 3 or 4 systemic AR (any dose)	2590/14744 (17.6)	557/14738 (3.8)	38/347 (11.0)	13/337 (3.9)
Unsolicited AE				
Unsolicited AE up to 28 days after any dose	4652/14750 (31.5)	4233/14741 (28.7)	77/347 (22.2)	92/337 (27.3)
Non-serious unsolicited AE	4617/14750 (31.3)	4189/14741 (28.4)	76/347 (21.9)	92/337 (27.3)
Related non-serious unsolicited AE	2027/14750 (13.7)	1199/14741 (8.1)	30/347 (8.6)	30/337 (8.9)
Severe non-serious unsolicited AE	224/14750 (1.5)	180/14741 (1.2)	1/347 (0.3)	5/337 (1.5)
Related severe non-serious unsolicited AE	82/14750 (0.6)	29/14741 (0.2)	0	1/337 (0.3)
MAAE up to 28 days after any dose	178/14750 (12.1)	1902/14741 (12.9)	25/347 (7.2)	35/337 (10.4)
Related MAAE	197/14750 (3.1)	90/14741 (0.6)	1/347 (0.3)	5/337 (1.5)
SAE up to 28 days after any dose	96/14750 (0.7)	101/14741	1/347 (0.3)	3/337 (0.9)
Related SAE	8/14750 (<0.1)	3/14741	0	0
Deaths up to 28 days after any dose	2/14750 (<0.1)	2/14741	0	0
AE leading to discontinuation of the vaccine up to 28 days after any dose	54/14750 (0.4)	84/14741 (0.6)	6/347 (1.7)	8/337 (2.4)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1.3.1, Table 14.3.1.1.3.2, Table 14.3.1.1.3.3, Table 14.3.1.7.3.1, Table 14.3.1.3.3.1, Table 14.3.1.3.3.2; Ad hoc Table 14.3.1.23.9.1.

Abbreviations: AE=adverse event; AR=adverse reaction; IP=investigational product; MAAE=medically attended adverse event; SAE=serious adverse event.

Notes: The Safety Set consists of all randomized participants who received at least one dose of IP. Percentages for unsolicited AEs are based on the number of safety participants (N) who received Dose 1, Dose 2, or any dose.

The Solicited Safety Set consists of randomized participants who received at least one dose of IP and contributed any solicited AR data, i.e., had at least one post-baseline solicited safety (eDiary) assessment. The First (Second) Dose Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) dose and contributed any solicited AR data (eDiary) from the time of first (second) dose through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1).

Reviewer Comment: Small differences in rates of adverse events based on baseline serostatus for SARS-CoV-2 were not clinically meaningful. Only about 2% of participants were seropositive at baseline (N=684).

Immediate AEs

Immediate AEs were defined as events occurring within 30 minutes after vaccination. Participants were to remain in the clinic for observation for 15 minutes after each dose, or for 30 minutes if they had a history of allergic reaction to vaccination. The frequencies of immediate AEs after Dose 1 and Dose 2 were 0.5% and 0.3%, respectively, among mRNA-1273 vaccine recipients and 0.4% and 0.3%, respectively, among placebo recipients. The most frequently reported immediate AE was hypertension, reported at low rates in both groups (<0.1% in vaccine group and <0.1% in placebo group). Tachypnea was reported at similarly low rates. There were no anaphylactic reactions reported during the first 30 minutes after any dose of mRNA-1273 vaccine. In addition, there were no reports of immediate allergic reaction that were considered by the study investigator to be related to vaccine or placebo.

Reviewer Comment: Many of the reported immediate adverse events were those often associated with physiological responses to vaccine administration, such as hypertension and tachypnea.

Solicited local reactions and systemic adverse events

Solicited local reactions

[Table 31](#) and [Table 32](#) present the frequency and severity of reported solicited local reactions within 7 days following each dose of study vaccine in the younger age group (18-64 years of age) and the older age group (≥65 years of age), respectively. For each age subgroup in the solicited safety subset and overall, the median onset of solicited local reactions in the mRNA-1273 vaccine group was within the first day after either dose.

The incidence of solicited local reactions was higher in the mRNA-1273 vaccine group (84.2%) compared to the placebo group (19.9%). For both age subgroups, injection site pain was the most frequent solicited local adverse reaction. The younger age group reported local adverse reactions more frequently than the older age group after Dose 1 and Dose 2. The median duration of any local adverse reaction in the mRNA-1273 vaccine group was 2 days (Dose 1) to 3 days (Dose 2), and in the placebo group was 1 day (Dose 1 and Dose 2).

Table 31. Frequency of Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 18-64 Years of Age, Part A, Solicited Safety Set

Event	mRNA-1273 Dose 1 N=11406	Placebo Dose 1 N=11402	mRNA-1273 Dose 2 N=11000	Placebo Dose 2 N=10929
	n (%)	n (%)	n (%)	n (%)
Any local AR	N1=11402	N1=11400	N1=10999	N1=10928
Any	9961 (87.4)	2436 (21.4)	9936 (90.3)	2262 (20.7)
Grade 1	8151 (71.5)	2334 (20.5)	6424 (58.4)	2145 (19.6)
Grade 2	1358 (11.9)	63 (0.6)	2709 (24.6)	73 (0.7)
Grade 3	452 (4.0)	39 (0.3)	803 (7.3)	44 (0.4)
Pain ^a	N1=11402	N1=11400	N1=10999	N1=10928
Any	9908 (86.9)	2183 (19.1)	9893 (89.9)	2048 (18.7)
Grade 1	8360 (73.3)	2116 (18.6)	6933 (63.0)	1978 (18.1)
Grade 2	1182 (10.4)	44 (0.4)	2454 (22.3)	48 (0.4)
Grade 3	366 (3.2)	23 (0.2)	506 (4.6)	22 (0.2)
Erythema (redness) ^b	N1=11402	N1=11400	N1=10998	N1=10928
Any	354 (3.1)	54 (0.5)	989 (9.0)	53 (0.5)
Grade 1	222 (1.9)	39 (0.3)	358 (3.3)	36 (0.3)
Grade 2	98 (0.9)	4 (<0.1)	421 (3.8)	5 (<0.1)
Grade 3	34 (0.3)	11 (<0.1)	210 (1.9)	12 (0.1)
Swelling (hardness) ^c	N1=11402	N1=11400	N1=10998	N1=10928
Any	766 (6.7)	42 (0.4)	1399 (12.7)	46 (0.4)
Grade 1	499 (4.4)	35 (0.3)	706 (6.4)	32 (0.3)
Grade 2	205 (1.8)	4 (<0.1)	510 (4.6)	9 (<0.1)
Grade 3	62 (0.5)	3 (<0.1)	183 (1.7)	5 (<0.1)
Axillary swelling or tenderness ^a	N1=11402	N1=11400	N1=10998	N1=10928
Any	1322 (11.6)	567 (5.0)	1777 (16.2)	474 (4.3)
Grade 1	1180 (10.3)	534 (4.7)	1468 (13.3)	435 (4.0)
Grade 2	105 (0.9)	20 (0.2)	262 (2.4)	27 (0.2)
Grade 3	37 (0.3)	13 (0.1)	47 (0.4)	12 (0.1)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1 2.1.1, Table 14.3.1.1.2.1.2.

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: Any=Grade 1 or higher. The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, i.e., had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1).

a. Pain, axillary swelling or tenderness: Grade 1= does not interfere with activity, Grade 2= repeated use of over the counter pain reliver >24 hours or interferes with activity, Grade 3= any use of prescription (narcotic) pain reliver or prevents daily activity;

b. Erythema (redness) is defined as: Grade 1=25 to 50 mm; Grade 2=51 to 100mm; Grade 3= >100mm;

c. Swelling: Grade 1=25-50mm, Grade 2=51-100mm, Grade 3 = >100mm;

There were no grade 4 solicited local ARs reported.

Table 32. Frequency of Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants ≥65 Years of Age, Part A, Solicited Safety Set*

Event	mRNA-1273	Placebo	mRNA-1273	Placebo
	Dose 1 N=3760 n (%)	Dose 1 N=3749 n (%)	Dose 2 N=3691 n (%)	Dose 2 N=3649 n (%)
Any local AR	N1=3760	N1=3747	N1=3689	N1=3649
Any	2804 (74.6)	573 (15.3)	3093 (83.8)	495 (13.6)
Grade 1	2574 (68.5)	508 (13.6)	2365 (64.1)	449 (12.3)
Grade 2	153 (4.1)	26 (0.7)	508 (13.8)	15 (0.4)
Grade 3	77 (2.0)	39 (1.0)	220 (6.0)	31 (0.8)
Pain ^a	N1=3760	N1=3747	N1=3689	N1=3649
Any	2780 (73.9)	482 (12.9)	3071 (83.2)	438 (12.0)
Grade 1	2625 (69.8)	435 (11.6)	2575 (69.8)	406 (11.1)
Grade 2	105 (2.8)	15 (0.4)	396 (10.7)	13 (0.4)
Grade 3	50 (1.3)	32 (0.9)	100 (2.7)	19 (0.5)
Erythema (redness) ^b	N1=3760	N1=3747	N1=3689	N1=3649
Any	91 (2.4)	23 (0.6)	285 (7.7)	15 (0.4)
Grade 1	59 (1.6)	18 (0.5)	98 (2.7)	12 (0.3)
Grade 2	24 (0.6)	3 (<0.1)	110 (3.0)	0
Grade 3	8 (0.2)	2 (<0.1)	77 (2.1)	3 (<0.1)
Swelling (hardness) ^c	N1=3760	N1=3747	N1=3689	N1=3649
Any	169 (4.5)	23 (0.6)	408 (11.1)	14 (0.4)
Grade 1	109 (2.9)	15 (0.4)	194 (5.3)	6 (0.2)
Grade 2	40 (1.1)	5 (0.1)	142 (3.8)	1 (<0.1)
Grade 3	20 (0.5)	3 (<0.1)	72 (2.0)	7 (0.2)
Axillary swelling or tenderness ^a	N1=3760	N1=3747	N1=3689	N1=3649
Any	231 (6.1)	155 (4.1)	315 (8.5)	97 (2.7)
Grade 1	214 (5.7)	134 (3.6)	267 (7.2)	88 (2.4)
Grade 2	5 (0.1)	7 (0.2)	27 (0.7)	1 (<0.1)
Grade 3	12 (0.3)	14 (0.4)	21 (0.6)	8 (0.2)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1 2.1.1, Table 14.3.1.1.2.1.2.

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: Any=Grade 1 or higher.

*The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, i.e., had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1).

a. Pain, axillary swelling or tenderness: Grade 1= does not interfere with activity, Grade 2= repeated use of over the counter pain reliever >24 hours or interferes with activity, Grade 3= any use of prescription (narcotic) pain reliever or prevents daily activity;

b. Erythema (redness) is defined as: Grade 1=25 to 50 mm; Grade 2=51 to 100mm; Grade 3= >100mm;

c. Swelling: Grade 1=25-50mm, Grade 2=51-100mm, Grade 3 = >100mm;

There were no grade 4 solicited local ARs reported.

Reviewer Comment: Within 7 days of receipt of mRNA-1273 vaccine, axillary swelling was reported in 11%-16% of younger participants and 6%-8% of older participants. This local reaction was also reported as an unsolicited adverse event within 28 days of vaccination with the following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs): *Lymphadenopathy, Vaccination site or injection site lymphadenopathy*. Adverse events of axillary lymphadenopathy of the vaccination arm suggest a causal relationship to vaccination that may extend beyond 7 days and therefore support inclusion in the Adverse Reactions section of the USPI.

Solicited systemic reactions

[Table 33](#) and [Table 34](#) present frequencies and severities of reported solicited systemic reactions within 7 days following each dose of study vaccine in the younger age group (18-64 years of age) and the older age group (≥ 65 years of age), respectively. In each age group in the solicited safety subset and overall, the median onset of solicited systemic adverse reactions among recipients of mRNA-1273 vaccine was approximately 1 to 2 days after either dose. The median duration for solicited systemic reactions was 1 to 2 days.

The frequencies of any and severe solicited systemic adverse reactions were higher in the younger than the older age group. In both age groups, frequencies of any and severe systemic adverse reactions were higher after Dose 2 than Dose 1. Fatigue, headache, and muscle pain were most common in both age groups. After Dose 2, temperature $\geq 38^{\circ}\text{C}$ was reported in 1909 participants (17.4%) 18-64 years of age and in 367 participants (9.9%) ≥ 65 years of age. In both age groups, the proportions of participants who reported use of antipyretic or analgesic medications were higher after Dose 2 (42%-57%) than after Dose 1 (18%-23%).

The rates of temperature $>40.0^{\circ}\text{C}$ were low across treatment groups and age groups. Twelve recipients (0.1%) of mRNA-1273 vaccine reported Grade 4 fever ($>40.0^{\circ}\text{C}$) after Dose 2. Among 18-64-year-olds, 4 recipients ($<0.1\%$) of mRNA-1273 vaccine reported Grade 4 fever ($>40.0^{\circ}\text{C}$). A 31-year-old reported Grade 4 fatigue and arthralgia after Dose 1 ([Table 33](#)). Per the eDiary, the participant noted that the fatigue and arthralgia resulted in some interference with activity, but it is unclear why these events were assessed as Grade 4 as there was no ER visit or hospitalization documented (definition of Grade 4). These events resolved within 1-6 days and were not reported as SAEs. No further details on this event were available. This participant withdrew from study vaccination due to work-related reasons but continued to be followed in the study until Part B.

Among ≥ 65 -year-old mRNA-1273 vaccine recipients, there were no Grade 4 adverse reactions after Dose 1, and there were 2 mRNA-1273 vaccine recipients ($<0.1\%$) with Grade 4 adverse reactions after Dose 2. One of these recipients had Grade 4 fever ($>40.0^{\circ}\text{C}$) and 1 recipient had Grade 4 nausea and vomiting and fever of 101°F starting on Day 1. This participant's adverse reactions and reviewer's assessment are further described in the SAE section.

Table 33. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants 18-64 Years of Age, Part A, Solicited Safety Set*

Event	mRNA-1273	Placebo	mRNA-1273	Placebo
	Dose 1 N=11406 n (%)	Dose 1 N=11402 n (%)	Dose 2 N=11000 n (%)	Dose 2 N=10929 n (%)
Any systemic AR	N1=11406	N1=11402	N1=10999	N1=10928
Any	6499 (57.0)	5063 (44.4)	9023 (82.0)	4208 (38.5)
Grade 1	4079 (35.8)	3367 (29.5)	2615 (23.8)	2731 (25.0)
Grade 2	2050 (18.0)	1442 (12.6)	4458 (40.5)	1248 (11.4)
Grade 3	365 (3.2)	250 (2.2)	1938 (17.6)	227 (2.1)
Grade 4	5 (<0.1)	4 (<0.1)	12 (0.1)	2 (<0.1)
Fever ^a	N1=11404	N1=11400	N1=10993	N1=10925
≥38.0°C	102 (0.9)	37 (0.3)	1909 (17.4)	38 (0.3)
38.0°C to 38.4°C	66 (0.6)	25 (0.2)	1112 (10.1)	30 (0.3)
38.5°C to 38.9°C	22 (0.2)	7 (<0.1)	600 (5.5)	4 (<0.1)
39°C to 40.0°C	10 (<0.1)	1 (<0.1)	185 (1.7)	2 (<0.1)
>40.0°C	4 (<0.1)	4 (<0.1)	12 (0.1)	2 (<0.1)
Headache ^b	N1=11402	N1=11400	N1=10998	N1=10926
Any	4028 (35.3)	3303 (29.0)	6929 (63.0)	2775 (25.4)
Grade 1	3168 (27.8)	2668 (23.4)	3669 (33.4)	2182 (20.0)
Grade 2	640 (5.6)	472 (4.1)	2701 (24.6)	461 (4.2)
Grade 3	220 (1.9)	163 (1.4)	559 (5.1)	132 (1.2)
Grade 4	0	0	0	0
Fatigue ^c	N1=11402	N1=11400	N1=10998	N1=10926
Any	4385 (38.5)	3281 (28.8)	7453 (67.8)	2701 (24.7)
Grade 1	2732 (24.0)	2100 (18.4)	2527 (23.0)	1701 (15.6)
Grade 2	1531 (13.4)	1098 (9.6)	3748 (34.1)	912 (8.3)
Grade 3	121 (1.1)	83 (0.7)	1178 (10.7)	88 (0.8)
Grade 4	1 (<0.1)	0	0	0
Myalgia ^c	N1=11402	N1=11400	N1=10998	N1=10926
Any	2700 (23.7)	1625 (14.3)	6789 (61.7)	1425 (13.0)
Grade 1	1874 (16.4)	1200 (10.5)	2415 (22.0)	1002 (9.2)
Grade 2	752 (6.6)	387 (3.4)	3258 (29.6)	381 (3.5)
Grade 3	74 (0.6)	38 (0.3)	1116 (10.1)	42 (0.4)
Grade 4	0	0	0	0
Arthralgia ^c	N1=11402	N1=11400	N1=10998	N1=10926
Any	1892 (16.6)	1327 (11.6)	5010 (45.6)	1180 (10.8)
Grade 1	1368 (12.0)	966 (8.5)	2111 (19.2)	841 (7.7)
Grade 2	476 (4.2)	331 (2.9)	2249 (20.4)	302 (2.8)
Grade 3	47 (0.4)	30 (0.3)	650 (5.9)	37 (0.3)
Grade 4	1 (<0.1)	0	0	0
Nausea/vomiting ^d	N1=11402	N1=11400	N1=10998	N1=10926
Any	1068 (9.4)	908 (8.0)	2355 (21.4)	807 (7.4)
Grade 1	889 (7.8)	749 (6.6)	1755 (16.0)	651 (6.0)
Grade 2	173 (1.5)	151 (1.3)	589 (5.4)	148 (1.4)
Grade 3	6 (<0.1)	8 (<0.1)	11 (0.1)	8 (<0.1)
Grade 4	0	0	0	0
Chills ^e	N1=11402	N1=11400	N1=10998	N1=10926
Any	1050 (9.2)	730 (6.4)	5357 (48.7)	662 (6.1)
Grade 1	780 (6.8)	584 (5.1)	2316 (21.1)	505 (4.6)
Grade 2	253 (2.2)	138 (1.2)	2877 (26.2)	142 (1.3)
Grade 3	17 (0.1)	8 (<0.1)	164 (1.5)	15 (0.1)
Grade 4	0	0	0	0

Event	mRNA-1273 Dose 1 N=11406 n (%)	Placebo Dose 1 N=11402 n (%)	mRNA-1273 Dose 2 N=11000 n (%)	Placebo Dose 2 N=10929 n (%)
Use of antipyretic or pain medication	2656 (23.3)	1523 (13.4)	6307 (57.3)	1254 (11.5)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1 2.1.1, Table 14.3.1.1.2.1.2, Table 14.1.5.5.1, Table 14.1.5.5.2.

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: Any=Grade 1 or higher.

*The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, i.e., had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1). Medications were collected on the eDiary.

a. Fever is defined as: Grade 1=38 to 38.4°C; Grade 2=38.5 to 38.9°C; Grade 3=39 to 40°C; Grade 4=greater than 40°C.

b. Headache: Grade 1: no interference with activity, Grade 2: repeated use of over the counter pain reliever >24 hours or some interference with activity, Grade 3: significant, any use of prescription pain reliever or prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

c. Fatigue, myalgia, arthralgia: Grade 1: no interference with activity, Grade 2: some interference with activity, Grade 3: significant, prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

d. Nausea/vomiting: Grade 1: no interference with activity or 1-2 episodes/24 hours, Grade 2: some interference with activity or >2 episodes/24 hours, Grade 3: prevents daily activity, requires outpatient intravenous hydration; Grade 4: requires emergency room visit or hospitalization for hypotensive shock.

e. Chills: Grade 1: no interference with activity, Grade 2: some interference with activity not requiring medical intervention, Grade 3: prevents daily activity and requires medical intervention; Grade 4: requires emergency room visit or hospitalization.

Table 34. Frequency of Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose, Participants ≥65 Years of Age, Part A, Solicited Safety Set*

Event	mRNA-1273 Dose 1 N=3760 n (%)	Placebo Dose 1 N=3749 n (%)	mRNA-1273 Dose 2 N=3691 n (%)	Placebo Dose 2 N=3649 n (%)
Any systemic AR	N1=3760	N1=3749	N1=3691	N1=3649
Any	1817 (48.3)	1334 (35.6)	2655 (71.9)	1135 (31.1)
Grade 1	1279 (34.0)	967 (25.8)	1102 (29.9)	788 (21.6)
Grade 2	454 (12.1)	304 (8.1)	1153 (31.2)	287 (7.9)
Grade 3	84 (2.2)	61 (1.6)	398 (10.8)	59 (1.6)
Grade 4	0	2 (<0.1)	2 (<0.1)	1 (<0.1)
Fever ^a	N1=3759	N1=3749	N1=3689	N1=3648
≥38.0°C	10 (0.3)	7 (0.2)	367 (9.9)	5 (0.1)
38.0°C to 38.4°C	7 (0.2)	3 (<0.1)	251 (6.8)	3 (<0.1)
38.5°C to 38.9°C	2 (<0.1)	1 (<0.1)	97 (2.6)	1 (<0.1)
39°C to 40.0°C	1 (<0.1)	1 (<0.1)	18 (0.5)	0
>40.0°C	0	2 (<0.1)	1 (<0.1)	1 (<0.1)
Headache ^b	N1=3760	N1=3746	N1=3689	N1=3649
Any	922 (24.5)	723 (19.3)	1708 (46.3)	652 (17.9)
Grade 1	779 (20.7)	629 (16.8)	1146 (31.1)	558 (15.3)
Grade 2	90 (2.4)	60 (1.6)	455 (12.3)	61 (1.7)
Grade 3	53 (1.4)	34 (0.9)	107 (2.9)	33 (0.9)
Grade 4	0	0	0	0
Fatigue ^c	N1=3760	N1=3746	N1=3689	N1=3649
Any	1251 (33.3)	852 (22.7)	2154 (58.4)	717 (19.6)
Grade 1	853 (22.7)	605 (16.2)	904 (24.5)	480 (13.2)
Grade 2	368 (9.8)	225 (6.0)	995 (27.0)	217 (5.9)
Grade 3	30 (0.8)	22 (0.6)	255 (6.9)	20 (0.5)
Grade 4	0	0	0	0

Event	mRNA-1273 Dose 1 N=3760 n (%)	Placebo Dose 1 N=3749 n (%)	mRNA-1273 Dose 2 N=3691 n (%)	Placebo Dose 2 N=3649 n (%)
Myalgia ^c	N1=3760	N1=3746	N1=3689	N1=3649
Any	742 (19.7)	444 (11.9)	1740 (47.2)	399 (10.9)
Grade 1	568 (15.1)	360 (9.6)	827 (22.4)	305 (8.4)
Grade 2	157 (4.2)	75 (2.0)	708 (19.2)	84 (2.3)
Grade 3	17 (0.5)	9 (0.2)	205 (5.6)	10 (0.3)
Grade 4	0	0	0	0
Arthralgia ^c	N1=3760	N1=3746	N1=3689	N1=3649
Any	618 (16.4)	457 (12.2)	1293 (35.1)	399 (10.9)
Grade 1	474 (12.6)	367 (9.8)	698 (18.9)	302 (8.3)
Grade 2	131 (3.5)	82 (2.2)	470 (12.7)	90 (2.5)
Grade 3	13 (0.3)	8 (0.2)	125 (3.4)	7 (0.2)
Grade 4	0	0	0	0
Nausea/vomiting ^d	N1=3760	N1=3746	N1=3689	N1=3649
Any	194 (5.2)	167 (4.5)	439 (11.9)	134 (3.7)
Grade 1	158 (4.2)	138 (3.7)	339 (9.2)	110 (3.0)
Grade 2	32 (0.9)	24 (0.6)	89 (2.4)	21 (0.6)
Grade 3	4 (0.1)	5 (0.1)	10 (0.3)	3 (<0.1)
Grade 4	0	0	1 (<0.1)	0
Chills ^e	N1=3760	N1=3746	N1=3689	N1=3649
Any	201 (5.3)	148 (4.0)	1143 (31.0)	151 (4.1)
Grade 1	158 (4.2)	122 (3.3)	591 (16.0)	124 (3.4)
Grade 2	36 (1.0)	20 (0.5)	525 (14.2)	25 (0.7)
Grade 3	7 (0.2)	6 (0.2)	27 (0.7)	2 (<0.1)
Grade 4	0	0	0	0
Use of antipyretic or pain medication	673 (17.9)	477 (12.7)	1548 (41.9)	331 (9.1)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.1 2.1.1, Table 14.3.1.1.2.1.2, Table 14.1.5.5.1, Table 14.1.5.5.2.

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: Any=Grade 1 or higher. The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, i.e., had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days. Percentages for solicited ARs are based on the number of exposed participants who submitted any data for the event (N1). Medications were collected on the eDiary.

a. Fever is defined as: Grade 1=38 to 38.4°C; Grade 2=38.5 to 38.9°C; Grade 3=39 to 40°C; Grade 4=greater than 40°C.

b. Headache: Grade 1: no interference with activity, Grade 2: repeated use of over the counter pain reliever >24 hours or some interference with activity, Grade 3: significant, any use of prescription pain reliever or prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

c. Fatigue, myalgia, arthralgia: Grade 1: no interference with activity, Grade 2: some interference with activity, Grade 3: significant, prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

d. Nausea/vomiting: Grade 1: no interference with activity or 1-2 episodes/24 hours, Grade 2: some interference with activity or >2 episodes/24 hours, Grade 3: prevents daily activity, requires outpatient intravenous hydration; Grade 4: requires emergency room visit or hospitalization for hypotensive shock.

e. Chills: Grade 1: no interference with activity, Grade 2: some interference with activity not requiring medical intervention, Grade 3: prevents daily activity and requires medical intervention; Grade 4: requires emergency room visit or hospitalization.

Reviewer Comment:

1. Overall, for participants of any age and after any dose, fever >38°C was reported in 15.5% of mRNA-1273 vaccine recipients, and fever >40°C was reported in <0.1% of participants.

2. Overall, solicited systemic reactions and use of antipyretic or pain medication use were reported more frequently after Dose 2 than Dose 1 of mRNA-1273 vaccine, indicative of greater reactogenicity after Dose 2.
3. As noted in Section [3.1](#) (Submission Quality and Completeness), inconsistencies were observed in categorization of solicited systemic adverse reactions. Some solicited systemic adverse reactions were incorrectly attributed to COVID-19 symptoms. Upon CBER’s request, the Applicant performed a sensitivity analysis of solicited systemic adverse reactions including the events in participants with negative SARS-CoV-2 PCR as adverse reactions and not as COVID-19 symptoms. The results were consistent with the original analyses in terms of frequencies of solicited systemic adverse reactions across treatment groups.

Solicited local and systemic adverse reactions persisting beyond 7 days

Solicited local reactions that persisted beyond 7 days were reported in 2.4% of mRNA-1273 vaccine recipients after Dose 1 and 2.1% after Dose 2, and in 0.9% of placebo recipients after either dose. Axillary swelling or tenderness and injection site pain were the most reported persistent local ARs; axillary swelling or tenderness was more common after Dose 1 and injection site pain was more common after Dose 2.

Solicited systemic reactions that persisted beyond 7 days were reported in 5.7% mRNA-1273 vaccine recipients after each of Dose 1 and Dose 2, and in 5.6% placebo recipients after Dose 1 and 4.9% of placebo recipients after Dose 2. Fatigue and headache were the most reported persistent solicited systemic ARs after any dose.

Delayed local reactions reported by the investigator

[Table 35](#) presents the frequency of delayed onset (>7 days after vaccination) local reactions after each dose. These events were assessed by the investigator and consistent with the reactogenicity adverse reactions collected within 7 days of any vaccination. Overall, local reactions with delayed onset were not frequently reported. Delayed local injection site reactions that began >7 days after any vaccination were reported in 219 (1.4%) participants in the mRNA-1273 group and 100 (0.7%) participants in the placebo group. In the mRNA-1273 vaccine group, delayed local reactions were reported in 174 participants (1.1%) and 49 participants (0.3%) after Dose 1 and Dose 2, respectively. In the placebo group, delayed local reactions were reported in 29 participants (0.2%) and 72 participants (0.5%) after Dose 1 and Dose 2, respectively.

Table 35. Frequency of Delayed Local Injection Site Reactions (Onset After 7 Days) for Dose 1 and Dose 2, Part A, Safety Set

Event	mRNA-1273	Placebo	mRNA-1273	Placebo
	Dose 1 N=15184	Dose 1 N=15162	Dose 2 N=14731	Dose 2 N=14631
Delayed local injection site reaction				
Any – n (%)	174 (1.1)	29 (0.2)	49 (0.3)	72 (0.5)
Severe – n (%)	8 (<0.1)	0	0	0
Medically attended – n (%)	13 (<0.1)	4 (<0.1)	4 (<0.1)	9 (<0.1)
SAE – n (%)	0	0	0	0
Day of onset: median (min, max)	9.0 (8, 34)	12.0 (8, 74)	11.0 (8, 76)	24.0 (8, 152)
Duration (days): median (min, max)	4.0 (1, 183)	6.0 (1, 104)	4.0 (1, 141)	3.0 (1, 172)

Event	mRNA-1273 Dose 1 N=15184	Placebo Dose 1 N=15162	mRNA-1273 Dose 2 N=14731	Placebo Dose 2 N=14631
Pain				
Any – n (%)	66 (0.4)	17 (0.1)	37 (0.3)	60 (0.4)
Severe – n (%)	2 (<0.1)	0	0	0
Day of onset: median (min, max)	10.0 (8, 34)	16.0 (8, 31)	13.0 (8, 54)	24.0 (8, 152)
Duration (days): median (min, max)	4.0 (1, 183)	6.0 (1, 104)	4.0 (1, 31)	3.0 (1, 136)
Erythema (redness)				
Any – n (%)	89 (0.6)	9 (<0.1)	10 (<0.1)	8 (<0.1)
Severe – n (%)	6 (<0.1)	0	0	0
Day of onset: median (min, max)	10.0 (8, 29)	12.0 (8, 32)	8.5 (8, 76)	32.0 (8, 125)
Duration (days): median (min, max)	4.0 (1, 47)	4.0 (2, 58)	4.5 (1, 31)	13.0 (1, 172)
Swelling (hardness)				
Any – n (%)	62 (0.4)	6 (<0.1)	8 (<0.1)	6 (<0.1)
Severe – n (%)	1 (<0.1)	0	0	0
Day of onset: median (min, max)	9.0 (8, 32)	9.0 (8, 74)	8.0 (8, 43)	26.5 (8, 129)
Duration (days): median (min, max)	4.0 (1, 172)	3.0 (2, 8)	8.5 (2, 141)	3.5 (1, 158)

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.21.1.3.1, Table 14.3.1.21.1.3.2; Ad hoc Table 14.3.1.21.1.3.5.2, Ad hoc Table 14.3.1.21.1.3.6.2, Ad hoc Table 14.3.1.21.1.5.1.1, Ad hoc Table 14.3.1.21.1.5.1.2, Ad hoc Table 14.3.1.21.1.6.1.1, Ad hoc Table 14.3.1.21.1.6.1.2, Ad hoc Table 14.3.1.21.1.7.1.1, Ad hoc Table 14.3.1.21.1.7.1.2.

Abbreviations: IP=investigational product; max=maximum; min=minimum; SAE=serious adverse event.

Notes: Solicited (local) injection site reaction includes pain, erythema, and swelling. Any=Grade 1 or higher. Severe=Grade 3 or higher. The Safety Set consists of all randomized participants who received at least 1 dose of IP. Percentages are based on the number of safety participants who received the corresponding dose (N).

Reviewer Comment: In the clinical study report, the Applicant calculated the duration of the 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 that the Applicant conduct sensitivity analyses which evaluated these events using an alternate definition of duration as one plus the last day minus first day for which the event was reported, regardless of how many days the event was reported in between. The findings of the sensitivity analyses did not differ from those of the original analyses with regard to the median duration of solicited reactions.

Unsolicited adverse events in blinded phase (Part A)

Unsolicited AEs up to 28 days after any dose

A slightly higher frequency of unsolicited adverse events was reported in the mRNA-1273 vaccine group (31.3%) than the placebo group (28.6%). These excess AEs were primarily attributed to local reactions and systemic adverse reactions reported during the 7 days postvaccination.

Unsolicited adverse events (any and severe) that occurred within 28 days after any dose in $\geq 1\%$ of participants in any treatment group are presented in [Table 36](#). The most frequently reported severe AEs that occurred at a greater rate in vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain. The proportions of participants who reported severe unsolicited AEs were 1.7% following any vaccine dose (258 participants) and 1.5% following any placebo dose (233 participants). During the 28 days following any vaccination, unsolicited AEs considered to be related to study vaccination by the investigator were reported by 13.6% of vaccine recipients and 8.2% of placebo recipients.

Table 36. Frequency of Any and Severe Unsolicited Adverse Events Occurring in ≥1% of Participants in Any Treatment Group up to 28 Days After Any Dose, Part A, Safety Set

Primary System Organ Class Preferred Term	mRNA-1273	mRNA-1273	Placebo	Placebo
	N=15184 Any n (%)	N=15184 Severe n (%)	N=15162 Any n (%)	N=15162 Severe n (%)
Infections and infestations				
Adverse events in any PT ^a	783 (5.2)	20 (0.1)	952 (6.3)	34 (0.2)
COVID-19	22 (0.1)	0	156 (1.0)	7 (<0.1)
Blood and lymphatic system disorders				
Adverse events in any PT ^a	292 (1.9)	3 (<0.1)	148 (1.0)	0
Lymphadenopathy	264 (1.7)	1 (<0.1)	127 (0.8)	0
Nervous system disorders				
Adverse events in any PT ^a	1008 (6.6)	26 (0.2)	881 (5.8)	23 (0.2)
Headache	744 (4.9)	14 (<0.1)	687 (4.5)	11 (<0.1)
Vascular disorders				
Adverse events in any PT ^a	198 (1.3)	33 (0.2)	204 (1.3)	44 (0.3)
Hypertension	153 (1.0)	28 (0.2)	161 (1.1)	34 (0.2)
Respiratory, thoracic and mediastinal disorders				
Adverse events in any PT ^a	603 (4.0)	15 (<0.1)	667 (4.4)	12 (<0.1)
Cough	177 (1.2)	3 (<0.1)	165 (1.1)	1 (<0.1)
Oropharyngeal pain	158 (1.0)	0	232 (1.5)	2 (<0.1)
Nasal congestion	155 (1.0)	2 (<0.1)	165 (1.1)	0
Rhinorrhea	130 (0.9)	2 (<0.1)	145 (1.0)	0
Gastrointestinal disorders				
Adverse events in any PT ^a	599 (3.9)	21 (0.1)	567 (3.7)	16 (0.1)
Diarrhea	204 (1.3)	3 (<0.1)	199 (1.3)	1 (<0.1)
Nausea	162 (1.1)	5 (<0.1)	164 (1.1)	1 (<0.1)
Musculoskeletal and connective tissue				
Adverse events in any PT ^a	1007 (6.6)	26 (0.2)	1017 (6.7)	35 (0.2)
Arthralgia	391 (2.6)	7 (<0.1)	389 (2.6)	7 (<0.1)
Myalgia	387 (2.5)	9 (<0.1)	388 (2.6)	4 (<0.1)
General disorders and administration site conditions				
Adverse events in any PT ^a	1606 (10.6)	55 (0.4)	1065 (7.0)	20 (0.1)
Fatigue	752 (5.0)	20 (0.1)	666 (4.4)	9 (<0.1)
Injection site pain	258 (1.7)	4 (<0.1)	118 (0.8)	1 (<0.1)
Injection site erythema	157 (1.0)	8 (<0.1)	39 (0.3)	0

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 14.3.1.8.1.1, Table 14.3.1.17.1.1.

Abbreviations: COVID-19=coronavirus disease 2019; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

Note: The Safety Set consists of all randomized participants who received at least 1 dose of IP. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants

a. Participant experienced at least 1 TEAE within the SOC regardless of the MedDRA PT.

Reviewer Comment: While the Applicant had accounted for all safety events following vaccination, there were inconsistencies in how safety events were reported in the safety datasets (See Section 3.1: Submission Quality and Completeness). According to CDISC standards, all safety events that occur on or after Day 8 are to be reported as unsolicited adverse events in the “Adverse Event” AE dataset, irrespective of whether they represent the same clinical events as solicited reactions within 7 days following any vaccination. Therefore, some safety events reported on Day 8 were incorrectly reported as solicited adverse events in the Clinical Event dataset. CBER conducted sensitivity analyses that did not demonstrate any clinically meaningful imbalances across groups when the safety

events were recategorized according to CDISC standards. These did not change the overall interpretation of the safety results. Please refer to the Statistical Review by Ye Yang, PhD for further details.

MedDRA queries for CDC adverse events of special interest

The Applicant conducted MedDRA queries for unsolicited AEs included in the CDC's list of COVID-19-related AESI after COVID-19 vaccination (CDC 2021b) and found that the following PTs were not reported during the study: acute disseminated encephalomyelitis, transverse myelitis, chronic inflammatory demyelinating polyneuropathy, encephalitis, myelitis, encephalomyelitis, meningoencephalitis, ataxia, narcolepsy, cataplexy, immune thrombocytopenia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A), and acute respiratory distress syndrome. There was 1 report of multiple sclerosis (MS) in each treatment group. See detail of the MS case in mRNA-1273 vaccine recipient in Section [6.1.12.4](#) on SAEs.

Unsolicited adverse events of clinical interest in the blinded phase (Part A)

The safety data presented below includes unsolicited AEs (serious and non-serious) by PTs that are of clinical interest due to their underlying inflammatory mechanisms of onset. MedDRA queries of these PTs were reported overall and within 28 days of any vaccination and are presented below to explore a potential relationship with the investigational product.

Herpes zoster

Herpes zoster was reported in more mRNA-1273 vaccine recipients than placebo recipients. Overall, in the blinded phase (Part A), there were 73 participants with reported AEs of herpes zoster: 50 mRNA-1273 vaccine recipients and 23 placebo recipients.

Within 28 days of any dose, there were 22 mRNA-1273 vaccine recipients and 15 placebo recipients who reported herpes zoster. In mRNA-1273 vaccine recipients, the majority (81%) of these events occurred after Dose 1, and onset ranged from 4 to 26 days after vaccination. In the placebo recipients, the majority (54%) of herpes zoster occurred after Dose 2, and onset ranged from 4 to 28 days after vaccination. Of the 22 herpes zoster events reported among mRNA-1273 vaccine recipients, 14 events occurred in participants 18-64 years of age, and 8 events in participants ≥ 65 -year-old participants. Of the 15 herpes zoster events reported in placebo recipients, 11 occurred in 18-64-year-olds, and 4 were in ≥ 65 -year-olds. Post-herpetic neuralgia was reported 2 mRNA-1273 vaccine recipients ages 61 years and 70 years, and there were no such events in the placebo group.

Of the 22 herpes zoster events in the mRNA-1273 vaccine group, 2 events were considered related to study vaccination. The first event was in a 70-year-old participant with a history of malignant melanoma (approximately 3 years prior) who developed herpes zoster of the right hip 5 days after Dose 1. The event was classified as moderate and resolved with sequelae. The second event was in a 77-year-old participant with no previous medical history who developed herpes zoster on left thigh 7 days after Dose 1 of the vaccine. The event was classified as mild and resolved without sequela.

Reviewer Comment:

1. The reviewer agrees with the investigator's assessment of relatedness of two events that were considered related to mRNA-1273 vaccine.
2. There was one herpes zoster event in a 61-year-old male mRNA-1273 vaccine recipient that was considered unrelated to study vaccination by the investigator. However, in this reviewer's opinion the circumstances of the event appear consistent with at least possible causality. This participant, who had no predisposing factors, developed severe herpes zoster 9 days after Dose 1.
3. Within 28 days after any vaccination, the number of herpes zoster events in the mRNA-1273 vaccine group was higher (n=22) than in the placebo group (n=15). The majority of cases in the mRNA-1273 vaccine group followed Dose 1 and occurred in individuals who were not taking severe immunosuppressants and did not have risk factors other than age that predispose to herpes zoster.
4. To further characterize the imbalance in herpes zoster cases seen in the clinical trial, post-authorization analyses using VAERS database were conducted for a risk window of 28 days, stratified by age and vaccine dose. These analyses did not show an increase in observed incidence rates of herpes zoster among mRNA-1273 vaccine recipients compared to background incidence rates. Please see CBER's Pharmacovigilance Memorandum by Dr. Jane Baumblatt, MD for further details.
5. The imbalance seen in the clinical trial warrants inclusion of herpes zoster under Adverse Reactions in the USPI; however, as post-authorization pharmacovigilance data did not show rates of herpes zoster among mRNA-1273 vaccine recipients to be higher than background rates, the following sentence has been added: "Currently available information on herpes zoster is insufficient to determine a causal relationship with the vaccine."

Lymphadenopathy

During the 28 days following any vaccination in the blinded phase (Part A), lymphadenopathy was reported in 264 (1.7%) mRNA-1273 vaccine recipients and 127 (0.8%) placebo recipients. Injection site lymphadenopathy was reported in 66 mRNA-1273 vaccine recipients and 15 placebo recipients; most cases were of mild to moderate grade. Following mRNA-1273 vaccine, median onset of lymphadenopathy was 6 days (range 1-28 days) and 2 days (range 1-26 days) following Dose 1 and Dose 2, respectively. Among mRNA-1273 vaccine recipients, the median duration of lymphadenopathy was 6 days after Dose 1 and 10 days after Dose 2. Two mRNA-1273 vaccine recipients discontinued from the study due to lymphadenopathy events that were considered related to the vaccine.

Reviewer Comment: A greater number of participants reported lymphadenopathy and injection site lymphadenopathy in the mRNA-1273 vaccine group as compared to the placebo group. This observation is consistent with the higher reported rates of solicited local adverse reaction of axillary swelling within 7 days postvaccination in the mRNA-1273 vaccine group than the placebo group ([Table 31](#) and [Table 32](#)). These events support a causal relationship to the vaccine and have been included in the Adverse Reactions section of the USPI.

Clinical events associated with myocarditis and pericarditis

There were no reports of myocarditis in either treatment group. In the blinded phase, there were 2 mRNA-1273 vaccine recipients and 3 placebo recipients with pericarditis/pericardial effusion. These events are discussed in greater detail in the SAE

section. There were no reports of myocarditis in either group. The Applicant evaluated for the occurrence of specific PTs that may be associated with myocarditis and pericarditis (chest pain, dyspnea, syncope, myocardial infarction) within 28 days following any vaccination.

Within 28 days after any vaccination, a greater number of mRNA recipients (n=10) than placebo recipients (n=5) experienced chest pain. Post-authorization data shows that the risk of vaccine-associated myocarditis is greatest in males under 40 years of age, and within 7 days of the second dose. Therefore, a risk window of 7 days after any vaccination was chosen to further evaluate the incidence of these events. In the 7-day period after any vaccination, there were 3 events of chest pain in the mRNA-1273 vaccine group, of which 1 was considered related to study vaccine (59-year-old female with pericardial effusion discussed in the SAE section). A second event was in a 60-year-old female with multiple chronic medical conditions including history of chest pain, asthma, COPD, hiatal hernia, and dyspepsia who presented with chest pain 7 days after Dose 1. She was given nitroglycerin in the ER and observed overnight; the event resolved, and she was discharged home. No additional workup was documented. The investigator assessed the event as unrelated to the study vaccine. The third event was in a 28-year-old male with a history of non-cardiac chest pain who reported chest pain 4 days after Dose 1. This event was assessed as Grade 1 in severity, and no medical intervention was documented. The event was assessed as unrelated by the investigator. There was 1 event in the placebo group: a 71-year-old male with history of hypertension who reported Grade 1 chest pain 3 days after Dose 1.

Myocardial infarction also occurred more frequently among mRNA-1273 vaccine recipients (n=5) than placebo recipients (n=2). None of the events were considered related to study vaccination by the investigator. None of the myocardial infarction events occurred within 7 days of any vaccination.

During the 28 days postvaccination period, no imbalances between treatment groups were noted in adverse events of dyspnea or syncope. However, in the 7 days postvaccination period, greater numbers of mRNA-1273 vaccine recipients (n=15) than placebo recipients (n= 3) reported dyspnea, of which 5 events in mRNA recipients were considered related, and all episodes resolved. In addition, 5 participants (all in mRNA-1273 vaccine group) reported dyspnea as an SAE, none of which were considered related. Please refer to SAE section for additional details on these SAEs of dyspnea. Within 28 days postvaccination, syncope was reported in 7 mRNA-1273 vaccine recipients and 3 placebo recipients. None of these events were considered related.

Reviewer Comment: The reviewer agrees with the investigator's assessment that the 5 dyspnea SAEs were unrelated to study vaccination.

Bell's palsy/facial paralysis

In the blinded phase of the study, Bell's palsy (facial paralysis) was reported by 8 mRNA-1273 vaccine recipients and 3 placebo recipients. Within the mRNA-1273 vaccine group, 3 events were of severe grade, and 4 participants had concurrent infections (AEs) during these events. In the mRNA-1273 vaccine group, Bell's palsy onset occurred 81 days after Dose 1, and from 8 to 87 days after Dose 2. In the placebo group, onset occurred 17 to 115 days after Dose 2. In the mRNA-1273 vaccine group, 1 event was considered related by the investigator, and the remaining 7 were considered unrelated. The event considered related occurred in a 40-year-old mRNA-

1273 vaccine recipient with several predisposing risk factors, including history of facial paralysis and type 2 diabetes mellitus, who had onset of Bell's Palsy 71 days after Dose 2. At the time of data cutoff date, this event was not resolved.

In the 28-day period following any vaccination, facial paralysis was reported in 2 mRNA-1273 vaccine recipients (verbatim terms of Bell's palsy and left side face paralysis) and 1 placebo recipient (verbatim term of Bell's palsy). None of these events were considered related by the investigator to study vaccination.

One reported Bell's palsy event in a 67-year-old mRNA-1273 vaccine recipient was reported as an SAE that occurred 31 days after Dose 2, which was considered unrelated by the investigator.

Reviewer Comment:

In the reviewer's assessment there are alternate etiologies for this Bell's palsy event that was considered related by the investigator. The participant had several predisposing factors to Bell's palsy and the event was not temporally associated with vaccination (onset 71 days after Dose 2).

1. There was a case of mild facial palsy in a 44-year-old mRNA-1273 vaccine recipient, 8 days following Dose 2. She had injection of botulinum toxin 62 days prior (unclear if prior to Dose 1 or 2). In this reviewer's assessment this event of facial palsy is at least possibly related to mRNA-1273 vaccine.
2. The reports of facial paralysis during the blinded phase of the study and within 28 days postvaccination warrant inclusion under Adverse Reactions in the USPI, with the following statement: "Currently available information on facial paralysis is insufficient to determine a causal relationship with the vaccine".

FDA-conducted Standard MedDRA Queries, blinded phase (Part A)

FDA independently conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events from the administration of Dose 1 through the blinded phase of the study. Queried PTs represented various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions.

Embolic and thromboembolic events

During the blinded phase-Part A of the study, 8 participants in the mRNA-1273 vaccine group and 6 participants in the placebo arm developed deep vein thrombosis (DVT). Within 28 days of any vaccination, 1 mRNA-1273 vaccine recipient and 3 placebo recipients developed DVT. The one event in the mRNA-1273 vaccine recipient was considered related to study vaccination by the investigator. In Part A, SAEs of DVT were reported in 4 mRNA-1273 vaccine recipients and 1 placebo recipient. (These SAE events are discussed in Section [6.1.12.4](#) of this memo). There were no imbalances noted in the other embolic events in this SMQ. None of the embolic/thromboembolic events were associated with thrombocytopenia per the Applicant.

Reviewer Comment: In the safety database, and on review of the case narratives, the observed embolic events do not suggest an association with mRNA-1273 vaccine. There were no events suggestive of TTS.

Guillain-Barre syndrome

Events of Guillain-Barre syndrome were reported in three placebo recipients and zero mRNA-1273 vaccine recipients.

Hypersensitivity

In the blinded portion of the study, hypersensitivity events were reported in 336 mRNA-1273 vaccine recipients (2.2%) and 278 placebo recipients (1.8%). Within 7 days postvaccination, 12% of the 336 mRNA-1273 vaccine recipients and 10.7% of the 278 placebo recipients reported at least 1 hypersensitivity event, and 6 mRNA-1273 vaccine recipients and no placebo recipients reported injection site rash or injection site urticaria. The investigator considered these events related to vaccination.

Reviewer Comment: Hypersensitivity events of injection site rash and injection site urticaria were more common in the mRNA-1273 vaccine group compared to the placebo group, and this reviewer agrees with the investigators' assessments that the events in the mRNA-1273 vaccine group were likely related to study vaccination. These findings support inclusion in the Adverse Reactions section of the USPI.

No imbalances were noted between the mRNA-1273 vaccine and placebo groups in the following SMQs: arthritis, convulsion, demyelination, thrombophlebitis, vasculitis, hematopoietic cytopenia, and cardiomyopathy.

Unsolicited AEs in the open-label phase (Part B)

FDA-conducted Standard MedDRA Queries in Part B

The same set of SMQs as mentioned above were conducted on safety data collected from the time of participant unblinding to the March 26, 2021 data cutoff date. Independent FDA analyses of SMQs for non-serious AEs occurring in the unblinded follow-up period did not demonstrate any notable patterns of AEs that would suggest a causal relationship to mRNA-1273 vaccine.

Original mRNA-1273 vaccine recipients

Of 14,618 participants originally randomized to the mRNA-1273 vaccine group, 1729 (11.8%) experienced at least 1 unsolicited AE in the unblinded phase (Part B). Of these, 22 (0.2%) participants had unsolicited AEs that were considered related to the vaccine by the investigator, including 9 (<0.1%) participants with MAAEs and 1 (<0.1%) participant with an SAE.

No specific unsolicited AE (by PT) occurred in $\geq 1\%$ participants. No unexpected findings or new safety signals were apparent upon review of unsolicited AEs in the original mRNA-1273 vaccine group. The most frequently reported events occurred in the System Organ Class (SOC) *Infections and infestations* with 552 (3.8%) participants reporting at least 1 event. The most frequently reported unsolicited AEs by PT included urinary tract infection, COVID-19, and upper respiratory tract infection. No SAE, fatal AE, or AE leading to withdrawal from injection or study was considered related to the study vaccine by the investigator. Two mRNA-1273 vaccine recipients with unsolicited AEs leading to discontinuation received both doses of mRNA-1273 vaccine in Part A.

Crossover group (originally randomized to placebo)

Of the 12,648 participants originally randomized to placebo recipients who received mRNA-1273 vaccine after unblinding, 2446 (19.3%) experienced at least 1 unsolicited

AE following mRNA-1273 vaccine. Of 12,648 participants in the crossover group, 758 (6.0%) participants experienced AEs which were considered related to study vaccine by the investigator, including 74 (0.6%) participants with MAAEs, 24 (0.2%) participants with severe AEs, and 4 (<0.1%) participants with SAEs (refer to Section [6.1.12.4](#) on SAEs for details).

AEs reported in $\geq 1\%$ mRNA-1273 vaccine recipients in the open-label portion of the study (Part B) were similar to the most frequently reported AEs following mRNA-1273 vaccine in the blinded phase (Part A). However, these study periods are not entirely comparable as Part B was unblinded and had a shorter duration of follow-up after mRNA-1273 vaccine than Part A.

The most frequently reported unsolicited AEs were headache, hypertension, injection site pain, fatigue, pain, pyrexia, and chills. These events were also frequently reported solicited adverse reactions within 7 days of vaccination and unsolicited adverse events within 28 days of mRNA-1273 vaccine in Part A. No new safety signals were identified in participants who received mRNA-1273 vaccine in Part B. Twelve (<0.1%) participants experienced AEs leading to discontinuation from the study vaccine, and 4 (<0.1%) participants experienced AEs leading to discontinuation from the study.

Subgroup analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited or unsolicited in these subgroups were generally consistent with the overall study population.

6.1.12.3 Deaths

Overall, there were 24 deaths in mRNA-1273 vaccine recipients (Parts A and B), 17 deaths in placebo recipients (Part A and B), and 3 deaths in the crossover group (Part B). See [Table 37](#) for listing of deaths in Part A and Part B. None of the reported deaths were considered related to vaccination by the study investigators.

Of the 24 mRNA-1273 vaccine recipients who died during the study, 16 (0.1%) died during Part A and 8 died during Part B. Of the 17 placebo recipients who died during the study, 16 died in Part A and 1 in Part B. In Part A, 9 of 16 mRNA recipients and 6 of 16 placebo recipients were ≥ 65 years of age at baseline.

The timing of the deaths in mRNA-1273 vaccine recipients ranged from 21 to 175 days after Dose 1 and 8 to 210 days after Dose 2. The timing of deaths in placebo recipients ranged from 7 to 128 days after Dose 1 and 29 to 145 days after Dose 2.

Cardiac conditions were the most common cause of death in both treatment groups, accounting for 41.6% and 35.7% of deaths in the mRNA and placebo groups, respectively. These participants had multiple predisposing conditions.

In general, the causes of death among study participants are representative of the most common causes of death among adults in the general U.S. population (i.e., heart disease, cancer, accidents). COVID-19 was reported as the event leading to death for 1 mRNA-1273 vaccine recipient and 3 placebo recipients. The mRNA-1273 vaccine recipient was 74 years old and had received only Dose 1.

Table 37. Deaths From Dose 1 Through May 4, 2021, Part A and Part B, Safety Set

Product	Age/Sex	Number of Doses	Relative Day Since Last Dose	Cause of Death
mRNA-1273	77/M	2	45	Myocardial infarction
mRNA-1273	37/F	2	54	Head injury (updated to "toxicity to various agents" ^{tb})
mRNA-1273	70/M	2	58	Myocardial infarction
mRNA-1273	72/M	2	60	Gastrointestinal haemorrhage, multiple organ dysfunction syndrome, acute respiratory failure
mRNA-1273	61/M	2	70	Death ^e
mRNA-1273	62/M	2	71	Coronary artery disease, diabetic complication
mRNA-1273	65/M	2	89	Cardiac arrest
mRNA-1273	69/M	2	95	Myocardial infarction ^c
mRNA-1273	56/M	2	107	Hepatocellular carcinoma
mRNA-1273	75/F	2	108	Pulmonary mass ^a
mRNA-1273	59/M	2	110	Death ^e
mRNA-1273	37/F	2	138	Illicit drug intoxication ^b
mRNA-1273	80/M	2	145	Cardiac failure congestive
mRNA-1273	72/M	2	155	Cardio-respiratory arrest
mRNA-1273	72/F	2	155	Cardiac arrest ^c
mRNA-1273	41/M	2	180	Head injury ^c
mRNA-1273	56/F	2	182	Illicit drug intoxication ^{b,c}
mRNA-1273	62/M	2	184	Acute myocardial infarction ^c
mRNA-1273	71/M	2	210	Cerebrovascular accident ^c
mRNA-1273	49/M	2	130 138	Pulmonary embolism ^c Pulseless electrical activity, gastrointestinal haemorrhage ^c
mRNA-1273	78/M	1	21	Cardio-respiratory arrest
mRNA-1273	62/M	1	21	Suicide
mRNA-1273	56/F	1	37	Head injury
mRNA-1273	74/M	1	175	COVID-19
Crossover to mRNA-1273	30/F	2	8 ^d	Accidental overdose ^c
Crossover to mRNA-1273	79/M	2	27 ^d	Cardiac failure congestive, gastrointestinal haemorrhage, anticoagulation drug level above therapeutic ^c
Crossover to mRNA-1273	61/F	2	40 ^d	Cerebrovascular accident ^c
Placebo	74/M	2	29	Myocardial infarction
Placebo	64/M	2	47	Myocardial infarction
Placebo	54/M	2	64	COVID-19
Placebo	50/M	2	64	Death ^e
Placebo	73/M	2	86	Amyotrophic lateral sclerosis
Placebo	62/M	2	86	Myocardial infarction
Placebo	25/M	2	87	Suicide
Placebo	59/M	2	97	Seizure
Placebo	67/M	2	103	Myocardial infarction
Placebo	57/M	2	109	COVID-19
Placebo	55/M	2	120	Death ^e
Placebo	63/M	2	143	COVID-19

Product	Age/Sex	Number of Doses	Relative Day Since Last Dose	Cause of Death
Placebo	76/M	2	145	Pancreatic carcinoma stage IV
Placebo	43/M	1	7	Cardio-respiratory arrest
Placebo	75/M	1	13	Gastric perforation
Placebo	83/M	1	38	Systemic inflammatory response syndrome associated with chronic lymphocytic leukemia
Placebo	84/F	1	128	Ventricular arrhythmia ^c

Source: Adapted from mRNA-1273-P301 Clinical Study Report Listing 16.2.7.14, Listing 16.2.12, and Appendix 16.3.1; mRNA-1273-P301 Clinical Study Report Addendum 1 (Part B) Listing 16.2.7.10, Listing 16.2.7.9.3, and Appendix 16.3.1. Abbreviations: BMI=body mass index; COVID-19=coronavirus disease 2019; EF=ejection fraction; F=female; HbA1C=glycated hemoglobin; HIV=human immunodeficiency virus; IP=investigational product; M=male; NA=not applicable; STEMI=ST-segment elevation myocardial infarction.

Note: The Safety Set consists of all randomized participants who received at least 1 dose of IP. All deaths through the database lock of 04 May 2021 are presented. Unless otherwise noted, the table presents only data that were available as of the database lock date (04 May 2021).

- a. The event started during Part A, but the fatal outcome occurred during Part B.
- b. Updated with information received after the database lock.
- c. The event occurred during Part B.
- d. Days since last dose for crossover participants is the days since last dose of mRNA-1273
- e. Unknown cause of death

Reviewer Comment: Based on clinical review of the narratives, the lack of a clear temporal association to vaccination and the presence of confounding factors (e.g., predisposing conditions), the reviewer assessed the deaths in this study as unrelated to mRNA-1273 vaccine.

6.1.12.4 Serious Adverse Events (SAEs)

SAES during blinded phase (Part A)

Overall, in the blinded phase of the study (Part A), SAEs were reported in 1.8% (n=268) mRNA-1273 vaccine recipients and 1.9% (n=292) placebo recipients. SAEs within 28 days of vaccination were reported in 0.6% (n=98) mRNA-1273 vaccine recipients and 0.7% (n=104) placebo recipients.

Reviewer Comment: The reviewer presents the serious adverse events below based on investigator's assessment of causality. Overall, this reviewer's assessment of SAE causality did not differ significantly from the investigator's assessment. However, specific SAEs where the assessments differed are described below along with SAEs of clinical importance.

SAEs considered related to mRNA-1273 by the investigator

SAEs are presented in [Table 38](#). Of the 12 SAEs considered related in the mRNA-1273 vaccine recipients, 2 events were not resolved at the time of database lock (May 4, 2021).

Table 38. Serious Adverse Events Considered Related by Investigator, Part A, Safety Set

Product	Age/Sex	Number of Doses	Relative Day Since Last Dose	SAE Preferred Term	Risk Factors	Resolution	Applicant Assessment	Reviewer Assessment
mRNA-1273	46/F	2	1	Swelling face	Hx of dermal filler injection	Resolved	Related	Related
mRNA-1273	46/F	2	1	Autonomic nervous system imbalance	Hypothyroidism	Resolved with sequelae	Not related	Not related
mRNA-1273	65/F	2	1	Nausea	History of headache-induced nausea/vomiting leading to hospitalizations	Resolved	Related	Related
			1	Vomiting		Resolved	Related	Related
mRNA-1273	29/F	2	2	Angioedema	Angioedema following flu vaccine; hx of dermal filler lip injection	Resolved	Related	Related
mRNA-1273	51/F	2	3	Swelling face	Hx of dermal filler injection	Resolved	Related	Related
mRNA-1273	66/F	2	8	Graves' disease	History of rosacea and Meniere's disease	Resolved with sequelae	Not related	Not related
mRNA-1273	31/M	2	9	Alopecia areata ^a	HIV positive, Herpes simplex virus 2, previous history of facial hair loss	Not resolved	Not related	Not related
mRNA-1273	75/F	2	30	B-cell small lymphocytic lymphoma	History of metastatic lung cancer and breast cancer	Resolved with sequelae	Not related	Not related
mRNA-1273	59/F	2	68	Pericardial effusion	Flublok (RIV4) vaccination, history of sinus congestion, history of dilatation of the ascending aorta	Resolved	Related	Related
			68	Pericarditis		Resolved	Related	Related
			69	Pleural effusion		Resolved	Related	Related
mRNA-1273	36/F	2	72	Multiple sclerosis	None known	Not resolved	Not related	Not related
mRNA-1273	57/M	1	1	Rheumatoid arthritis	Hypothyroidism	Resolving	Related	Not related
mRNA-1273	34/F	1	67	Cerebrovascular accident	COVID-19 infection 1 month prior; patent foramen ovale	Resolved	Not related	Not related
Placebo	52/M	2	16	Procedural hemorrhage	Cardiopulmonary bypass, intravenous heparin intraoperatively	Resolved	Not related	Not related

Product	Age/Sex	Number of Doses	Relative Day Since Last Dose	SAE Preferred Term	Risk Factors	Resolution	Applicant Assessment	Reviewer Assessment
Placebo	41/F	2	7	Swelling face	Recent root canal procedure, history of multiple sinus surgeries, and concomitant	Resolved	Not related	Not related
			7	Paresthesia		Resolved	Not related	
			7	Immunization anxiety related reaction		Resolved	Not related	
			26	Feeling hot	Nexplanon implant	Resolved	Not related	
			26	Paresthesia		Resolved	Not related	
Placebo	83/M	1	16	Polymyalgia rheumatica	Monoclonal gammopathy of undetermined significance (MGUS), hypothyroidism	Resolving	Not related	Not related
Placebo	70/M	1	29	Acute myocardial infarction	History of myocardial infarction, coronary artery disease with percutaneous intervention/stent placement, hypertension, hyperlipidemia, diabetes mellitus type 2, chronic kidney disease, obesity, advanced age	Resolved	Not related	Not related
			29	Hypomagnesemia		Resolved	Not related	
			29	Acute kidney injury		Resolved	Not related	
			29	Atrial fibrillation		Resolved with sequelae	Not related	
			29	Organizing pneumonia		Resolved	Not related	
			31	Respiratory failure	Resolved	Not related		

Source: Adapted from mRNA-1273-P301 Clinical Study Report Listing 16.2.7.10 and Appendix 16.3.1.

Abbreviations: COVID-19=coronavirus disease 2019; F=female; IP=investigational product; M=male; SAE=serious adverse event.

Note: The Safety Set consists of all randomized participants who received at least 1 dose of IP. Unless otherwise noted, the table presents only data that were available as of the database lock date (04 May 2021).

a. This event did not meet SAE criteria based on further information and review after database lock.

The following are the reviewer's assessment of specific SAEs.

Due to the association of myocarditis/pericarditis with mRNA vaccines (see Section 4.6), the SAE of pericarditis/pericardial effusion in an mRNA-1273 vaccine recipient is discussed:

1. A 59-year-old female mRNA-1273 vaccine recipient with history of aortic dilatation developed pericarditis/pericardial effusion 2 months after Dose 2. This participant had presented to an ER with chest pain 5 days after Dose 2, where troponin levels and EKG were not obtained. Subsequently, the participant developed pericarditis/pericardial effusion 2 months after Dose 2.

Based on available data from post-authorization studies, most cases of myo/pericarditis related to vaccination have occurred in males under 40 years of age and occurred within 7 days of Dose 2 (See Section 4.6). This mRNA-1273 vaccine recipient was a 59-year-old female and had underlying cardiac pathology. The event did not fall within the typical window of presentation for these events. The likelihood that this episode was at least possibly related to the investigational product cannot be ruled out. This reviewer agrees with the investigator/Applicant's assessment that the SAE (pericarditis/pericardial effusion) was possibly related to the investigational product.

The following are SAEs where the investigator considered the events related to mRNA-1273 vaccine, but the Applicant did not consider the events related.

2. A 46-year-old female mRNA-1273 vaccine recipient with prior history of hypothyroidism, thyroidectomy reported autonomic nervous system imbalance 24 days after Dose 2. She developed fever (T_{max} 102.5° F) on the day she received Dose 2. The fever resolved in 2 days. Twenty-four days after Dose 2, she developed intense vertigo, intermittent palpitation, and dizziness. She was diagnosed with autonomic nervous system imbalance that resolved with sequelae (palpitation). The reviewer agrees with the Applicant's assessment that this event is not related to study vaccination given her prior history of hypothyroidism and the timing of the event with respect to the vaccine administration.
3. A 66-year-old female mRNA-1273 vaccine recipient with a history of breast cancer and Meniere disease presented to the ER with symptoms consistent with Graves' disease 7 days after vaccination with Dose 2. (The event was also reported as Basedow's disease). Following appropriate medical management, the event was considered resolved with sequelae.

The Applicant conducted a risk analysis evaluating the observed vs expected rates of Graves' disease. During 12,500 person-years of observation in mRNA-m1273 recipients, 5 cases of Graves' disease would be expected but only one report occurred. The Applicant did not consider the event related to vaccination.

To further evaluate for any imbalances across groups, CBER conducted a query of adverse events associated with Graves' disease and related conditions. Findings of this query demonstrated two additional non-serious adverse events of Graves' disease in placebo recipients, in addition to the one event in the 66-year-old mRNA-1273 vaccine recipient. The events in the placebo recipients occurred 28 days after vaccination and were not considered related to the placebo. CBER also

conducted a Standard MedDRA Query of Autoimmune Disorders and did not find any imbalances between the mRNA-1273 vaccine group and the placebo group. This reviewer agrees with the Applicant's assessment that the adverse event of Graves' disease in a mRNA-1273 vaccine recipient was not related to study vaccination.

4. A 34-year-old female mRNA-1273 vaccine recipient with patent foramen ovale (PFO) had a cardiovascular accident (CVA) 2 months after Dose 1, and 1 month after COVID-19. COVID-19 is a known risk factor for thrombotic events and is a confounder in determining the etiology of the CVA event in this participant, which may preclude a causal relation with the investigational product. Therefore, this reviewer agrees with the Applicant's assessment that this event is not related to the investigational product.
5. A 31-year-old male mRNA-1273 vaccine recipient with HIV and a history of beard hair loss 3 years prior to study enrollment, developed alopecia areata in his beard 8 days after Dose 2. The reviewer agrees with the Applicant that this event is not related to vaccination as the participant had prior history of beard hair loss.
6. A 36-year-old female mRNA-1273 vaccine recipient developed symptoms of multiple sclerosis (MS) 71 days after Dose 2. The investigator considered this event related to vaccination because it occurred within a plausible timeframe and lacked other clear etiologies. The Applicant considered this not related to the investigational product because MS is common in females during young adulthood. The prevalence of MS in females is 224.2 per 100,000 individuals. Upon reviewing unsolicited AEs in the mRNA-1273 vaccine vs placebo group, there was only 1 other placebo recipient who developed MS, therefore there was no imbalance observed across treatment groups. The reviewer agrees with the Applicant that this event is not related to vaccination.
7. A 75-year-old female mRNA-1273 vaccine recipient with history of multiple malignancies including basal cell carcinoma, pre-melanoma, stage-IV non-small cell lung cancer. Lung nodule with metastasis was diagnosed with small lymphocytic lymphoma 29 days after Dose 1. The investigator considered the event related to study vaccination due to its temporal association with study vaccination. However, the reviewer agrees with the Applicant that the causality is confounded by the participant's prior history of neoplastic disease.

SAEs of facial swelling in the mRNA-1273 vaccine and the placebo group

8. There were two female mRNA-1273 vaccine recipients with SAEs of facial swelling following Dose 2. One additional female mRNA-1273 vaccine recipient experienced angioedema following Dose 2. All three participants had prior history of dermal fillers. These cases were considered related to the investigational product by the investigator and the Applicant.

The investigator considered an SAE of facial swelling in a placebo recipient to be related to the study vaccination. A 41-year-old female placebo recipient with no history of dermal fillers developed right-sided facial swelling 6 days after Dose 1. Twenty days prior to the onset of facial swelling the participant had a dental procedure (root canal); however, it is unclear if the procedure was done on the right side. In the reviewer's opinion, the event of facial swelling was not associated

with the study product but with the recent dental procedure (associated dental pain, evaluated by oral surgeon who assessed the pain and swelling on that side to be associated with a crown). The reviewer and the Applicant disagree with the investigator's assessment of relatedness to placebo. Therefore, there appears to be imbalance between treatment groups of facial swelling considered related (3 in mRNA-1273 vaccine group vs 0 in placebo group).

SAE of rheumatoid arthritis

9. A 57-year-old male mRNA-1273 vaccine recipient with medical history of hypertension, hypothyroidism, and asthma, experienced an unexpected event of rheumatoid arthritis. The participant reported myalgia and arthralgia, which were considered Grades 1 to 2 in severity, starting on the day of Dose 1 and lasting for 7 days. Subsequently, the participant reported myalgia and arthralgia 10 days after Dose 1; these were accompanied by joint stiffness in the mornings and were reported to be different in quality than the symptoms the participant reported during the first week. Due to ongoing symptoms, he presented to a rheumatologist and was initially diagnosed with reactive arthritis. However, following laboratory investigations, including elevated rheumatoid factor and cyclic citrullinated peptide antibody, he was diagnosed with rheumatoid arthritis 29 days after Dose 1. The participant did not receive Dose 2. The investigator and Applicant considered the event related to the study vaccine.

Reviewer Comment: This reviewer disagrees with the investigator and Applicant's assessment of relatedness of the diagnosis of rheumatoid arthritis. Symptom onset within the day of vaccination would suggest against a causal relationship for new onset autoimmune disease, although the initial myalgia and arthralgia may reflect reactogenicity from the vaccine. History of autoimmune disease (hypothyroidism) may also be a confounding factor.

SAEs considered not related to mRNA-1273 vaccine by the investigator

The following SAEs were not considered related to mRNA-1273 vaccine by investigator but are considered clinically significant events.

Dyspnea

In Part A, dyspnea SAEs were reported in 5 mRNA-1273 vaccine recipients and no placebo recipients. All 5 events occurred in participants ≥ 52 years of age with conditions that could predispose to dyspnea. One participant had dyspnea 13 days after Dose 1 and had an extensive history of cardiac conditions including hypertension, heart murmur, irregular heart rhythm, and closure of atrial septal defect. The other dyspnea events had onset 35-137 days after Dose 2. Four of the five participants had pre-existing cardiac disease and one had a preexisting cancerous tumor. None of these events were considered related to the investigational product, nor were clinically consistent with myocarditis or pericarditis.

Reviewer Comment: This reviewer agrees with the investigator's assessment that these events of dyspnea are not related to the investigational product.

Pericarditis/pericardial effusion

In Part A, pericarditis/pericardial effusion was reported as an SAE in 2 mRNA-1273 vaccine recipients and 3 placebo recipients.

mRNA-1273 vaccine group: Other than the SAE of pericarditis/pericardial effusion in the 59-year-old female (described above and listed in [Table 38](#)), a 65-year-old participant with prior history of cardiac disease experienced an episode of myocardial infarction and associated pericarditis 54 days after Dose 2. The event was not considered to be related to investigational product.

Placebo group:

- A 46-year-old with multiple co-morbidities developed myocardial infarction, severe atherosclerosis, and post-surgical pericarditis secondary to coronary bypass surgery 26 days after Dose 1 of placebo. This participant received mRNA-1273 vaccine in the Part B of the study more than 3 months after onset of the myocardial infarction. A 64-year-old placebo recipient developed infective pericarditis associated with COVID-19 approximately 4 months after Dose 2.
- A 52-year-old placebo recipient with multiple co-morbidities developed COVID-19 and pericarditis approximately 1 month after Dose 1. The events in the placebo group were considered unrelated.

Reviewer Comment: This reviewer agrees with the investigator's assessment of relatedness of the cases of pericarditis/pericardial effusion to the investigational product.

Stroke and other thrombotic/thromboembolic events

Cerebrovascular accident, stroke, or transient ischemic attack were reported as SAEs in 10 mRNA-1273 vaccine recipients and 7 placebo recipients. Event onset occurred within 28 days of the last dose in 3 mRNA-1273 vaccine recipients and 2 placebo recipients, and more than 28 days after the last dose for 7 mRNA-1273 vaccine recipients and 5 placebo recipients. No cases were associated with thrombocytopenia.

A 34-year-old mRNA-1273 vaccine recipient had an episode of CVA 67 days after Dose 1 and had COVID-19 a month prior to the CVA. This event was considered related by the Applicant ([Table 38](#)) and discussed in the subsection above. In addition, a 45-year-old with history of hyperlipidemia developed transient ischemic attack 15 days after Dose 2 of mRNA-1273 vaccine. The event resolved the same day.

In Part A, there were 6 mRNA-1273 vaccine recipients and 7 placebo recipients with pulmonary embolism, and there were 4 mRNA-1273 vaccine recipients and 1 placebo recipient who developed DVT. None of the DVT cases in mRNA-1273 vaccine recipients were considered related to study vaccination by the investigator.

Reviewer Comment:

1. The age and sex distribution of the participants with SAEs of CVA or transient ischemic attack were similar between treatment groups, and most participants had risk factors for the event including age, previous stroke, hypertension, hypercholesterolemia, type 2 diabetes, heart failure, and congenital heart disease. During Part A, there were no reports of idiopathic thrombocytopenic purpura (ITP) or thrombosis with thrombocytopenia (TTS) and there were no reports of cerebral venous sinus thrombosis or dural venous thrombosis. These events, and surveillance during the post-authorization period, do not indicate a safety signal for TTS following mRNA-1273 vaccine.
2. No imbalances were noted in the cases of pulmonary embolism between treatment groups.

3. The reviewer agrees with the investigator's assessment of the cases of DVT in mRNA-1273 vaccine recipients as not related to vaccination. In all these cases the patients were older, had multiple co-morbidities that were reasonable causes of the DVT.

SAEs during open-label phase (Part B)

The following SAEs reported were reported from participant unblinding to the March 26, 2021 data cutoff

Original mRNA-1273 vaccine recipients

Of the 14,618 original mRNA-1273 vaccine recipients, 141 (1.0%) reported 181 SAEs in Part B. Of these, none of the SAEs were considered related to the study vaccine. No new safety concern was identified.

Crossover mRNA-1273 vaccine recipients

Of the 12,648 original placebo recipients who were unblinded and received mRNA-1273 vaccine in Part B, 148 (1.2%) reported 190 SAEs; of these, 87 participants (0.7%) reported SAEs within 28 days after vaccination. SAEs considered by the investigator to be related to the study vaccine were reported in 5 participants.

Reviewer Comment: The reviewer agrees with the investigator's assessment for SAEs considered unrelated.

SAEs considered related by study investigator in the crossover mRNA-1273 recipients

- A 41-year-old female experienced Grade 3 paresthesia (left arm) within 24 hours of receiving Dose 1 of mRNA-1273 vaccine in that arm. The participant presented to an emergency room due to swelling, redness, and tenderness at the injection site. The participant was discharged the same day and her symptoms were assessed as a histamine response. The event resolved within 2 days. The event was considered medically significant. Dose 2 of mRNA-1273 vaccine was delayed to 37 days after the Dose 1 because of the SAE, and the participant was treated prophylactically with antihistamines prior to dosing. Due to the onset of the event on the day of vaccination, laterality of the dose, and assessment by the emergency room provider as a histamine response, the investigator considered this SAE related to mRNA-1273 vaccine. At the time of data cutoff the Applicant was awaiting further information to make their assessment on causality.
- A 74-year-old male with a history of peripheral neuropathy and generalized osteoarthritis experienced an SAE of muscular weakness in the lower extremities 1 day after receiving Dose 2 of mRNA-1273 vaccine in Part B. In the evening after vaccination, the patient developed fever of 102°F, generalized fatigue and sustained a minor fall due to extremity weakness. He also developed urinary retention. He presented to an emergency room with fever, muscle weakness, and inability to walk. Treatment included paracetamol for fever. No lab or imaging workup was reported. The urinary retention and weakness resolved, and he was discharged from the hospital the next day. The Applicant agreed with the investigator's assessment as related to vaccination.
- A 28-year-old female experienced an SAE of spontaneous abortion 10 days after Dose 1 of mRNA-1273 vaccine. The Applicant did not consider this event related to mRNA-1273 vaccine.

- A 39-year-old male participant with a family history of Hashimoto's disease experienced an SAE of autoimmune thyroiditis 27 days after Dose 1 of mRNA-1273 vaccine. The event was ongoing at the time of data cutoff. The Applicant considered this event not related to mRNA-1273 vaccine due to the confounding factor of a history of Hashimoto's disease in the participant's parent and sibling.
- A 23-year-old with pericardial effusion. The details are presented under the section on pericarditis/pericardial effusion.

Reviewer Comment: The following comments pertain to the above-described SAEs in crossover mRNA-1273 vaccine recipients considered related by PI:

1. The reviewer agrees with the Applicant's assessment of relatedness of the events, where specified.
2. In the reviewer's opinion, the SAE of paresthesia in a 41-year-old female appears to be causally related to mRNA-1273 vaccine, as it occurred within 1 day of vaccination and is clinically consistent with adverse reactions of injection site erythema, swelling, and pain. In addition, the above-described events in the 74-year-old male appear to be consistent with systemic adverse reactions (fever, myalgia, fatigue) that occurred 1 day after Dose 2. These events appear to be causally related to mRNA-1273 vaccine. However, his initial symptoms appeared to be aggravated by a subsequent fall. Both participants' initial clinical events are not unexpected reactions and were categorized as serious adverse events because they subsequently presented to the emergency room.
3. As discussed in Section [9.1.1](#), in Part A there were 5 spontaneous abortions (2 in mRNA, 3 in placebo) and in Part B, there were 3 spontaneous abortions in crossover mRNA-1273 vaccine recipients. Data are not yet available from observational studies to inform risks specific to vaccination during pregnancy; however, there have been no post-authorization safety signals associated with receipt of mRNA-1273 vaccine in pregnant women. Sections 8.1 and 13.1 of the USPI state that based on available non-clinical data (see Section [4.3](#) of this review), there is no evidence of harm to fetus due to mRNA-1273 vaccine.

Pericarditis/pericardial effusion

A 23-year-old male in the crossover group developed pericardial effusion and pericarditis 18 days after Dose 2 of mRNA-1273 vaccine in Part B. Approximately 2 months prior to vaccination with mRNA-1273 vaccine, this participant tested positive for COVID-19 and had symptoms of fatigue and loss of smell. The investigator assessed this SAE of pericardial effusion as related to the investigational product.

Reviewer Comment: Post-authorization data demonstrate increased risk of myocarditis and pericarditis, particularly among males 18 through 24 years of age and within 7 days following the second dose. This 23-year-old male participant had onset of pericardial effusion/pericarditis outside the typical window of onset for this AE. Prior to vaccination with mRNA-1273 vaccine, the participant had COVID-19, a confounding factor in the etiology of pericardial effusion/pericarditis. However, in this reviewer's assessment, there is at least reasonable likelihood that this event could be related to the study vaccination.

Original placebo group

Among the 1,698 original placebo recipients who remained in placebo group in Part B, 7 participants reported 8 SAEs. No SAEs were considered related to the study vaccine.

Subgroup analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of non-fatal serious adverse events in these subgroups were generally consistent with the overall study population.

6.1.12.5 Dropouts and/or Discontinuations

Blinded phase (Part A)

Of the 30,346 participants who received at least one dose of study vaccine, 440 (2.9%) mRNA-1273 vaccine recipients and 691 (4.5%) placebo recipients discontinued from the study. Approximately 36% of these discontinuations were due to withdrawal of consent by participant; 155 (1.0%) mRNA-1273 vaccine recipients and 250 (1.6%) placebo. Approximately 31% of discontinuations were due to loss of follow up; 160 (1.1%) mRNA-1273 vaccine recipients and 191 (1.3%) placebo recipients. The remainder were due mostly to protocol deviations; 46 (0.3%) mRNA-1273 vaccine recipients and 160 (1.1%) placebo recipients.

Reviewer Comment: Factors that could have contributed to a greater number of discontinuations in the placebo group than the mRNA-1273 vaccine group include the higher number of placebo recipients with COVID-19, and the opportunity to receive a COVID-19 vaccine under EUA.

Study withdrawal due to an unsolicited AE

Overall in the blinded phase of the study, there were 26 (0.2%; 30 events) mRNA-1273 vaccine recipients and 23 (0.2%; 24 events) placebo recipients who discontinued from the study due to an AE. Only one was assessed as related to the study vaccine, in a participant in the mRNA-1273 vaccine group who reported induration and urticaria in the vaccinated arm starting 8 days after Dose 1.

AEs in the SOC *Cardiac disorders* were the most common AEs leading to withdrawal, reported in 7 participants (<0.1%) in the mRNA-1273 vaccine group and 5 participants (<0.1%) in the placebo group. Please refer to Sections [6.1.12.2](#) and [6.1.12.3](#) for additional details on unsolicited AEs and deaths under this SOC.

To better characterize study discontinuations due to AEs, an analysis of the time period from Dose 1 through 28 days after any injection was also evaluated. In this analysis, there were 9 participants (10 events) in the mRNA-1273 vaccine group compared to 6 participants (6 events) in the placebo group who discontinued the study due to an AE.

Open-label phase (Part B)

Overall, in the open-label portion of the study, 12 participants (<0.1%) (7 in original mRNA, 1 in original placebo, 4 in the crossover mRNA-1273 vaccine recipients), experienced unsolicited AEs leading to discontinuation from the study. None of the events were considered related to the study vaccination.

Reviewer Comment: Overall, the proportion of participants who discontinued from the study was small, and discontinuations due to adverse events were rare (<1%). Dropouts and discontinuations did not impact the interpretation of the safety results.

6.1.13 Study Summary and Conclusions

The randomized, blinded, placebo-controlled trial P301 evaluated the safety and efficacy of mRNA-1273 vaccine in approximately 30,000 participants 18 years of age and older. In updated efficacy analysis of the blinded phase, vaccine efficacy against symptomatic COVID-19 starting 14 days after Dose 2 was 93.2%, (95% CI 91.0, 94.8). Efficacy was similarly high across demographic subgroups, although interpretation of some subgroup analyses was limited by low number of cases and/or participants. Updated vaccine efficacy against severe COVID-19 starting 14 days after Dose 2 was 98.2% (95% CI 92.8, 99.6). Overall, the updated efficacy analysis results were consistent with the VE results reported in the protocol-specified event-driven interim and primary analyses that supported issuance of an EUA for this vaccine. Vaccine efficacy appears consistent across time intervals following vaccination, through ≥ 4 months after Dose 2. However, as the median follow-up duration for the blinded phase of the study was approximately 4 months post Dose 2, follow-up data after this time point were not sufficient to support assessment of potentially waning efficacy. SARS-CoV-2 identified in the majority of COVID-19 cases in the study were sequenced to be the B.1.2 variant, and a small number of cases were attributable to Epsilon, Gamma, and Zeta variants. Data are not available from this study to assess VE against current variants of concern as the data cutoff occurred prior to the widespread circulation of Delta and the emergence of Omicron.

Solicited local reactions and systemic reactions after vaccination were frequent in the mRNA-1273 vaccine group; these were mostly mild to moderate, generally of short duration, more frequent in the younger age group than the older age group, and more frequent and more severe after Dose 2 than Dose 1. Overall, the most common solicited adverse reactions were injection site pain, fatigue, headache, muscle pain, chills, and joint pain. As compared with placebo recipients, fever was more frequent in mRNA-1273 vaccine recipients (15.5% after any dose), with low rates of fever $>40^{\circ}\text{C}$ ($<0.1\%$).

Numerical imbalances in unsolicited adverse events between treatment groups from Dose 1 through 1 month after Dose 2 included lymphadenopathy, hypersensitivity, Bell's palsy, and herpes zoster. These events have been included in the Adverse Reactions section of the USPI. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, cardiac and thrombotic events) that would suggest a causal relationship to mRNA-1273 vaccine.

Overall, deaths and SAEs were reported by similar proportions of participants in both treatment groups. More deaths occurred in the older age group, as expected due to increased age and comorbidities. The frequency of non-fatal serious adverse events was low (1.8%). There were no cases suggestive of myocarditis in this study; however, postmarketing safety surveillance data has supported a risk of myocarditis in mRNA-1273 vaccine recipients, in particular following Dose 2 and especially in males under 40 years of age. As a result, this information has been included in Warning and Precautions section of the USPI. In mRNA-1273 vaccine recipients, there were 3 cases of angioedema/ facial swelling following vaccination in participants with prior history of dermal fillers and no such events in placebo recipients. These events were likely related to the study vaccination and have been included under Adverse Reactions in the USPI.

The clinical data submitted exceed FDA's expectations for data to support licensure of vaccines for prevention of COVID-19 regarding relevant efficacy success criteria, numbers of vaccinated study participants, and safety database (i.e., at least 3,000 vaccinated participants in each age group had at least 6 months of safety follow-up).

6.2 Study P201

NCT04405076

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

6.2.1 Objectives (Part A)

Primary safety objective: to evaluate the safety and reactogenicity of 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart

Primary immunogenicity objective: to evaluate 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart, as assessed by the level of bAb

Secondary immunogenicity objective: to evaluate 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart, as assessed by the titer of nAb

6.2.2. Design Overview

Study mRNA-1273-P201 is an ongoing, phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 vaccine in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older. Participants were randomized equally to three groups to receive two doses of either 50 mcg of mRNA-1273, 100 mcg of mRNA-1273, or saline placebo given 28 days apart. In addition to evaluation of the two dose levels for the primary series (Part A), the protocol for P201 was amended to include the study of a booster dose of 50 mcg of mRNA-1273 (Part B) and the study of a booster dose of a modified vaccine targeted against different SARS-CoV-2 variants (Part C). The booster phases of the study (Part B and Part C) are ongoing and will not be discussed in this review as they are not relevant to the BLA. Participants will be followed for safety and immunogenicity for 12 months after the last vaccination.

The immunogenicity objectives for Part A (primary series) were to evaluate two doses of mRNA-1273 vaccine at the two dose levels (50 mcg and 100 mcg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants were followed for solicited adverse reactions through 7 days after each vaccination. Unsolicited AEs were collected through 28 days after each vaccination. SAEs and MAAEs will be collected through the end of the study.

6.2.3. Population

The study enrolled adults 18 years of age and older in good health, with a body mass index of 18 kg/m² to 30 kg/m² and without a known history of COVID-19 or SARS-CoV-2 infection.

6.2.4. Study Treatments or Agents Mandated by the Protocol

Same as Study P301.

6.2.5. Directions for Use

Same as Study P301 except that two dose levels of mRNA-1273 were evaluated: 50 mcg and 100 mcg.

6.2.6. Sites and Centers

This study is being conducted at 8 study sites in the U.S.

6.2.7 Surveillance/Monitoring

Safety

In Part A, in addition to 10 scheduled study site visits, scheduled participant contact continued approximately every 2 weeks after Day 57 to collect the following information: adverse events, concomitant medications associated with these events, receipt of non-study vaccinations, exposure to someone with known COVID-19 or SARS-CoV-2 infection, and participant experience of COVID-19 symptoms. Each participant completed an eDiary questionnaire every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363. Safety telephone calls occurred every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377. Participants were followed for safety through 12 months after the last dose of study vaccine.

To test for the presence of SARS-CoV-2, NP swab samples were collected at Day 1, Day 29, and Day 57. During the study, participants meeting prespecified disease criteria suggestive of SARS-CoV-2 infection were asked to contact the study site to arrange for a prompt assessment.

Immunogenicity

All participants provided pre- and postvaccination blood specimens for immunogenicity through 12 months after the last dose of study vaccine. The following immunogenicity assessments were performed:

- Serum bAb level against SARS-CoV-2 as measured by ELISA specific to the SARS-CoV-2 spike protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum bAb level against SARS-CoV-2 as measured by ELISA specific to the SARS-CoV-2
- nucleocapsid protein (as a measure of asymptomatic infection)

6.2.8. Endpoints and Criteria for Study Success

Primary safety endpoints:

- Solicited local and systemic ARs through 7 days after each dose
- Unsolicited AEs through 28 days after each dose
- MAAEs through the entire study period
- SAEs throughout the entire study period
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only)
- Vital sign measurements and physical examination findings

Primary immunogenicity endpoint:

- Level of SARS-CoV-2-specific bAb measured by ELISA on Day 1, Day 29 (M1), Day 43, D57 (M2), Day 209 (M7), and Day 394 (M13).

Secondary immunogenicity endpoints:

- Titer of SARS-CoV-2-specific nAb on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13)
- Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the LLOQ to equal to or above LLOQ, or 4-times higher titer in participants with pre-existing nAb titers

6.2.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive without formal hypothesis testing.

6.2.10. Study Population and Disposition

Among the 600 participants enrolled in the study, all received at least one dose of the study vaccine and 98% received both doses. Few participants discontinued from the study, with a slightly higher percentage in the placebo group (9%) compared to the 50-mcg mRNA-1273 vaccine group (6%) or the 100-mcg mRNA-1273 vaccine group (8%).

Participants included in the population used for the analyses of safety were 65% female, 95% White, and 92% non-Hispanic/Latino. Demographic characteristics were similar between the Safety Set and the population used for analyses of immunogenicity.

6.2.11 Effectiveness Analyses

Immunogenicity

The immune response as assessed by binding antibody IgG ELISA after two doses was slightly higher in the 100-mcg group than in the 50-mcg group (Day 57 GMT: 657.2 vs 519.5). This difference persisted at 6 months after Dose 2 (D209 GMT: 128.0 vs 97.0 for the 100-mcg and 50-mcg groups, respectively).

Immune responses measured by microneutralization antibody titers were comparable between the 100-mcg and 50-mcg groups (MN50 of 1656.1 and 1632.4, respectively) at 28 days post-Dose 2. By 6 months after Dose 2, the 100-mcg group had slightly higher antibody levels compared to the 50-mcg group (MN50 of 538.8 vs 401.5). In both the 50-mcg and 100-mcg dose groups, the older age cohort (≥ 55 years) had slightly lower antibody titers when compared to the younger age cohort (18 to < 55 years) at 28 days

and 6 months post-Dose 2.

COVID-19 cases

Participants were swabbed for SARS-CoV-2 RT-PCR testing during scheduled study visits (Days 1, 29, 57), as well as at unscheduled illness visits if they reported suspected COVID-19 symptoms or exposure to close contact with COVID-19. During the blinded phase of the study, the following participants were found to have a positive SARS-CoV-2 RT-PCR as collected in the study or a positive diagnostic test outside of the study by a local laboratory:

- 24 participants in the placebo group (12 with symptomatic COVID-19)
- 4 participants in the 50-mcg mRNA-1273 vaccine group, (1 with symptomatic COVID-19)
- 2 participants in the 100-mcg mRNA-1273 vaccine group, (1 with symptomatic COVID-19)

Reviewer Comment: Both dose groups had relatively similar immune titers at 28 days post Dose-2 and the 50-mcg dose group had infrequent SARS-CoV-2 infection/COVID-19 during the study compared to the placebo group. As there is currently no immunologic correlate of protection and the study design did not include a formal immunobridging comparison between the 50-mcg and 100-mcg dose levels, it is not possible to draw firm conclusions about the clinical benefit of the 50-mcg dose when administered as a 2-dose primary dose series. Based on the data in this study alone it is unclear if the efficacy would be as high or as durable following a 2-dose 50-mcg primary series as compared with a 2-dose 100-mcg primary series.

6.2.12 Safety Analyses

The overall safety profile of mRNA-1273 vaccine was similar to that observed in Study P301. The rates of solicited ARs were slightly higher in the 100-mcg group compared to the 50-mcg group. As of the blinded phase database lock on June 10, 2021 (median follow-up of 7 months post-Dose 2), there were 7 participants who experienced SAEs in the mRNA-1273 vaccine group (2 participants in the 100mcg group and 5 participants in the 50-mcg group) and no SAEs in the placebo group. The SAEs were:

100-mcg group:

- 32-year-old female with spontaneous abortion 7 months after Dose 2
- 72-year-old male with cardiac arrhythmia after being struck by lightning 29 days after Dose 2

50-mcg group:

- 86-year-old male with acute myocardial infarction 3 months after Dose 2
- 33-year-old female with spontaneous abortion 5 months after Dose 2
- 68-year-old male with spinal nerve cyst and spondylolisthesis 6 days after Dose 2
- 87-year-old female with worsening of chronic bradycardia 44 days after Dose 2
- 65-year-old male with pneumonia (not due to COVID-19) 32 days after Dose 1

None of the SAEs were considered related to the vaccine by the investigators. There were no deaths reported in the blinded phase of the study.

Reviewer Comment: The clinical reviewer agrees with the investigators'

assessments that none of the reported SAEs were considered related to study vaccines.

6.2.13 Study Summary and Conclusions

Two doses of mRNA-1273 vaccine at either the 50-mcg or 100-mcg dose level were immunogenic, with a slightly higher immune response as measured by binding antibody and microneutralization antibody titers after the 100-mcg series compared to 50-mcg, and a slightly higher response in the younger age cohort (18 to <55 years) compared to the older cohort (≥ 55 years). The safety profile of both dose levels was comparable and there were no major safety concerns identified in the study.

6.3 Study 20-0003

Study design

Study 20-0003 (NCT04283461, sponsored by the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health) is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 vaccine in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 groups (by age and dose level) to receive two doses of mRNA-1273 vaccine separated by 28 days. The dose groups were 25 mcg, 50 mcg, 100 mcg, or 250 mcg and the age groups were 18 through 55 years, 56 through 70 years, and 71 years and older. The protocol has been amended over time to include the evaluation of a booster dose of 100 mcg of mRNA-1273 vaccine after the primary series. The booster phase of the study is ongoing and will not be discussed in this review as it is not relevant to the BLA. Participants will be followed for safety and immunogenicity for 12 months after the last vaccination.

Study objectives/endpoints relevant to the BLA

The immunogenicity objectives of the primary series portion of the study were to evaluate the bAb concentrations for spike IgG as measured by ELISA and nAb titers as measured by PsVNA for all dose levels at baseline and various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants were followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs were collected through 28 days after each vaccination. All SAEs and MAAEs are collected through the end of the study.

Statistical analysis

All analyses were descriptive without formal hypothesis testing.

Study results

Dose response was measured by both binding and neutralizing antibodies after two doses administered to 60 participants 18-55 years of age, 30 participants 56-70 years of age, and 30 participants ≥ 71 years of age. Comparable antibody responses were observed in the 100-mcg and 250-mcg dose groups, and greater immune responses were observed in both of these dose groups compared to the 25-mcg group and 50-mcg groups. The bAb and nAb levels seen after two doses of either 100 mcg or 250 mcg were similar in magnitude compared to those seen in pooled convalescent sera from patients who had recovered from COVID-19. At 6 months post Dose 2, nAb titers

across all dose levels were lower compared to the respective levels observed at 1 month post Dose 2, though some had overlapping intervals. For all dose levels, participants in the younger age cohorts had a higher immune response compared to participants in the older age cohorts. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of T helper type 1 cytokines with minimal T helper type 2 cytokine expression, suggestive of decreased risk of vaccine-induced enhanced disease. Safety data showed a lower incidence of reactogenicity in the 100-mcg group compared to the 250-mcg group. There was one SAE reported in this study, in a 73-year-old male in the 100-mcg group who reported a renal mass 5 months after Dose 2 and was later diagnosed with renal cell carcinoma. The event was assessed as not related to the study vaccine by the investigator. No safety concerns were identified in this study. Based on both the immunogenicity and safety data, the 100-mcg dose was selected for further evaluation in Phase 2 and 3 studies.

Reviewer Comment: The reviewer agrees with the investigator's assessment that the SAE reported in the study was not related to the study vaccine. Safety data from this Phase 1 study demonstrated a similar profile to those observed in the Phase 3 study.

7. INTEGRATED OVERVIEW OF EFFICACY

Study P301 was the only study with robust clinical efficacy evaluation of the 2-dose primary series of mRNA-1273 vaccine. Therefore, an integrated overview of efficacy is not applicable to this review.

8. INTEGRATED OVERVIEW OF SAFETY

The safety data reviewed in this application to support the final mRNA-1273 vaccine formulation/dose (100 mcg) were primarily from Study P301. The safety database from the other studies included 235 participants who received the final dose/formulation of mRNA-1273 vaccine compared to 15,184 participants in Study P301. The overall safety conclusions for mRNA-1273 vaccine are sufficiently characterized by data from Study P301 and reflect the safety findings from the other two studies. Therefore, an integrated overview of safety is not applicable to this review.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in discontinuation from study vaccination. Participants are followed for outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening. A total of 27 pregnancies (16 in mRNA-1273 vaccine group and 11 in placebo group) were reported during the blinded phase of the study ([Table 39](#)). Of these, outcomes are known for 3 participants in the mRNA-1273 vaccine group and 5 participants in the placebo group. The known pregnancy outcomes of spontaneous abortion/miscarriage, elective termination, and live births occurred with similar frequencies in the vaccine and the placebo groups. One participant in the mRNA-1273 vaccine group and 2

participants in the placebo group were lost to follow-up; the remaining pregnancies were ongoing at the time of the database lock on May 4, 2021.

Table 39. Pregnancies Reported in Part A, Safety Set

Parameter	mRNA-1273	Placebo
	N=15184	N=15162
	n	n
Total number of pregnancies	16	11
Timing of last dose relative to LMP ^a		
Prior to LMP	10	7
Within 30 days after LMP	3	2
>30 days after LMP	0	2
LMP unknown	3	0
Lost to follow-up	1	2
Known outcomes	3	5
Spontaneous abortion/miscarriage	2	3
Elective termination	1	1
Live born	0	1

Source: Adapted from mRNA-1273-P301 Clinical Study Report Table 7-28, and Appendix 16.3.1, Sponsor's response to IR #44 dated January 12, 2022.

a. last menstrual period

During the open-label phase of the study (Part B), among the 12,648 participants who crossed over from placebo to mRNA-1273 vaccine, there were 19 pregnancies reported. There were 19 additional pregnancies reported in the original mRNA-1273 vaccine group. Pregnancies with known outcomes in Part B included 4 spontaneous abortions (3 in the crossover group and 1 in the original mRNA-1273 vaccine group) and one elective termination. Two participants were lost to follow-up and the remaining pregnancies were ongoing as of the database lock.

Reviewer Comment: One spontaneous abortion in Part B was considered a related SAE by the investigator. See Section [6.1.12.4](#) for further discussion.

The data on pregnancy and pregnancy outcomes from this study is limited. Data are not yet available from observational studies to inform risks specific to vaccination during pregnancy; however, there have been no post-authorization safety signals associated with receipt of mRNA-1273 vaccine in pregnant women. As part of the postmarketing surveillance, the Applicant plans to conduct a prospective, observational pregnancy exposure registry study in the U.S., Canada, and European Union to evaluate pregnancy and birth outcomes in women exposed to mRNA-1273 vaccine during pregnancy (Study P902).

9.1.2 Use During Lactation

It is not known if mRNA-1273 vaccine is secreted in human breast milk. Data are not available to assess the effects of mRNA-1273 vaccine on the breastfed infant or on milk production.

9.1.3 Pediatric Use and PREA Considerations

To address PREA requirements, the Applicant submitted a request for deferral of the following studies in pediatric individuals <18 years of age because mRNA-1273 vaccine

would be ready for approval for use before such studies could be completed. The deferred studies are:

- Deferred pediatric study P203 to evaluate the safety and effectiveness of mRNA-1273 vaccine in children 12 years through 17 years of age
- Deferred pediatric study P204 to evaluate the safety and effectiveness of mRNA-1273 vaccine in children 6 months to <12 years of age
- Deferred pediatric study to evaluate the safety and effectiveness of mRNA-1273 vaccine in infants <6 months of age

The deferral request and pediatric plans were accepted without revisions by the Pediatric Review Committee on December 14, 2021.

9.1.4 Immunocompromised Individuals

Study P301 enrolled 185 participants with stable HIV infection (CD4 count >350 cells/mm³ and undetectable HIV viral load in past 1 year) who received at least one dose of mRNA-1273 vaccine (n=94) or placebo (n=91). Among participants in the Per-Protocol Set with HIV infection (n=82 placebo; n=85 mRNA-1273 vaccine), there were 4 cases of COVID-19 starting 14 days after Dose 2 in the placebo group compared to none in the mRNA-1273 vaccine group. The safety profile in this subgroup was comparable to the overall study population.

Reviewer Comment: Given the small number of participants considered immunocompromised included in the study, data in the BLA submission are insufficient to robustly inform vaccine safety and effectiveness in immunocompromised populations. In August 2021, FDA re-issued an EUA for administration of a third dose of Moderna COVID-19 Vaccine, at least 28 days following the second dose, in individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. Authorization was supported by data from published reports of low antibody responses and breakthrough infections among significantly immunocompromised individuals (mainly solid organ transplant recipients) who received the two-dose vaccination series (See [EUA memorandum for third dose in certain immunocompromised individuals](#)).

9.1.5 Geriatric Use

Of the 15,184 study participants in P301 who were originally randomized to mRNA-1273 vaccine and included in the Safety Set, 24.8% (n=3,769) were ≥65 years of age and 4.3% (n=657) were ≥75 years of age. Vaccine efficacy in geriatric participants was consistent with that seen in younger adult participants, and no safety concerns specific to the geriatric age group were identified.

9.2 Booster Dose

During the review period for this BLA, data have become available to inform the need for, and safety and effectiveness of, a booster dose to address both waning immunity and decreased effectiveness against emerging variants (e.g., Delta and Omicron).

On October 20, 2021, the EUA was amended to allow for a booster dose (50 mcg) of mRNA-1273 vaccine at least 6 months after completing a primary series with mRNA-1273 vaccine to individuals:

- 65 years of age and older
- 18 through 64 years of age at high risk of severe COVID-19
- 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2

The primary data to support the authorization of a booster dose were immunogenicity data from P201 Part B, which inferred effectiveness of a booster dose using immunobridging to the 2-dose primary series. Other sources of information to inform the need for a booster dose consist of observational data suggesting waning of vaccine effectiveness, including an exploratory analysis conducted by Moderna to identify COVID-19 cases which occurred among study participants in P301 during the time of the Delta surge in the U.S. (which occurred after the database lock for the BLA). Supporting data are available in the [decision memorandum for the Moderna booster dose](#) (FDA 2021c).

On the same date as the homologous booster authorization, a single booster dose of 50 mcg of mRNA-1273 vaccine was also authorized as a [heterologous booster following completion of primary vaccination with another authorized or approved COVID-19 vaccine](#) (FDA 2021d).

With the continued rise in COVID-19 cases globally in the setting of Delta, and with an increasing body of evidence suggesting waning vaccine effectiveness over time, on November 19, 2021, the EUA was amended to expand the eligible population for the 50 mcg mRNA-1273 vaccine [booster to all individuals 18 years of age and older](#) (FDA 2021e).

After the emergence of the Omicron variant and the resultant surge in COVID-19 cases in the U.S. and globally, on January 7, 2022, the EUA was further amended to revise the authorized dosing interval of the 50 mcg mRNA-1273 vaccine booster in individuals ≥ 18 years to at least [5 months after completion of the primary series](#) (FDA 2022).

While the current BLA submission is limited to use of a 2-dose primary series, BLA supplements for full approval of additional doses may be considered once clinical trial and real-world data are sufficiently mature.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of mRNA-1273 vaccine (100 mcg), administered as two doses 1 month apart, for prevention of COVID-19 caused by SARS-CoV-2.

The clinical data submitted to the BLA include results of a randomized, blinded, placebo-controlled clinical trial that evaluated the safety and efficacy of mRNA-1273 vaccine in >30,000 participants 18 years of age and older. The updated efficacy analysis, including cases accrued during the blinded phase of the study from July 27, 2020 through the data cutoff of March 26, 2021, showed that mRNA-1273 vaccine had a vaccine efficacy of 93% in preventing symptomatic COVID-19, and 98% in preventing severe COVID-19, starting 14 days after Dose 2. Efficacy outcomes across

demographic subgroups as well as for subgroups of participants with comorbidities associated with increased risk of severe COVID were consistent with the efficacy seen in the overall study population, although limited by the small number of cases in some subgroups. These findings are consistent with the VE results reported in the protocol-specified event-driven interim and primary analyses that supported issuance of an EUA for this vaccine in December 2020 and provide more robust evidence of vaccine effectiveness based on a much larger number of cases observed over a longer period of placebo-controlled follow-up than was available at the time of the EUA request.

The clinical safety data submitted exceeded FDA expectations for an acceptable pre-licensure safety database of at least 3000 participants in each age group (16-64 years and ≥ 65 years) with at least 6 months of total safety follow-up. In the clinical trial, local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the mRNA-1273 vaccine group than the placebo group. Severe events, when they did occur, were more common in the younger age group. Overall, deaths and SAEs were reported by similar proportions of participants in each treatment group. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data include lymphadenopathy, hypersensitivity, herpes zoster. These imbalances support labeling of lymphadenopathy, hypersensitivity, herpes zoster and Bell's palsy as potential adverse reactions. A slight imbalance in hypersensitivity-related events was observed during the trial, and hypersensitivity reactions reported during post-authorization use further supports inclusion of these reactions in labeling. The safety results for individuals with confirmed stable HIV disease were summarized descriptively.

Post-authorization safety surveillance has identified two additional clinically important but infrequent adverse reactions: anaphylaxis and myocarditis/pericarditis. The risk of myocarditis, observed as highest in males younger than 40 years of age, is being addressed by labeling in the Warnings and Precautions Section of the USPI, by ongoing monitoring through active and passive surveillance, and by postmarketing studies to be conducted by the Applicant, U.S. Government agencies, and other healthcare stakeholders to further evaluate and understand these risks.

Based on the totality of data and the risk-benefit considerations as described in Section [11](#) below, the clinical reviewers conclude that the clinical trial data submitted in this application, and complemented by available post-authorization data and plans for post-licensure studies, support approval of a 2-dose primary series of mRNA-1273 vaccine for the indication of active immunization to prevent symptomatic coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 40. STN125752: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> SARS CoV-2, a novel respiratory coronavirus causing COVID-19, is currently responsible for a global pandemic that has significantly disrupted human activity on a global scale. COVID-19 is associated with significant morbidity, mortality (5.5 million deaths worldwide to date) and long-term sequelae among survivors. In the U.S., COVID-19 has been responsible for 3.8 million hospitalizations and 835,000 deaths to date. While the greatest risk of severe or fatal COVID-19 is in individuals >65 years of age and those with comorbid conditions (e.g., obesity, diabetes, immunocompromising conditions), significant morbidity and mortality and long-term sequelae from COVID-19 has occurred in healthy individuals of all ages. Individuals with asymptomatic SARS-CoV-2 infection may transmit the virus to others. Multiple genetic variants of the virus are circulating and continue to emerge. Evidence of an increase in transmissibility, shorter incubation periods and more severe disease (e.g., increased hospitalizations or deaths) has been associated with some of these variants. Uncertainties include the following: lack of complete understanding of mechanisms of pathogenesis and individual risk for severe disease; evolving epidemiology of the pandemic; and potential for emergence of SARS-CoV-2 variants with altered infectivity, virulence, and/or capacity to evade immunity from natural infection or vaccination. 	<ul style="list-style-type: none"> COVID-19 is a serious/life-threatening disease responsible for a globally disruptive pandemic. Control of the COVID-19 pandemic will be necessary to return to the normal activities of pre-pandemic times. The emergence of variants of the SARS CoV-2 virus may lead to more transmissible viruses or more severe disease. Further research is needed to understand SARS-CoV-2 immunology, COVID-19 pathogenesis, and individual risk factors for severe disease.
<p>Unmet Medical Need</p>	<ul style="list-style-type: none"> The antiviral remdesivir is the only product currently approved by the FDA for use in adults and pediatric patients 12 years of age and older for treatment of COVID-19 requiring hospitalization. Other antivirals, monoclonal antibodies, immune modulators, and convalescent plasma are authorized for emergency use in high-risk patients. mRNA-1273 vaccine is one of three COVID-19 vaccines for which an Emergency Use Authorization (EUA) has been issued. At the time of review of this BLA, only one COVID-19 vaccine (Pfizer) has been approved by FDA for the prevention of COVID-19. Original public health vaccination goals of immunizing 75% of the population (to achieve herd immunity) have not yet been achieved. With the emergence 	<ul style="list-style-type: none"> Public health measures of social distancing and masking are helpful but do not prevent all transmission of the virus. There is an unmet medical need for more FDA-approved vaccines to prevent COVID-19 caused by SARS-CoV-2. Ongoing epidemiological and clinical surveillance is needed to inform needs related to development of pharmacologic interventions (including vaccines) for treatment and

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<p>of more transmissible variants, a higher percentage compared to the original goal will likely be needed.</p> <ul style="list-style-type: none"> • Non-pharmacologic measures to prevent transmission of SARS-CoV-2 include masks, social distancing, and avoidance of high-risk situations. These actions do not prevent all infections. • With the emergence of the Delta and Omicron variants, there has been an increased incidence of breakthrough COVID-19 cases in vaccinated individuals; however, most severe COVID-19 cases and COVID-19 related deaths continue to be among unvaccinated individuals. • Some available data suggest waning vaccine effectiveness against these more recent variants (although effectiveness against severe disease is maintained), and booster doses have been authorized under EUA for all three COVID-19 vaccines authorized/approved in the U.S. • Uncertainties include the effectiveness of current available vaccines and therapies against Omicron variant and trajectory of the Omicron surge. 	<p>prevention of COVID-19 and public health recommendations for their use.</p>
<p>Clinical Benefit</p>	<ul style="list-style-type: none"> • In a population of >28,000 participants 18 years of age and older without evidence of prior SARS-CoV-2 enrolled in an ongoing randomized placebo-controlled Phase 3 trial, vaccine efficacy against symptomatic COVID-19 starting 14 days after Dose 2 during the blinded, placebo-controlled follow-up period was 93.2% [95%CI: 91.0, 94.8]. • Vaccine efficacy against severe COVID-19 during the blinded, placebo-controlled phase starting from 14 days after Dose 2 was 98.2% [95% CI: 92.8, 99.6]. • Subgroup analyses of vaccine efficacy suggest similarly high efficacy across demographic subgroups and among participants with comorbidities associated with increased risk of severe COVID-19, although these analyses were limited by the small number cases and participants in some subgroups. • In an exploratory analysis, there was a lower incidence of asymptomatic infection observed in the mRNA-1273 vaccine group compared to the placebo group. • Uncertainties in clinical benefit include the following: longer-term duration of protection; effectiveness in certain populations not well represented in the clinical trial (e.g., substantially immunocompromised); effectiveness against SARS-CoV-2 variants that are antigenically or biologically different from those circulating during the time of the study; and effectiveness against viral transmission. 	<ul style="list-style-type: none"> • The evidence for clinical benefit of mRNA-1273 vaccine meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 18 years of age and older. • Data from additional studies (post-authorization and post-approval), are needed to address uncertainties in clinical benefit, including vaccine effectiveness against emerging variants. • Despite evidence from published observational studies of waning protection following primary vaccination and decreased effectiveness against some SARS-CoV-2 variants (e.g., Omicron), the clinical benefits of primary vaccination with mRNA-1273 vaccine remain clear, especially regarding protection against more severe COVID-19 and its serious sequelae. Additional doses (e.g., 3rd primary series dose for certain immunocompromised adults and booster dose for the general adult population) improve upon the benefits provided by the primary series and are currently available under EUA.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p style="text-align: center;">Risk</p>	<ul style="list-style-type: none"> • The most frequently reported adverse reactions in the ongoing placebo-controlled trial were solicited injection site reactions of injection site pain and localized axillary swelling or tenderness and systemic adverse reactions of fatigue, headache, muscle pain, chills and joint pain, which were generally less frequent in older (≥65 years) vs younger (18-65 years) participants. Solicited adverse reactions were transient and severe adverse reactions were infrequent (~4-7% among younger participants and ~2-6% among older participants). • Among all unsolicited adverse events reported in the trial, a substantial imbalance in lymphadenopathy (1.7% in mRNA-1273 vaccine recipients and 0.8% in placebo recipients), particularly injection site lymphadenopathy (66 vaccine recipients ipsilateral and regional to the injection site, vs 15 events in placebo recipients) supports a causal association with the vaccine. • During the blinded, placebo-controlled study, and within 28 days following any vaccination, there were numerical imbalances in cases of herpes zoster in the vaccine vs placebo groups. Postmarketing surveillance demonstrated that observed rates did not exceed expected rates of herpes zoster. • The risk of myocarditis and pericarditis following mRNA-1273 vaccine appear to be elevated for multiple age groups and in males, with greatest risk in males under the age of 40. Across similar mRNA vaccines, postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. Uncertainties related to risks of myocarditis and pericarditis include lack of precise estimates for excess risk across various age and gender subgroups, including whether and how frequently subclinical cases occur, and longer-term outcomes and prognoses. • Post-authorization safety surveillance has also identified anaphylaxis as an infrequent risk associated with the vaccine. • Extensive clinical and nonclinical experience has yielded no evidence of vaccine-enhanced disease (or more severe COVID-19 as a marker for vaccine-enhanced disease) following mRNA-1273 vaccine. • Other uncertainties related to risks in general include more robust characterization of the safety profile through active safety surveillance and/or controlled observational studies in specific populations (e.g., individuals with prior COVID-19, pregnant women, and significantly immunocompromised individuals); and whether additional rare adverse reactions could be identified with increased exposure and longer follow up. 	<ul style="list-style-type: none"> • The most frequently reported risks are mild to moderate, self-limited injection site and systemic adverse reactions. • Less frequently reported, but potentially serious risks include severe allergic reactions and myocarditis/pericarditis. Additional data are needed to better quantify the risks of myocarditis and pericarditis and to understand long-term prognoses for vaccine-associated myocarditis and pericarditis. • An imbalance in events of herpes zoster (vaccine group > placebo group) was identified in the clinical trial data. However, an increased rate of herpes zoster (relative to the expected rate among vaccine recipients) has not been observed in the postmarketing surveillance data. • Although the potential for vaccine enhanced disease has been evaluated throughout vaccine development and post-authorization use, this theoretical risk is not substantiated by the totality of evidence from nonclinical studies, clinical trials, and post-authorization COVID-19 case surveillance and observational studies.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p>Risk Management</p>	<ul style="list-style-type: none"> Labeling for SPIKEVAX describes the common and uncommon (but potentially serious) risks associated with the vaccine. The labeling includes warning statements for severe allergic reactions and myocarditis/pericarditis. The Applicant will be required to conduct post-approval studies to further evaluate vaccine safety and effectiveness, and specifically to better understand the identified risks of vaccine-associated myocarditis and pericarditis and their long-term sequelae. 	<ul style="list-style-type: none"> Risk mitigation strategies for mRNA-1273 vaccine for use in individuals 18 years of age and older include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks. Ongoing monitoring of COVID-19 epidemiology (including emergence of variants) and vaccine effectiveness will also be critical to updating benefit risk assessments and risk mitigation strategies as the pandemic evolves over time.

11.2 Risk-Benefit Summary and Assessment

COVID-19 caused by SARS-CoV-2 is associated with a wide spectrum of manifestations that range from mild illness to severe morbidity, with the potential for long-term sequelae and/or mortality. Approximately 5.5 million deaths attributable to COVID-19 have been reported worldwide since the beginning of the pandemic in late 2019. In the U.S., 835,000 deaths and 3.8 million hospitalizations have been reported to date. Currently, the U.S. is experiencing a surge of COVID-19 associated with widespread transmission of the SARS-CoV-2 Omicron variant. While the greatest risk of severe or fatal COVID-19 is in individuals >65 years of age and those with comorbid conditions (e.g., obesity, diabetes, immunocompromising conditions), significant morbidity, mortality, and long-term sequelae from COVID-19 has occurred in healthy individuals of all ages. The COVID-19 pandemic has overwhelmed healthcare systems during periods of high incidence, and the effects of SARS-CoV-2 infection, COVID-19 disease, and the necessary public health measures implemented to prevent infection and illness have severely disrupted human activities on a global scale.

Three COVID-19 vaccines (Pfizer, Janssen, and Moderna) have received authorization for emergency use in the U.S. The Pfizer COVID-19 vaccine is authorized for use in individuals 5 years of age and older and is the only COVID-19 vaccine to receive FDA approval (trade name Comirnaty) for use in individuals 16 years of age and older. Due to the risk of thrombosis with thrombocytopenia syndrome associated with the Janssen COVID-19 vaccine, the U.S. Advisory Committee on Immunization Practices issued a preferential recommendation for use of mRNA COVID-19 vaccines in December 2021. Approval of this BLA for mRNA-1273 vaccine would help address the continued unmet medical need for an increased number of available safe and effective vaccines for the prevention of COVID-19.

A randomized, placebo-controlled, observer-blind trial (Study P301) conducted in the U.S. in approximately 30,000 participants demonstrated that mRNA-1273 vaccine was highly effective, with a vaccine efficacy of >90% in the prevention of PCR-confirmed symptomatic COVID-19 starting 14 days after completion of the 2-dose regimen. Efficacy was consistently high across demographic subgroups and subgroups of participants with underlying comorbidities, though limited by the small number of participants and cases in some subgroups.

Data from numerous published observational studies of real-world use of the vaccine, although not independently reviewed and confirmed by FDA, appear to corroborate the high level of protection observed in the clinical trial, including against COVID-19-associated hospitalization and death, across various patient populations and geographic regions. Although published observational studies that evaluated vaccine effectiveness during the emergence of the Delta variant appear to suggest decreased protection against less severe COVID-19 caused by this variant, protection against hospitalization and death appears stable. Early observational data indicates that vaccine efficacy against mild symptomatic disease attributable to Omicron is reduced compared to against Delta or the ancestral strain, but efficacy against hospitalizations and deaths remains high. Remaining uncertainties regarding the clinical benefits of mRNA-1273 vaccine include its level of protection against symptomatic disease and asymptomatic infection from newly emerging and future variants, durability of protection beyond 6-8 months (the current limit of observation in the clinical trial and observational

studies), and confirmation of more robust estimates of effectiveness in certain populations not well represented in the clinical trial (including individuals with prior SARS-CoV-2 infection and immunocompromised individuals). Despite evidence from published observational studies of waning protection following primary vaccination and decreased effectiveness against some SARS-CoV-2 variants (e.g., Omicron), the clinical benefits of primary vaccination with mRNA-1273 vaccine remain clear, especially regarding protection against more severe COVID-19 and its serious sequelae. Additional doses (e.g., 3rd primary series dose for certain immunocompromised adults and booster dose for the general adult population) improve upon the benefits provided by the primary series and are currently available under EUA.

Risks demonstrated to be associated with use of mRNA-1273 vaccine in individuals 18 years of age and older include common self-limited local and systemic adverse reactions characterized in the clinical trial, which are mostly mild to moderate but can be severe in some individuals (~7% or fewer, depending on the adverse reaction), and two rare but clinically important serious adverse reactions were detected through post-authorization safety surveillance: anaphylaxis and myocarditis/pericarditis. The crude reporting rate for anaphylaxis in VAERS through November 2021 (which includes unconfirmed and potentially duplicate reports) has been ~10 cases per million doses, which is similar in magnitude to rates of anaphylaxis reported for other preventive vaccines.

Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support (with several suspected fatal cases under CDC investigation but not confirmed at the time of this review), available data from short-term follow-up suggest that most individuals affected by vaccine-associated myocarditis/pericarditis have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, and additional uncertainties regarding the risk of myocarditis/pericarditis include whether and to what extent subclinical cases might occur, and if they do what are the long-term outcomes; the mechanism of pathogenesis; and individual factors conferring increased risk for vaccine-associated myocarditis/pericarditis. Other risk uncertainties for mRNA-1273 vaccine in general include more robust characterization of the safety profile through active safety surveillance and/or controlled observational studies in specific populations (e.g., individuals with prior COVID-19, pregnant women, and significantly immunocompromised individuals); and whether additional rare but clinically important adverse reactions could be identified with increased exposure and longer follow up.

To address the identified risk of myocarditis/pericarditis with mRNA-1273 vaccine, FDA conducted a quantitative, age-stratified benefit-risk analysis in males ≥ 18 years of age, using healthcare claims and CDC surveillance databases, to evaluate the balance of benefits of vaccine-preventable COVID-19 cases, hospitalizations, ICU visits, and deaths against risk of vaccine-related myocarditis/pericarditis cases, hospitalizations, ICU visits, and deaths under various conditions of COVID-19 incidence and vaccine effectiveness informed by real-world data. The modeling attempted to account for preliminary estimates of Omicron-specific vaccine efficacy. While COVID-19 is known to cause myocarditis, and COVID-19-associated myocarditis may be more severe than vaccine-associated myocarditis, the model does not specifically estimate the number of COVID-19-associated cases of myocarditis that would have resulted in hospitalizations,

ICU admission, or deaths in the absence of COVID-19 vaccination. Please refer to Section 4.7 for details. Modeling in ages ≥ 65 years and in females was not conducted due to few cases of vaccine-related myocarditis/pericarditis for these populations. However, this evidence indicates a more favorable benefit-risk profile in individuals ≥ 65 years of age and in females as compared with males 18-64 years of age. The analyses support that, based on the current understanding of vaccine-associated myocarditis/pericarditis, the benefits of vaccination would outweigh risks of myocarditis/pericarditis for individuals 18 years of age and older under all conditions examined. Mitigation of the observed risks of myocarditis/pericarditis and associated uncertainties will be accomplished through labeling (including warning statements about the risks of vaccine-associated myocarditis/pericarditis) and through continued safety surveillance and postmarketing studies to be conducted by the Applicant, U.S. government agencies (including FDA and CDC), and other healthcare stakeholders.

11.3 Discussion of Regulatory Options

The data submitted in the BLA indicate the safety and efficacy of mRNA-1273 vaccine (trade name SPIKEVAX) and meet the statutory requirements to support licensure of this vaccine for use in individuals 18 years of age and older to prevent COVID-19 caused by SARS-CoV-2. Included in the indicated population are young adult males who may be at increased risk for vaccine-associated myocarditis after vaccination with mRNA-1273 vaccine. However, as discussed in the previous sections, current available evidence indicates that the benefits of the vaccine far outweigh its risks and supports the approval of this vaccine for use in all individuals >18 years, including young adult males.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of a 2-dose primary series of mRNA-1273 vaccine (100 mcg each dose administered 28 days apart) for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

11.5 Labeling Review and Recommendations

The USPI was submitted in the format required by FDA's Final Rule titled "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling", referred to as the "Pregnancy and Lactation Labeling Rule (PLLR)" effective June 30, 2015. Communications between the Applicant and CBER resulted in revisions to the original prescribing information language proposed by the Applicant. The final language contained in the label was found to be reflective of the data in the BLA application.

11.6 Recommendations on Postmarketing Actions

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis. Furthermore, the pharmacovigilance system that FDA is

required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies described below.

Postmarketing requirement (PMR) safety studies under section 505(o) of the Federal Food, Drug, and Cosmetic Act to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis:

1. Study mRNA-1273-P903, entitled “Postmarketing safety of SARS-CoV-2 mRNA-1273 vaccine in the U.S.: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity”, to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
2. Study mRNA-1273-P904, entitled “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe,” to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
3. Study mRNA-1273-P911, entitled “Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273),” to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.
4. Study mRNA-1272-P301 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older.
5. Study mRNA-1273-P203 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 to <18 years of age.
6. Study mRNA-1273-P204 substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months to <12 years of age.

Postmarketing commitment (PMC) safety studies agreed upon by FDA and Applicant:

1. Study mRNA-1273-P901, entitled “Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine.”
2. Study mRNA-1273-P902, entitled “Moderna mRNA-1273 Observational Pregnancy Outcome Study.”
3. Study mRNA-1273-P905, entitled “Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries.”

At this time, the available safety data do not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy.