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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AR	adverse reaction
ARDS	acute respiratory distress syndrome
bAb	binding antibody
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMV	cytomegalovirus
CoV	coronavirus
COVID-19	disease caused by the novel 2019 coronavirus
DBL	database lock
DMID	Division of Microbiology and Infectious Diseases
DSMB	data safety monitoring board
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERD	enhanced respiratory disease
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic
GLP	Good Laboratory Practice
GM	geometric mean
GMFR	geometric mean fold-rise
GMT	geometric mean titer
hMPV	human metapneumovirus
HR	hazard ratio
IA	interim analysis
IA#1	interim analysis #1
ICS	intracellular cytokine staining

Abbreviation	Definition
ID50	50% inhibitory dilution
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IP	investigational product
IRT	interactive response technology
LL	lower limit
LNP	lipid nanoparticle
LOD	limit of detection
MAAE	medically attended adverse event
MERS-CoV	Middle East respiratory syndrome coronavirus
mITT	modified intent-to-treat
MN	microneutralization
MN50	50% microneutralization
mRNA	messenger RNA
nAb	neutralizing antibody
NE	not evaluable
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
PaO ₂ /FiO ₂	arterial oxygen partial pressure to fractional inspired oxygen
PBMC	peripheral blood mononuclear cell
PIV3	parainfluenza virus type 3
PP	per-protocol
PRNT	plaque-reduction neutralization test
PsVNA	pseudotyped lentivirus reporter single-round-of-infection neutralization assay
PsVNT50	50% pseudotyped lentivirus reporter test
PT	preferred term
RBD	receptor binding domain
RT-PCR	reverse transcription polymerase chain reaction
S-2P	spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus

Abbreviation	Definition
SARS-CoV-2	2019 novel coronavirus
SMC	safety monitoring committee
TEAE	treatment-emergent adverse event
Th1	T-helper 1
Th2	T-helper 2
VE	vaccine efficacy
WHO	World Health Organization

2.5.1 PRODUCT DEVELOPMENT RATIONALE

2.5.1.1 Pharmacologic Class of Agent

Moderna TX, Inc. (Sponsor) has developed a rapid-response proprietary vaccine platform based on a mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The estimated half-life for mRNA after injection is expected to be approximately 8 to 10 hours, before degradation by native RNases in the body, but the duration of effect also depends on the half-life of the expressed protein, which is expected to persist in the body for several days. mRNA vaccines have been used to induce immune responses against infectious pathogens such as CMV (NCT03382405), hMPV and PIV3 (NCT03392389), Zika (NCT04064905), and influenza virus (NCT03076385 and NCT03345043).

A schematic of mRNA is provided in [Figure 1](#). The mRNA is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N1-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs ([Rozenski et al 1999](#); [Karikó et al 2005](#)). This nucleoside is included in the mRNA in place of the normal uridine base to minimize indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors ([Desmet and Ishii 2012](#)). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure ([Kozak 1991](#); [Fechter and Brownlee 2005](#)).

Figure 1: Structure of mRNA



Abbreviations: PolyA, polyadenylated; UTR, untranslated region.

2.5.1.2 Clinical/Pathophysiology of Condition

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV.

An outbreak of COVID-19 caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019, and the disease has since spread globally ([WHO 2020a](#)). The WHO declared COVID-19 a pandemic on 11 Mar 2020; however, widespread community transmission was already occurring in many locations. As of November 2020, more than 53 million cases and over 1.3 million deaths worldwide have been attributed to the COVID-19 pandemic ([WHO 2020a](#); [WHO 2020b](#)). Widespread community transmission of SARS-CoV-2 has been reported in the Americas, Europe, Africa, and Southeast Asia, and clusters of cases continue to be reported throughout Asia and Australia ([WHO 2020a](#)). During the winter, the combination of re-opening of schools and an increase in indoor activity, because of lower temperatures, is expected to further increase the number of COVID-19 cases and deaths in some parts of the world.

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (regardless of whether they are symptomatic) ([Chen et al 2020](#); [Licciardi et al 2020](#); [Rothan and Byrareddy 2020](#); [Shen et al 2020](#)). Airborne transmission may be possible during certain medical procedures and in indoor, crowded, or poorly ventilated environments ([WHO 2020c](#)). Common symptoms of COVID-19 include fever and cough, and other symptoms include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of COVID-19 and severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, serious heart conditions, compromised immune system, obesity, pregnancy, sickle cell disease, and type 2 diabetes mellitus. Smokers are also at increased risk for severe COVID-19 ([CDC 2020](#)).

2.5.1.3 Therapeutic Rationale Supporting Investigation

The Sponsor's scalable mRNA/LNP technology platform allowed for a rapid response to the pandemic and was used to develop mRNA-1273, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 contains a single mRNA that encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the spike protein into a prefusion conformation. The CoV spike protein mediates attachment and entry of the virus into host cells (by binding to the

angiotensin-converting enzyme 2 receptor followed by membrane fusion), making it a primary target for neutralizing antibodies that prevent infection (Corti et al 2015; Wang et al 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the prefusion conformation (Wrapp et al 2020).

To date, nonclinical and clinical evaluations demonstrate that mRNA-1273 is well tolerated, is immunogenic, and drives a robust SARS-CoV-2-specific antibody and T-cell response. Nonclinical viral challenge studies in animal models (mouse, hamster, nonhuman primates) demonstrated that mRNA-1273 fully protects immunized animals from viral challenge when administered on a prime-only or prime/boost schedule at dose levels ≥ 1 $\mu\text{g}/\text{dose}$ in mice and hamsters and when administered on a prime/boost schedule at ≥ 30 $\mu\text{g}/\text{dose}$ in nonhuman primates. In addition, these studies have shown that mRNA-1273 does not promote vaccine-associated ERD at dose levels predicted to be fully or partially protective. Consistent safety and tolerability profiles have been observed across 6 independent repeat-dose GLP rat toxicity studies of 5 mRNA-based vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs. Additionally, the safety profile of mRNA-1273 observed in a non-GLP repeat-dose rat pharmacology study was consistent with the results from previous GLP repeat-dose rat toxicity studies conducted with other vaccines developed with the Sponsor's mRNA platform. In vitro and in vivo genotoxicity studies demonstrated that the genotoxic risk of SM-102, the novel lipid used in mRNA-1273, to humans is considered low. The nonclinical evaluations supporting mRNA-1273 are summarized in Module 2.4 and fully described in Module 2.6.2 through Module 2.6.7.

Currently, there is no FDA-approved vaccine against SARS-CoV-2. Without further advances in the use of nonpharmaceutical interventions, over 2.5 million COVID-19 deaths are projected globally by 01 Mar 2021, with daily deaths peaking at approximately 15,000/day during this time (IHME 2020). Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for the rapid development of novel prophylactic therapies, including vaccines, to prevent the spread of this disease.

2.5.1.4 Summary of the Clinical Development Program and Timing of Application

2.5.1.4.1 Completed Studies

No clinical studies with mRNA-1273 have been completed.

2.5.1.4.2 Summary of Ongoing Studies and Interim Data Cuts

A dose-ranging Phase 1 safety and immunogenicity study; a dose-confirmation Phase 2a safety and immunogenicity study; and a pivotal Phase 3 efficacy, safety, and immunogenicity study are ongoing ([Table 1](#)). The data from each study that have been included in this application are as follows:

- **Phase 3 Study mRNA-1273-P301** – A pivotal randomized, observer-blind, placebo-controlled, stratified, efficacy, immunogenicity, and safety study in adults ≥ 18 years of age is being conducted in 99 sites across the United States. A data snapshot for interim analysis #1 (IA#1) was triggered by the 53rd confirmed case of COVID-19. Because cases accrued very rapidly, more than 53 cases were included in this snapshot (95) and all were adjudicated. The clinical database for study P301 is monitored, reconciled, and cleaned on an ongoing basis, and the “data snapshot” refers to data extracted from the open database prior to full database lock. Efficacy results from IA#1 are based on a data snapshot on 11 Nov 2020 with a cutoff date for efficacy of 07 Nov 2020. The data snapshot cutoff date for safety was 11 Nov 2020. Cases of COVID-19 reported by the efficacy data cutoff date of 07 Nov 2020 were adjudicated for participants who experienced at least 2 of the following systemic symptoms: fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); OR experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND had at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR (constituting the primary endpoint). Once cases were adjudicated, a data snapshot was taken on 11 Nov 2020.

Vaccine efficacy was demonstrated at the time of IA#1, based on 95 adjudicated cases of COVID-19 in the PP Set. Therefore, because the primary efficacy criteria stipulated by the FDA, EMA, and WHO guidance documents have been met (observed point estimate of efficacy is $> 50\%$ and LL of 95% CI is $> 30\%$), IA#1 is considered the basis for this

EUA application. As defined in the study protocol, the primary analysis for efficacy will be performed when 151 adjudicated cases have accrued.

Immunogenicity data for Study mRNA-1273-P301 are not yet available and thus are not included in this application.

A second data snapshot including 151 adjudicated cases (primary efficacy analysis) and a median of 2 months of efficacy and safety follow-up will be provided to supplement the EUA package.

- **Phase 2a Study mRNA-1273-P201** – A blinded, randomized, placebo-controlled study was designed to confirm the dose (100 µg) advanced into the pivotal Phase 3 study based on the observed safety profile and immunogenicity in healthy adults. The primary analysis of safety and immunogenicity of mRNA-1273-P201 for all participants through Day 57 (or 28 days after the second injection) is included in this application. The primary analysis was performed on the DBL date of 06 Nov 2020. Although the safety and immunogenicity data are locked, the study is ongoing for long-term safety follow-up and the evaluation of antibody persistence. Therefore, TEAEs that were ongoing at the time of DBL remain open in the database and are subject to change. Source tables, figures, and listings have been submitted to IND 19745 (Module 5.3.5.1).
- **Phase 1 Study 20-0003** – An open-label dose-ranging study was initiated to identify the dose to be brought forward in later-phase clinical studies. The safety data included were entered into the study database as of the data cutoff date of 07 Oct 2020. The immunogenicity data focus on cumulative immune responses elicited in participants aged 18 to 55 years, 56 to 70 years, and ≥ 71 years through Day 119 post-injection (3 months after the second injection) for participants who received 25 µg, 100 µg (target dose), and 250 µg. A 50 µg dose cohort was added to the study to be evaluated for the future potential for a dose sparing regimen, and immunogenicity data for this cohort are included only through Day 57 post-vaccination (or 28 days after the second injection). Key results are summarized in this document and have been submitted to IND 19745:
 - 20-0003 Safety Summary Report (dated 26 Oct 2020) (Module 1.11.3)
 - 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) and 20-0003 Immunogenicity Summary Report (dated 24 Sep 2020) (Module 1.11.3)

Additional details regarding the data analyses are provided in [Section 2.5.1.5](#). A summary of study populations from the ongoing studies is provided in [Section 2.5.4.1](#).

Table 1: Summary of Ongoing Clinical Studies With mRNA-1273

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot
mRNA-1273-P301 (US)/ Ongoing	<ul style="list-style-type: none"> Efficacy of mRNA-1273 to prevent COVID-19 (primary) Efficacy of mRNA-1273 to prevent COVID-19 regardless of prior SARS-CoV-2 infection (secondary) Efficacy of mRNA-1273 to prevent SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity (secondary) Efficacy of mRNA-1273 to prevent severe COVID-19 (secondary) 	<p>Safety and reactogenicity of mRNA-1273 vaccine:</p> <ul style="list-style-type: none"> Solicited local and systemic ARs through 7 days after each injection (primary) Unsolicited AEs through 28 days after each injection (primary) MAAEs or AEs leading to withdrawal through the entire study period (primary) SAEs throughout the entire study period (primary) Pregnancies and perinatal outcomes (primary) 	<p>Age Groups: 18+ (n=30000)</p> <p>Dose Groups: Placebo (n=15000) mRNA-1273 100 µg (n=15000)</p> <p>Stratification: Age and, if they are <65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 based on CDC recommendation as of Mar 2020</p>	Phase 3, randomized, stratified, observer-blind, placebo-controlled	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	<p>Data snapshot date^a: 11 Nov 2020</p> <p><u>Immunogenicity:</u> Not included in this application</p>

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot
mRNA-1273-P201 (US)/ Ongoing	<ul style="list-style-type: none"> Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the level of specific binding antibody (primary) Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the titer of neutralizing antibody (secondary) 	<p>Safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine:</p> <ul style="list-style-type: none"> Solicited local and systemic ARs through 7 days after each injection (primary) Unsolicited AEs through 28 days after each injection (primary) MAAEs through the entire study period (primary) SAEs throughout the entire study period (primary) Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only; ≥ 55 years of age) (primary) Vital sign measurements and physical examination findings (primary) 	<p>Age Groups: Cohort 1: ≥ 18 to < 55 (n=300), Cohort 2: ≥ 55 (n=300) Dose Groups: Placebo (n=200) mRNA-1273 50 μg (n=200), mRNA-1273 100 μg (n=200)</p>	Phase 2a, randomized, observer-blind, and placebo-controlled	50 or 100 μ g mRNA-1273 or placebo 2 IM injections, 28 days apart	<p><u>Immunogenicity:</u> Day 57</p> <p><u>Safety:</u> Day 57</p>

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot
20-0003 (US)/ Ongoing	<ul style="list-style-type: none"> Immunogenicity of mRNA-1273 measured by IgG bAb levels to SARS-CoV-2 spike protein and the receptor binding domain (secondary) Immunogenicity of mRNA-1273 measured by nAb levels against SARS-CoV-2 pseudovirus and wild-type virus (exploratory) The SARS-CoV-2 protein-specific T-cell responses in a subset of participants (exploratory) 	<p>Safety and reactogenicity of 4 dose levels of mRNA-1273 vaccine:</p> <ul style="list-style-type: none"> Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination (primary) Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination (primary) Frequency of SAEs, NOCMCs, and MAAEs from Day 1 to Day 394 (primary) 	<p>Age Groups: 18 to 55 (n=75), 56 to 70 (n=40), ≥71 (n=40)</p> <p>mRNA-1273 Dose Groups: 10 µg (n=15)^b, 25 µg (n=35), 50 µg (n=35), 100 µg (n=35), 250 µg (n=35)^c</p>	Phase 1, open-label, dose ranging	10, 25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart	<p><u>Immunogenicity:</u> Day 119^d</p> <p><u>Safety:</u> 07 Oct 2020</p>

Abbreviations: AE = adverse event; AR = adverse reaction; IM = intramuscular; MAAE = medically attended adverse event; NOCMC = new onset of chronic medical condition; SAE = serious adverse event.

- ^a A second analysis with data snapshot 25 Nov 2020 will be submitted to the EUA application when at least 151 cases have been adjudicated as meeting the case definition for the primary endpoint and at least 2 months of median safety and efficacy follow-up data have accumulated.
- ^b In Study DMID 20-0003, Cohort 13 (10 µg, 18-55 years, n=15) was not enrolled.
- ^c In Study DMID 20-0003, dosing at the 250-µg level was discontinued after Cohort 3 (18-55 years, n=15) and prior to enrollment in Cohorts 6 (56-70 years, n=10) and 9 (≥71 years, n=10).
- ^d Day 57 post-vaccination for participants who received the 50-µg dose.
- * Additional data will be provided as it accumulates.

2.5.1.4.3 Timing of Application

The initial regulatory pathway is an EUA described under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act as amended or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013.

The Sponsor will also subsequently submit a BLA under Section 351 of the Public Health Service Act and intends to seek Priority Review for the BLA. The BLA submission is planned as a rolling submission.

2.5.1.5 Adherence to Current Standard Research Approaches in the Design, Conduct, and Analysis of Studies

The clinical development of mRNA-1273 has been expedited to address the ongoing global public health emergency resulting from the SARS-CoV-2 pandemic. Since the submission of IND 19745, the Sponsor has regularly consulted with CBER on the clinical development of mRNA-1273 and provided packages of nonclinical and clinical data from the ongoing clinical studies to help assess the risk and benefit profile of mRNA-1273. The Phase 3 protocol and Statistical Analysis Plan have been designed in accordance with both FDA general guidance on COVID-19 vaccine development ([DHHS 2020](#)) and product-specific guidance (CBER responses for SN0002, SN0004, SN0007, SN0015, SN0017, SN0020, and SN0023). The study was conducted with oversight by an independent DSMB and adjudication committee. The EUA presubmission meeting request (SN0063, Module 1.6.1) provides a summary table of all previously submitted content supportive of an EUA submission.

An overview of the study designs for the 3 studies included in the clinical development plan is provided in [Table 1](#). Full study designs and study conduct details are available in the respective study protocols:

- Study mRNA-1273-P301 Protocol Amendment 5 (11 Nov 2020) is provided in Module 5.3.5.1 – (IND 19745, SN0074).
- Study mRNA-1273-P201 Protocol Amendment 3 (02 Sep 2020) is provided in Module 5.3.5.1 – (IND 19745, SN0033).
- Study 20-0003 Protocol Version 4 (20 May 2020) is located in the DMID IND 19635.

Data are provided from 3 independent ongoing studies; no pooling of the data was performed. Interim data cuts are described in [Section 2.5.1.4.2](#).

Details regarding the planned statistical analysis for each study are provided in the respective SAPs:

- Study mRNA-1273-P301 SAP (10 Sep 2020) is provided in Module 5.3.5.1 (IND 19745, SN0036).
- Study mRNA-1273-P201 SAP (27 Oct 2020) is provided in Module 5.3.5.1 (IND 19745, SN0068).
- Study 20-0003 SAP (18 Aug 2020) is located in the DMID IND 19635.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

During clinical development of mRNA-1273, the Sponsor is evaluating immunogenicity by assessing changes from baseline in SARS-CoV-2-specific bAb levels and nAb titers. Across the Phase 1, 2, and 3 studies, ELISA is being used to measure vaccine-induced binding IgG antibodies to the SARS-CoV-2 spike protein and, in some cases, to specific domains of the protein, (ie, the RBD of the spike protein). Multiple assays are being used to measure the titers of nAbs. In Study 20-0003, vaccine-induced neutralizing activity was assessed by PsVNA (performed at the NIAID Vaccine Research Center) and by live wild-type SARS-CoV-2 virus PRNT assay (performed at the Vanderbilt University Medical Center). These experimental assays were developed using a fit-for-purpose approach. Assays used in later phases followed more typical qualification and validation paths. A qualified MN assay (performed by Battelle) and qualified ELISAs (performed by PPD) were used to test samples from Study mRNA-1273-P201. A panel of validated assays will be used to assess immunogenicity in Study mRNA-1273-P301. Additional information about diagnostic bioassays is provided in the [EUA Request Document \(Section 6.2\)](#).

In addition, in Study 20-0003, convalescent sera obtained from 41 patients who recovered from SARS-CoV-2 infection were used during assay development to generate a relative benchmark (based on levels elicited by natural infection) ([Jackson et al 2020 supplementary appendix \[20-0003 Immunogenicity Summary Report {29 Oct 2020}\]](#)).

To address concerns about the theoretical risk of enhanced disease after injection with mRNA-1273, an additional series of in vitro studies were performed using peripheral blood

mononuclear cells isolated from participants in Study 20-0003. The induction of a Th2-directed response has been linked to ERD, as seen in vaccines for other respiratory virus infections, in particular, formalin-inactivated respiratory syncytial virus vaccine (Kim et al 1969; Haynes et al 2020). In animal models of vaccine-induced immunity against other coronaviruses, specifically MERS and SARS-CoV-1, a Th1-directed immune response has been correlated with a lack of ERD immunopathology (Grifoni et al 2020; Peng et al 2020; Sekine et al 2020; Weiskopf et al 2020). Activated CD4⁺ T cells can be segregated into Th1- and Th2-directed responses based on the production of specific cytokines; therefore, ICS assays were used to evaluate CD4⁺ and CD8⁺ T-cell responses elicited by the mRNA-1273 vaccine in clinical samples (PBMCs) collected on Day 1, Day 29, and Day 43 post-vaccination in Study 20-0003.

2.5.3.1 Dose Selection

The results of Study 20-0003 showed a consistent dose response across age groups by several measures of humoral immunogenicity for both binding and neutralizing antibodies. The advancement of the 100-μg dose (administered as 2 injections, 28 days apart) to the Phase 2a and 3 studies was based on several observations: (i) 2 injections of 100 μg stimulated serum bAb concentrations and titers greater than 2 injections of 25 μg in the 18 to 55 years of age stratum; (ii) 2 injections of 100 μg induced nAb responses (measured by PsVNA) similar to those measured in recipients of the 250-μg dose (in the evaluated age group: 18 to 55 years); and (iii) 2 injections of 100 μg led to a lower incidence of reactogenicity than 2 injections of 250 μg (safety described below; Jackson et al 2020; Anderson et al 2020). The 50-μg dose was added to the protocol only after the dose selection decision was made; therefore, those results were not considered in the selection of the 100-μg dose. Section 2.5.4.2.4.2 provides a summary of key Study 20-0003 immunogenicity results; an additional summary and details are provided in the 20-0003 Immunogenicity Summary Report [29 Oct 2020].

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 Study Populations

2.5.4.1.1 Phase 3 Study mRNA-1273-P301

2.5.4.1.1.1 Disposition

A total of 30,418 individuals were randomly assigned. As of 11 Nov 2020, 15,180 (99.8%) participants in the mRNA-1273 group and 15,170 (99.7%) participants in the placebo group

received the first injection, and 13,982 (91.9%) participants in the mRNA-1273 group and 13,916 (91.5%) participants in the placebo group received the second injection ([Table 2](#)). In both the mRNA-1273 group and the placebo group, the median follow-up time after the first injection was 78.0 days (11 weeks) and the median follow-up time after the second injection was 49.0 days (7 weeks, [Table 3](#)). Of the 442 (1.5%) participants who discontinued IP, the most common reasons for discontinuation were withdrawal of consent by participant (139 [0.5%] participants), confirmed SARS-CoV-2 infection (ie, diagnosed COVID-19 by detection of SARS-CoV-2 in Day 1 NP swab or symptomatic COVID-19 prior to Day 29; 84 [0.3%] participants), and other (70 [0.2%] participants), with a similar distribution between mRNA-1273 and placebo recipients.

Table 2: Participant Disposition in Study mRNA-1273-P301 (Randomization Set)

	Overall		
	Placebo (N=15210) n (%)	mRNA-1273 (N=15208) n (%)	Total (N=30418) n (%)
Number of randomized participants			
Received first injection	15170 (99.7)	15180 (99.8)	30350 (99.8)
Received second injection	13916 (91.5)	13982 (91.9)	27898 (91.7)
Discontinued study vaccine/placebo	254 (1.7)	188 (1.2)	442 (1.5)
Reason for discontinuation of study vaccine/placebo			
Adverse event	28 (0.2)	24 (0.2)	52 (0.2)
Serious adverse event	14 (<0.1)	5 (<0.1)	19 (<0.1)
Death	2 (<0.1)	3 (<0.1)	5 (<0.1)
Lost to follow-up	20 (0.1)	18 (0.1)	38 (0.1)
Physician decision	10 (<0.1)	15 (<0.1)	25 (<0.1)
Pregnancy	2 (<0.1)	2 (<0.1)	4 (<0.1)
Protocol deviation	4 (<0.1)	2 (<0.1)	6 (<0.1)
Study terminated by sponsor	0	0	0
Withdrawal of consent by participant	91 (0.6)	48 (0.3)	139 (0.5)
Due to SARS-CoV-2 ^a	49 (0.3)	35 (0.2)	84 (0.3)
Other	34 (0.2)	36 (0.2)	70 (0.2)
Completed study ^b	0	0	0
Discontinued from study	168 (1.1)	120 (0.8)	288 (0.9)
Reason for discontinuation of study			
Adverse event	0	2 (<0.1)	2 (<0.1)
Serious adverse event	0	1 (<0.1)	1 (<0.1)
Death	4 (<0.1)	3 (<0.1)	7 (<0.1)
Lost to follow-up	31 (0.2)	20 (0.1)	51 (0.2)
Physician decision	2 (<0.1)	17 (0.1)	19 (<0.1)
Pregnancy	0	0	0
Protocol deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Study terminated by sponsor	0	0	0
Withdrawal of consent by participant	120 (0.8)	67 (0.4)	187 (0.6)
Other	10 (<0.1)	9 (<0.1)	19 (<0.1)

- ^a Study participants were considered ineligible to receive the second injection if they were diagnosed with asymptomatic SARS-CoV-2 at Day 1 or symptomatic COVID-19 prior to Day 29.
- ^b Participants were considered to have completed the study if they completed the final visit at Day 759 (Month 25), 24 months after the last injection of investigational product.

Source: mRNA-1273-P301 [Table 14.1.1.1.1.1](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.1.1.1.1.1	Subject Disposition by Baseline SARS-CoV-2 Status - Randomization Set
14.1.6.2	Summary of Study Duration - Safety Set

2.5.4.1.1.2 Study Duration

The median study duration from randomization for participants was similar between the mRNA-1273 group (78.0 days [range: 4 to 108]) and the placebo group (78.0 days [range: 1 to 108]) ([Table 3](#)) based on the Safety Set, in which participants were included in the group corresponding to the IP they actually received.

Table 3: Summary of Study Duration in Study mRNA-1273-P301 (Safety Set)

	Placebo (N=15165)	mRNA-1273 (N=15184)	Total (N=30350)
Number of participants, n (%)			
Received first injection	15165 (100)	15184 (100)	30350 (100)
Received second injection	13913 (91.7)	13985 (92.1)	27898 (91.9)
≥28 days since second injection	11999 (79.1)	12136 (79.9)	24135 (79.5)
≥56 days since second injection	5048 (33.3)	5131 (33.8)	10179 (33.5)
Study duration from randomization (days)			
Median (min, max)	78.0+ (1+, 108+)	78.0 (4+, 108+)	78.0+ (1+, 108+)
Study duration from first injection (days)			
Median (min, max)	78.0+ (1+, 108+)	78.0+ (4+, 108+)	78.0+ (1+, 108+)
Study duration from second injection (days) ^a			
Median (min, max)	49.0+ (0+, 83+)	49.0+ (0+, 83+)	49.0+ (0+, 83+)
Study duration from second injection in participants who received second injection (days)			
Median (min, max)	50.0+ (1+, 83+)	50.0+ (1, 83+)	50.0+ (1+, 83+)

Abbreviations: max = maximum; min = minimum.

Notes: + indicates ongoing participants. Percentages were based on the number of participants in the Safety Set.

^a Study duration from the second injection is zero days for participants who did not receive the second injection.

Source: mRNA-1273-P301 [Table 14.1.6.2](#).

The number and title of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.1.6.2	Summary of Study Duration - Safety Set

2.5.4.1.1.3 Analysis Sets

The numbers of participants in the analysis sets for Study mRNA-1273-P301 are presented in [Table 4](#). The FAS included randomly assigned participants who received at least 1 injection of IP, and the mITT Set included participants in the FAS who had no immunologic or virologic evidence of prior COVID-19, ie, with baseline negative SARS-CoV-2 status defined as both negative Day 1 NP swab RT-PCR test and negative bAb against SARS-CoV-2 nucleocapsid below LOD (based on bAb specific to SARS-CoV-2 nucleocapsid as measured by Roche Elecsys Anti-SARS-CoV-2 assay). The PP Set included participants in the mITT Set who received planned injections of IP per schedule and had no major protocol deviations that impacted critical or key study data, as determined and documented by the Sponsor prior to the data snapshot and unblinding. The PP Set was used as the primary analysis population for efficacy unless specified otherwise. The reasons for exclusion from the PP Set included baseline SARS-CoV-2 status was positive or not known (1668 participants); received study vaccine or IP other than what the participant was randomized to; discontinued study or study vaccine without receiving the second injection; received the second injection out of the window for PP Set (outside of [-7, +14] relative to target Day 29 for the second injection); did not receive the second injection (at this IA#1, a participant was excluded from the PP Set if the participant had been followed up for at least 42 days after the first injection and did not yet receive the second injection as of 11 Nov 2020); and had a major protocol deviation that impacted key or critical data based on review prior to the data snapshot and unblinding. In the Randomized, FAS, mITT, and PP Sets, participants were included in the group to which they were randomly assigned.

The Safety Set included randomized participants who received at least 1 injection of IP. The Solicited Safety Set consisted of randomized participants who received at least 1 injection of IP and contributed any solicited AR data. In the Safety Set and Solicited Safety Set, participants were included in the group corresponding to the IP they actually received.

Of the 15,170 participants randomized to placebo, 7 participants received at least 1 injection of mRNA-1273 and were included under mRNA-1273 in the Safety Set; of the 15,180 participants randomized to mRNA-1273, 3 received placebo and were included under placebo in the Safety Set. One participant was randomized to placebo and had a dosing record in the eCRF but there was no information in the IRT; thus, this participant was included in the Safety Set with the vaccine group missing.

Table 4: Number of Participants in Each Analysis Set in Study mRNA-1273-P301 (Randomization Set)

	Overall		
	Placebo (N=15210) n (%)	mRNA-1273 (N=15208) n (%)	Total (N=30418) n (%)
Full Analysis Set	15170 (99.7)	15180 (99.8)	30350 (99.8)
Modified Intent-to-Treat (mITT) Set	14370 (94.5)	14312 (94.1)	28682 (94.3)
Per-Protocol (PP) Set	13883 (91.3)	13934 (91.6)	27817 (91.4)
Safety Set	15165	15184	30350
Solicited Safety Set	15162 (>99.9)	15176 (>99.9)	30339 (>99.9)
First Injection Solicited Safety Set	15154 (>99.9)	15167 (99.9)	30322 (>99.9)
Second Injection Solicited Safety Set	13870 (91.5)	13947 (91.9)	27817 (91.7)

Source: mRNA-1273-P301 [Table 14.1.2.3](#).

The number and title of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.1.2.3	Number of Subjects in Each Analysis Set by Randomization Stratum - Randomization Set

2.5.4.1.1.4 Demographics

Study mRNA-1273-P301 was designed to evaluate the safety and efficacy of the IP in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The study planned to enroll at least 25% and up to 50% of participants most at risk for severe complications of COVID-19, including those ≥ 65 years of age or < 65 years of age with co-morbid medical conditions such as diabetes mellitus (Type 1, Type 2, or gestational), significant cardiac disease, chronic pulmonary disease, severe obesity, liver disease, and human immunodeficiency virus infection (actual enrollment in these 2 strata was 24.8% and 16.7%, respectively). Overall, 2.2% of participants had detectable viral RNA or antibodies against SARS-CoV-2 at baseline.

The Sponsor intended to enroll a representative population of communities of color that have been disproportionately affected by COVID-19. The percentage of participants enrolled who self-reported as Black or African American (10.2%) or Hispanic or Latino (20.5%) approached that of the US population ([US Census Bureau 2019](#): Black [13.4%], Hispanic or Latino [18.5%]). Communities of color represented 37.2% of the study population.

[Table 5](#) presents the demographics of the study population in Study mRNA-1273-P301. Overall, the study included equal proportions of males and females, 41.5% of participants were at high

risk for severe COVID-19 (ie, the sum of participants < 65 and at risk and ≥ 65 years), and racial and ethnicity proportions were generally representative of US demographics. The majority (25.1%) of participants with a specified occupational risk for acquisition of SARS-CoV-2 were health care workers. The proportion of participants in each demographic category were generally similar between the 2 study groups.

Table 5: Baseline Demographics and Characteristics in Study mRNA-1273-P301 (Full Analysis Set)

	Overall		
	Placebo (N=15170)	mRNA-1273 (N=15180)	Total (N=30350)
Sex, n (%)			
Male	8067 (53.2)	7928 (52.2)	15995 (52.7)
Female	7103 (46.8)	7252 (47.8)	14355 (47.3)
Age at screening (years)			
n	15170	15180	30350
Mean (SD)	51.3 (15.60)	51.4 (15.50)	51.4 (15.55)
Median	52.0	53.0	52.0
Min, max	18, 95	18, 95	18, 95
Age group at screening, n (%)			
≥18 and <65 years	11418 (75.3)	11412 (75.2)	22830 (75.2)
≥65 years	3752 (24.7)	3768 (24.8)	7520 (24.8)
Age and health risk for severe COVID-19, n (%) ^a			
≥18 and <65 years and not at risk	8886 (58.6)	8887 (58.5)	17773 (58.6)
≥18 and <65 years and at risk	2535 (16.7)	2530 (16.7)	5065 (16.7)
≥65 years	3749 (24.7)	3763 (24.8)	7512 (24.8)
Baseline SARS-CoV-2 status, n (%) ^b			
Negative	14370 (94.7)	14312 (94.3)	28682 (94.5)
Positive	334 (2.2)	341 (2.2)	675 (2.2)
Missing	466 (3.1)	527 (3.5)	993 (3.3)
Race, n (%) ^c			
White	11994 (79.1)	12029 (79.2)	24023 (79.2)
Black or African American	1528 (10.1)	1562 (10.3)	3090 (10.2)
Asian	732 (4.8)	653 (4.3)	1385 (4.6)
American Indian or Alaska Native	120 (0.8)	110 (0.7)	230 (0.8)
Native Hawaiian or other Pacific Islander	32 (0.2)	34 (0.2)	66 (0.2)
Multiracial	320 (2.1)	314 (2.1)	634 (2.1)
Other	315 (2.1)	321 (2.1)	636 (2.1)
Not reported	75 (0.5)	99 (0.7)	174 (0.6)
Unknown	54 (0.4)	58 (0.4)	112 (0.4)

	Overall		
	Placebo (N=15170)	mRNA-1273 (N=15180)	Total (N=30350)
Ethnicity, n (%)			
Hispanic or Latino	3114 (20.5)	3120 (20.6)	6234 (20.5)
Not Hispanic or Latino	11917 (78.6)	11917 (78.5)	23834 (78.5)
Not reported	84 (0.6)	104 (0.7)	188 (0.6)
Unknown	55 (0.4)	39 (0.3)	94 (0.3)
Race and ethnicity group, n (%) ^d			
White	9460 (62.4)	9532 (62.8)	18992 (62.6)
Communities of color	5683 (37.5)	5622 (37.0)	11305 (37.2)
Missing	27 (0.2)	26 (0.2)	53 (0.2)
Body mass index, (kg/m ²)			
n	14955	14944	29899
Mean (SD)	29.32 (6.710)	29.32 (6.866)	29.32 (6.788)
Median	28.12	28.12	28.12

Abbreviations: IRT = interactive response technology; LLOQ = lower limit of quantification; LOD = limit of detection; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain reaction.

- ^a Based on stratification factor from IRT, participants who were <65 years old were categorized as at risk for severe COVID-19 if they had at least one of the risk factors specified in the study protocol at Screening.
- ^b Baseline SARS-CoV-2 status: Positive if there was immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test, or bAb against SARS-CoV-2 nucleocapsid above LOD or LLOQ at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
- ^c Participants could be under one or more categories and were counted once at each category. Race was assessed independently from ethnicity.
- ^d White is defined as White and non-Hispanic, and communities of color includes all others whose race or ethnicity is not unknown, unreported, or missing.

Source: mRNA-12732-P301 [Table 14.1.3.1.3](#).

The number and title of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.1.3.1.3	Baseline Demographics and Characteristics by Randomization Stratum - Full Analysis Set

2.5.4.1.2 Phase 2a Study mRNA-1273-P201

2.5.4.1.2.1 Disposition

As of 05 Nov 2020, 200 (100%) participants each in the mRNA-1273 50 µg group, mRNA-1273 100 µg group, and placebo group received the first injection, and 195 (97.5%) participants in the mRNA-1273 50 µg group, 198 participants (99.0%) in the mRNA-1273 100 µg group, and 194 (97.0%) participants in the placebo group received the second injection (mRNA-1273-P201 [Table 14.1.1.1](#)). Of the 13 participants who did not receive the second injection, the most common reason for discontinuation was lost to follow-up (5 [0.8%] participants).

The number and title of the mRNA-1273-P201 table referenced in this section are as follows:

Table Number	Title
14.1.1.1	Subject Disposition - Randomized Set

2.5.4.1.2.2 Analysis Sets

The numbers of participants in the Study mRNA-1273-P201 analysis sets are presented in [Table 6](#). Analysis sets are fully defined in the Study mRNA-1273-P201 SAP (27 Oct 2020).

Table 6: Number of Participants in Each Analysis Set in Study mRNA-1273-P201 (Randomized Set)

	Overall				
	Placebo (N=200) n (%)	mRNA-1273			Overall (N=600) n (%)
		50 µg (N=200) n (%)	100 µg (N=200) n (%)	Total ^a (N=400) n (%)	
Safety Set	200 (100)	200 (100)	200 (100)	400 (100)	600 (100)
Solicited Safety Set	200 (100)	200 (100)	200 (100)	400 (100)	600 (100)
First Injection Solicited Safety Set	199 (99.5)	200 (100)	200 (100)	400 (100)	599 (99.8)
Second Injection Solicited Safety Set	194 (97.0)	195 (97.5)	198 (99.0)	393 (98.3)	587 (97.8)
Full Analysis Set ^b					
Full Analysis Set for SARS-CoV-2-specific bAb	196 (98.0)	198 (99.0)	197 (98.5)	395 (98.8)	591 (98.5)
Day 29	194 (97.0)	196 (98.0)	195 (97.5)	391 (97.8)	585 (97.5)
Day 57	196 (98.0)	194 (97.0)	197 (98.5)	391 (97.8)	587 (97.8)
Full Analysis Set for SARS-CoV-2-specific nAb	191 (95.5)	192 (96.0)	195 (97.5)	387 (96.8)	578 (96.3)
Day 29	188 (94.0)	180 (90.0)	187 (93.5)	367 (91.8)	555 (92.5)
Day 57	191 (95.5)	167 (83.5)	170 (85.0)	337 (84.3)	528 (88.0)
Per-Protocol Set ^c					
PP Set for SARS-CoV-2-specific bAb	186 (93.0)	185 (92.5)	189 (94.5)	374 (93.5)	560 (93.3)
Day 29	184 (92.0)	184 (92.0)	189 (94.5)	373 (93.3)	557 (92.8)
Day 57	175 (87.5)	176 (88.0)	177 (88.5)	353 (88.3)	528 (88.0)
PP Set for SARS-CoV-2-specific nAb	181 (90.5)	179 (89.5)	186 (93.0)	365 (91.3)	546 (91.0)
Day 29	178 (89.0)	168 (84.0)	180 (90.0)	348 (87.0)	526 (87.7)
Day 57	171 (85.5)	150 (75.0)	152 (76.0)	302 (75.5)	473 (78.8)

Percentages were based on the number of randomized participants.

^a Total refers to all participants who received mRNA-1273.

^b Full Analysis Set for each visit included all randomly assigned participants who received any study vaccination and had immunogenicity data available at both baseline and the corresponding post-injection visit.

^c The PP Set for each visit included all participants in the Full Analysis Set who did not have SARS-CoV-2 infection at baseline, did not have a major protocol deviation that impacted immune response, and complied with the injection schedule and the timing of immunogenicity blood sampling to have post-injection results available for at least 1 assay component at the corresponding visit.

Source: mRNA-1273-P201 [Table 14.1.2](#).

The number and title of the mRNA-1273-P201 table referenced in this section are as follows:

Table Number	Title
14.1.2	Number of Subjects in Each Analysis Set - Randomized Set

2.5.4.1.2.3 Demographics

In Study mRNA-1273-P201, the majority of participants were White (94.0%, 94.0%, and 96.5% in the mRNA-1273 50 µg group, mRNA-1273 100 µg group, and placebo group, respectively), not of Hispanic or Latino ethnicity (92.0% each in the mRNA-1273 50 µg group, mRNA-1273 100 µg group, and placebo group), and female (68.5%, 62.0%, and 64.5% in the mRNA-1273 50 µg group, mRNA-1273 100 µg group, and placebo group, respectively) (mRNA-1273-P201 [Table 14.1.3.2](#)). The median age overall was 54.5 years (range: 18 to 87).

The number and title of the mRNA-1273-P201 table referenced in this section are as follows:

Table Number	Title
14.1.3.2	Baseline Demographics - Randomized Set

2.5.4.1.3 Phase 1 Study 20-0003

2.5.4.1.3.1 Disposition

In Study 20-0003, 120 participants were enrolled. All participants received the first injection of mRNA-1273, and 116 (96.7%) participants received the second injection. Four (3.3%) participants discontinued the IP after the first injection: 3 (2.5%) participants discontinued due to an AE (hives on lower extremities, sore throat, and maculopapular rash) and 1 (0.8%) participant discontinued treatment due to potential COVID-19 exposure (20-0003 Safety Summary Report [Table 2H, Table 2I, Table 2J, and Table 2K]).

2.5.4.1.3.2 Analysis Sets

In Study 20-0003, 120 participants were included in at least one of the immunogenicity analyses (20-0003 Immunogenicity Summary Report) and 120 participants were included in the safety analyses (20-0003 Safety Summary Report).

2.5.4.1.3.3 Demographics

In Study 20-0003, data were analyzed for each age cohort separately and were not analyzed for the study population as a whole.

Age Group 18 to 55 Years of Age

The majority of participants were White (88%) and not of Hispanic or Latino ethnicity (87%). The median age was 32.1 years (range: 18 to 54), and 52% of participants were male and 48% were female (20-0003 Safety Summary Report [Table 2A and Table 2D]).

Age Group 56 to 70 Years of Age

The majority of participants were White (90%), and all (100%) were not of Hispanic or Latino ethnicity. The median age was 65.0 years (range: 56 to 70), and 43% of participants were male and 57% were female (20-0003 Safety Summary Report [Table 2B and Table 2E]).

Age Group \geq 71 Years of Age

The majority of participants were White (97%) and not of Hispanic or Latino ethnicity (93%). The median age was 72.9 years (range: 71 to 83), and 57% of participants were male and 43% were female (20-0003 Safety Summary Report [Table 2C and Table 2F]).

2.5.4.2 Efficacy

This section contains an overview of the key efficacy data for the ongoing Study mRNA-1273-P301. Refer to IND 19745 (Module 5.3.5.1) for the comprehensive set of efficacy tables, figures, and listings.

As described in the mRNA-1273-P301 study protocol, VE of mRNA-1273 is defined as prevention of the first occurrence of COVID-19 starting 14 days after the second injection of IP, where COVID-19 is defined based on the following criteria:

- The participant must have experienced 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
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

To be considered a severe COVID-19 case, the following criteria must be met: confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following:

- Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, $\text{SpO}_2 \leq 93\%$ on room air at sea level or $\text{PaO}_2/\text{FIO}_2 < 300$ mm Hg, OR
- Respiratory failure or ARDS, (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
- Significant acute renal, hepatic, or neurologic dysfunction, OR
- Admission to an intensive care unit or death.

2.5.4.2.1 Primary Endpoint of Vaccine Efficacy

The primary efficacy endpoint was VE of mRNA-1273 to prevent the first occurrence of COVID-19, and the primary endpoint analysis included cases starting 14 days after the second injection in the PP Set, as adjudicated by an independent adjudication committee that was blinded to vaccine group assignment.

The primary analysis showed that mRNA-1273 prevented COVID-19 in baseline seronegative participants ([Table 7](#)). There were a total of 95 COVID-19 cases starting 14 days after the second injection based on adjudication committee assessments in the PP Set, representing 62.9% of the target total number of events (151 cases) for the study. There were 5 cases in the mRNA-1273 group and 90 cases in the placebo group. The VE of mRNA-1273 based on hazard ratio was 94.5% compared to placebo, with a 95% CI of 86.5%, 97.8%. The 1-sided p value was $< .0001$ to reject the null hypothesis of $\text{VE} \leq 30\%$, achieving the prespecified efficacy boundary based on the 1-sided nominal alpha of 0.0047 using the Lan-DeMets O'Brien-Fleming spending function using the O'Brien-Fleming boundary.

Table 7 Primary Efficacy Endpoint Analysis of Study mRNA-1273-P301 Starting 14 days After Second Injection (Per-Protocol Set)

	Placebo (N=13883)	mRNA-1273 (N=13934)
Number of participants with COVID-19, n (%)	90 (0.6)	5 (<0.1)
Vaccine efficacy based on hazard ratio (95% CI) ^a		0.945 (0.865, 0.978)
<i>p</i> value ^b		<.0001
Person-years ^c	2697.5	2716.9
Incidence rate per 1,000 person-years (95% CI) ^d	33.365 (26.829, 41.011)	1.840 (0.598, 4.295)
Vaccine efficacy based on incidence rate (95% CI) ^e		0.945 (0.866, 0.983)

^a Vaccine efficacy is defined as 1 – hazard ratio (mRNA-1273 vs placebo), and 95% CI was 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.

^b One-sided *p* value from stratified Cox proportional hazard model to test the null hypothesis $VE \leq 0.3$.

^c Person-years is defined as the total years from randomization date to the date of COVID-19 or last date of study participation, whichever is earlier.

^d 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. The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.

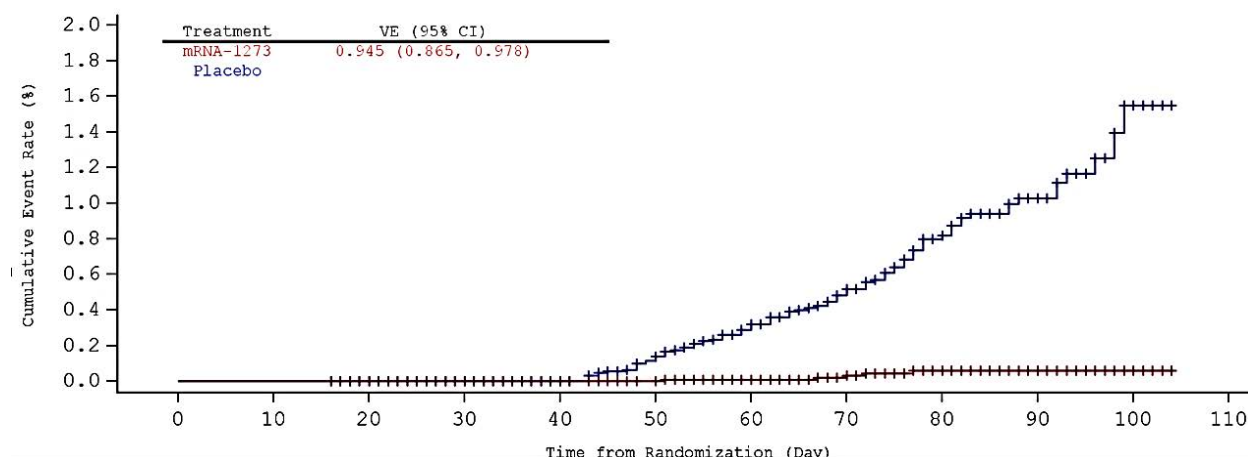
^e Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Source: mRNA-1273-P301 [Table 14.2.2.1.1.1.1](#).

The VE based on incidence rate (94.5%) was the same as the VE based on hazard ratio ([Table 7](#), mRNA-1273-P301 [Table 14.2.2.1.1.1.1](#)). Sensitivity analyses based on the mITT Set (mRNA-1273-P301 [Table 14.2.2.1.1.1.2](#)) gave similar results: VE based on hazard ratio was 93.4%, with a 95% CI of 84.8%, 97.1%.

Cumulative incidence rates of COVID-19 based on adjudication committee assessments with accrual starting 14 days after the second injection in the PP Set are presented in [Figure 2](#).

Figure 2: Cumulative Incidence Rate of Time to First Occurrence of COVID-19 Starting 14 Days After Second Injection in Study mRNA-1273-P301 (Per-Protocol Set)



Vaccine efficacy is defined as $1 - \text{hazard ratio (mRNA-1273 vs. placebo)}$ and 95% CI was 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.

Source: mRNA-1273-P301 [Figure 14.2.2.1.1.1.1](#).

Additional sensitivity analyses were performed at this interim analysis. Analyses of vaccine efficacy against COVID-19 based on the positive RT-PCR results and COVID-19 symptoms (requiring 2 eligible systemic symptoms or 1 respiratory symptom) as defined in the protocol were performed. Analysis of COVID-19 starting 14 days after the second injection (primary approach) based on the PP Set is provided in mRNA-1273-P301 [Table 14.2.2.1.2.1.1](#) (VE = 94.5%), and sensitivity analyses of COVID-19 starting 14 days after the first injection (mRNA-1273-P301 [Table 14.2.2.1.2.3.1](#) [PP Set]; VE = 95.4%), starting after randomization (mRNA-1273-P301 [Table 14.2.2.1.2.5.1](#) [PP Set]; VE = 94.6%), and starting from randomization based on the mITT Set (mRNA-1273-P301 [Table 14.2.2.1.2.5.2](#); VE = 91.6%) all yielded results consistent with those based on the adjudication committee assessments. However, these analyses must be interpreted with caution because the follow-up period was limited (approximately 28 days), the vast majority (>90%) of participants received a second dose, and cases were not censored from the analysis if they occurred after the second dose.

The VE of mRNA-1273 for the primary efficacy endpoint was consistent across major demographic and baseline characteristic subgroups ([Section 2.5.4.2.3](#); [Figure 3](#)).

The numbers and titles of the mRNA-1273-P301 tables and figures referenced in this section are as follows:

Table Number	Title
14.2.2.1.1.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.1.1.1.2	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - mITT Set
14.2.2.1.2.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.1.2.3.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After First Injection - Per-Protocol Set
14.2.2.1.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - Per-Protocol Set
14.2.2.1.2.5.2	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - mITT Set
Figure Number	Title
14.2.2.1.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set

2.5.4.2.2 Secondary Endpoints of Vaccine Efficacy

The VE for mRNA-1273 for the key secondary endpoints was similar to the VE for the primary endpoint, with point estimates of VE in the range from 93.5% to 100% based on hazard ratios ([Table 8](#)).

Table 8 Summary of Primary and Key Secondary Efficacy Endpoint Analysis Results in Study mRNA-1273-P301

Set	Endpoint	Placebo (N = 13883)	mRNA-1273 (N = 13934)
PP	Cases of COVID-19 based on adjudication committee assessments starting 14 days after the second injection (primary endpoint), n	90	5
	Vaccine efficacy based on hazard ratio (95% CI) ^a		0.945 (0.865, 0.978)
	<i>p</i> value ^b		<.0001
PP	Cases of severe COVID-19 based on adjudication committee assessments starting 14 days after the second injection (secondary endpoint), n	11	0
	Vaccine efficacy based on hazard ratio (95% CI) ^a		1.000 (NE, 1.000)
FAS	Cases of COVID-19 based on adjudication committee assessments starting 14 days after the second injection regardless of prior SARS-CoV-2 infection (secondary endpoint), n/N ^c	92/15170	6*/15180
	Vaccine efficacy based on hazard ratio (95% CI) ^a		0.935 (0.852, 0.972)
PP	Cases with a secondary (less restrictive) definition of COVID-19 starting 14 days after the second injection (secondary endpoint), n	121	6**
	Vaccine efficacy based on hazard ratio (95% CI) ^a		0.951 (0.889, 0.978)
PP	Cases of COVID-19 starting 14 days after the first injection (secondary endpoint), n	128	6**
	Vaccine efficacy based on hazard ratio (95% CI) ^a		0.954 (0.895, 0.980)

Abbreviations: n = number of events; N = number of participants; NE = not evaluable.

^a Vaccine efficacy defined as 1 – hazard ratio (mRNA-1273 vs placebo), and 95% CI was estimated using a Cox proportional hazard model stratified by randomization strata with Efron's method of tie handling, and with the treatment group as a covariate.

^b One-sided *p* value from stratified Cox proportional hazard model to test the null hypothesis $VE \leq 0.3$.

^c FAS was used for COVID-19 based on adjudication committee assessments starting 14 days after the second injection regardless of prior SARS-CoV-2 infection, n and N are based on the number of participants in the FAS.

*One COVID-19 case was under mRNA-1273 in the FAS and was excluded from the PP Set: the participant was randomized to mRNA-1273 but only received placebo; thus, the participant was included under mRNA-1273 in FAS and excluded from PP Set.

**One COVID-19 case was under mRNA-1273; the participant had positive RT-PCR at a scheduled RT-PCR test on the day of the second injection and was not adjudicated for this analysis.

Source: mRNA-1273-P301 [Table 14.2.1.1.1.1.1](#).

mRNA-1273 prevented severe COVID-19 starting 14 days after the second injection: the point estimate of VE was 100% based on the hazard ratio, with 11 cases in the placebo group and no cases in the mRNA-1273 group based on the PP Set with adjudication committee assessments ([Table 8](#); mRNA-1273-P301 [Table 14.2.2.2.1.1.1](#)). Sensitivity analyses for severe COVID-19 starting 14 days after the second injection based on the mITT Set with adjudication committee

assessments (mRNA-1273-P301 [Table 14.2.2.2.1.1.2](#); 11 cases in the placebo group) and based on the PP Set with (mRNA-1273-P301 [Table 14.2.2.2.2.1.1](#); 15 cases in the placebo group) also showed point estimates of VE of 100% based on hazard ratios, as did a sensitivity analysis for severe COVID-19 starting after randomization using the PP Set based on the positive RT-PCR results and severe COVID-19 symptoms (mRNA-1273-P301 [Table 14.2.2.2.2.5.1](#); 16 cases in the placebo group). A plot of cumulative incidence of severe COVID-19 is presented in mRNA-1273-P301 [Figure 14.2.2.2.1.1.1](#).

Efficacy analysis of mRNA-1273 to prevent COVID-19 based on adjudication committee assessments regardless of prior SARS-CoV-2 infection, for cases starting 14 days after the second injection, showed a VE of 93.5% based on hazard ratio ([Table 8](#); mRNA-1273-P301 [Table 14.2.2.7.1.1](#)). A subgroup analysis of the same data showed no cases in the mRNA-1273 group with positive SARS-CoV-2 infection status at baseline compared with 1 case in the placebo group (mRNA-1273-P301 [Table 14.2.2.7.1.6.10](#)). An analysis substituting programmatic derivation for the adjudication committee assessments produced a similar result (VE of 93.8%; mRNA-1273-P301 [Table 14.2.2.7.2.1](#)). A cumulative incidence plot of COVID-19 starting 14 days after second injection based on adjudication committee assessments and regardless of prior SARS-CoV-2 infection is presented in mRNA-1273-P301 [Figure 14.2.2.7.1.1.1](#). Any interpretation of efficacy in participants with positive SARS-CoV-2 infection status at baseline is severely limited by the small proportion of these participants enrolled (2.2%).

mRNA-1273 prevented COVID-19 cases defined using a secondary (less restrictive) definition of disease based on the presence of at least one of a list of COVID-19 symptoms: the point estimate of VE based on hazard ratio was 95.1% ([Table 8](#); mRNA-1273-P301 [Table 14.2.2.4.1.1](#)).

mRNA-1273 prevented COVID-19 cases starting 14 days after the first injection: VE based on hazard ratio was 95.4% with a 95% CI of 89.5%, 98.0% ([Table 8](#); mRNA-1273-P301 [Table 14.2.2.1.2.3.1](#)). This result needs to be interpreted with caution as > 90% of participants received a second injection of mRNA-1273 approximately 28 days after the first injection.

The numbers and titles of the mRNA-1273-P301 tables and figures referenced in this section are as follows:

Table Number	Title
14.2.1.1.1.1.1	Summary of Primary and Secondary Efficacy Endpoint Analysis Results - Per-Protocol Set
14.2.2.1.2.3.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After First Injection - Per-Protocol Set

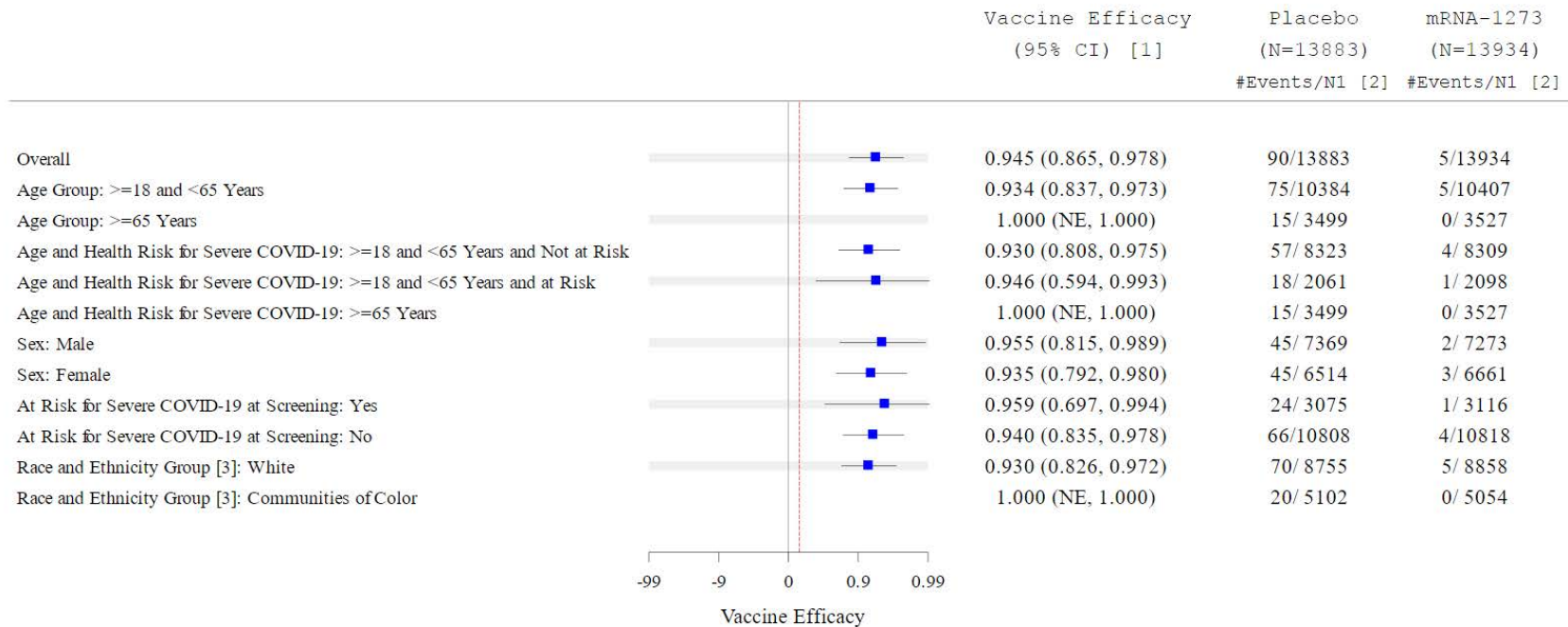
Table Number	Title
14.2.2.2.1.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection – Per-Protocol Set
14.2.2.2.1.1.2	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - mITT Set
14.2.2.2.2.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.2.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting After Randomization - Per-Protocol Set
14.2.2.4.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Secondary Definition of COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.7.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set
14.2.2.7.1.6.10	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection by Baseline SARS-CoV-2 Status - Full Analysis Set
14.2.2.7.2.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set
Figure Number	Title
14.2.2.2.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.7.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set

2.5.4.2.3 Subgroup Analyses

The efficacy of mRNA-1273 for the primary efficacy endpoint was consistent across major demographic and baseline characteristic subgroups: age (≥ 18 to < 65 years, ≥ 65 years; mRNA-1273-P301 [Table 14.2.2.1.1.6.1.1](#)); age and health risk for severe COVID-19 (age ≥ 18 to < 65 years and not at risk for severe COVID-19, age ≥ 18 to < 65 years and at risk for severe COVID-19, and age ≥ 65 years [regardless of comorbidity]); mRNA-1273-P301 [Table 14.2.2.1.1.6.3.1](#)); risk factor for severe COVID-19 at screening (mRNA-1273-P301 [Table 14.2.2.1.1.6.7.1](#)); sex (mRNA-1273-P301 [Table 14.2.2.1.1.6.4.1](#)); and race and ethnicity (White compared with communities of color; mRNA-1273-P301 [Table 14.2.2.1.1.6.10.1](#)). With respect to subgroup analysis for ethnicity, limited numbers of participants in each ethnic group contributed to the primary efficacy endpoint. The data was pooled together into a “communities of color” group for this analysis to ensure that 2 subpopulations in the study would be large enough for meaningful analysis.

A Forest plot of subgroup analyses of VE of mRNA-1273 to prevent COVID-19 (primary endpoint) is presented in [Figure 3](#).

Figure 3: A Forest Plot of Subgroup Analyses of VE of mRNA-1273 to Prevent COVID-19 in Study mRNA-1273-P301 (Per-Protocol Set)



Abbreviations: N1 = population in each subgroup; NE = not evaluable.

[1] Vaccine efficacy is defined as $1 - \text{hazard ratio (mRNA-1273 vs placebo)}$, and 95% CI was 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.

[2] Based on the number of participants in each subgroup.

[3] White is defined as White and non-Hispanic, and communities of color includes all other participants. Non-White racial and ethnic groups were pooled to ensure a sample size large enough for meaningful analysis.

Source: mRNA-1273-P301 [Figure 14.2.2.1.1.2.3](#).

The numbers and titles of the mRNA-1273-P301 tables and figures referenced in this section are as follows:

Table Number	Title
14.2.2.1.1.6.1.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Age Group (≥ 18 and < 65 Years, ≥ 65 Years) - Per-Protocol Set
14.2.2.1.1.6.3.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Age and Health Risk for Severe COVID-19 - Per-Protocol Set
14.2.2.1.1.6.4.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Sex - Per-Protocol Set
14.2.2.1.1.6.7.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Risk for Severe COVID-19 at Screening - Per-Protocol Set
14.2.2.1.1.6.10.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Race and Ethnicity Group (White, Communities of Colors) - Per-Protocol Set
Figure Number	Title
14.2.2.1.1.2.3	Forest Plot of Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set

2.5.4.2.4 Immunogenicity

2.5.4.2.4.1 Phase 2a Study mRNA-1273-P201 Immunogenicity Results

This section contains an overview of the key immunogenicity data for ongoing Study mRNA-1273-P201. Refer to IND 19745 (Module 5.3.5.1) for the comprehensive set of immunogenicity tables, figures, and listings. [Table 9](#) presents the anti-spike glycoprotein concentrations as measured by ELISA, and [Table 10](#) presents the MN titers.

In terms of the MN antibody titers, the responses to vaccination with either 50 or 100 μg of mRNA-1273 were similar. After the first injection (Day 29) participants who received 50 μg of mRNA-1273 had a GMFR of 5.59 (95% CI: 4.65; 6.71) and participants who received 100 μg of mRNA-1273 had a GMFR of 7.46 (95% CI: 6.32, 8.81). After the second injection (Day 57) participants who received 50 μg of mRNA-1273 had a GMFR of 53.65 (95% CI: 50.54, 56.95) and participants who received 100 μg of mRNA-1273 had a GMFR of 54.79 (95% CI: 51.94, 57.80).

The immunogenicity results when using ELISA to assess bAb responses were slightly different in that responses at Day 29 were higher in participants who received 100 μg of mRNA-1273 (GMFR: 4.29; 95% CI: 3.87, 4.76) than in those who received 50 μg of mRNA-1273 (GMFR:

3.36; 95% CI: 3.05, 3.69). Differences in bAb concentrations for participants receiving 100 µg of mRNA-1273 or 50 µg of mRNA-1273 were less apparent after the second injection at Days 43 and 57 ([Table 9](#) and [Table 10](#)).

At all visits for mRNA-1273 groups, the GMFR in the anti-spike glycoprotein concentrations was greater in the age 18 to 55 year cohort than in the age ≥ 55 year cohort (mRNA-1273-P201 [Table 14.2.1.1.1](#)). For MN titers values, the GMT and GMFR at Day 29 were higher in the age 18 to 55 year cohort than in the age ≥ 55 year cohort, (mRNA-1273-P201 [Table 14.2.2.1.1.1](#)). The MN titer values at Day 43 and Day 57 were similar between age cohorts.

Participants who received 2 doses of either 50 or 100 µg of mRNA-1273 separated by 28 days developed both binding and neutralizing antibodies against the SARS-CoV-2 virus, with GMFRs > 20 -fold (bAb) and > 50 -fold (MN assay), regardless of dose level. These data are supportive because of the magnitude of the antibody response to 2 doses of mRNA-1273 and confirm the selection of the 100-µg dose brought forward in the pivotal Phase 3 efficacy study.

Table 9: Summary of Binding (Anti-Spike Glycoprotein) Antibody Levels in Study mRNA-1273-P201 (Per-Protocol Set for SARS-CoV-2-Specific bAb)

Time Point Statistic	Overall			
	Placebo (N=186)	50 µg (N=185)	mRNA-1273 100 µg (N=189)	Total (N=374)
Antibody: VAC58 Spike IgG Antibody (µg/mL) (LLOQ: 3.9, ULOQ: 487)				
Baseline (Day 1)				
n ^a	186	185	189	374
GM level	5.952	6.078	5.875	5.975
95% CI ^b	5.592, 6.335	5.646, 6.543	5.485, 6.293	5.682, 6.282
Median	6.000	6.300	5.900	6.000
Min, max	1.95, 16.80	1.95, 37.70	1.95, 106.00	1.95, 106.00
Day 29				
n ^c	184	184	189	373
GM level	5.803	20.324	25.229	22.677
95% CI ^b	5.420, 6.213	18.601, 22.207	22.777, 27.944	21.179, 24.281
Median	5.900	20.200	25.600	22.000
Min, max	1.95, 40.40	4.10, 106.50	4.30, 431.60	4.10, 431.60
GM fold-rise	0.98	3.36	4.29	3.80
95% CI ^b	0.95, 1.01	3.05, 3.69	3.87, 4.76	3.54, 4.08
Day 43				
n ^c	180	175	181	356
GM level	5.735	169.460	198.134	183.478
95% CI ^b	5.361, 6.135	156.251, 183.786	182.865, 214.678	173.252, 194.309
Median	5.900	186.300	204.300	197.550
Min, max	1.95, 17.80	33.80, 487.00	20.10, 487.00	20.10, 487.00
GM fold-rise	0.97	27.46	33.51	30.38
95% CI ^b	0.95, 1.00	24.86, 30.33	30.37, 36.96	28.32, 32.59
Day 57				
n ^c	175	176	177	353
GM level	5.861	123.892	147.415	135.176
95% CI ^b	5.461, 6.291	113.072, 135.748	134.466, 161.612	126.651, 144.275
Median	5.900	136.000	166.100	149.600
Min, max	1.95, 62.50	21.40, 456.00	23.10, 487.00	21.40, 487.00
GM fold-rise	0.98	20.39	25.04	22.60
95% CI ^b	0.94, 1.03	18.31, 22.70	22.51, 27.86	20.94, 24.39

Abbreviations: GM = geometric mean; max = maximum; min = minimum; LLOQ = lower limit of quantification ; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ were replaced by $0.5 \times \text{LLOQ}$. Values that were greater than the ULOQ were converted to the ULOQ.

For visit Day 29, visit window (−3/+7 days) was used to define per-protocol. If the visit (Day 29) was disrupted and could not be completed at Day 29 (−3/+7 days) as a result of the COVID-19 pandemic, the window was extended to Day 29 + 21 days.

- ^a Number of participants with nonmissing baseline.
- ^b 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.
- ^c Number of participants in the Per-Protocol Set for SARS-CoV-2-specific bAb at the corresponding visit.

Source: mRNA-1273-P201 [Table 14.2.1.1.1](#).

Table 10: Summary of Neutralizing Antibody Titers in Study mRNA-1273-P201 (Per-Protocol Set for SARS-CoV-2-Specific nAb)

Time Point Data Category Statistic	Overall			
	Placebo (N=181)	50 µg (N=179)	mRNA-1273 100 µg (N=186)	Total (N=365)
Antibody: MN Endpoint Titer				
Baseline (Day 1)				
n ^a	181	179	186	365
GMT	20.0	20.3	20.0	20.1
95% CI ^b	NE, NE	19.9, 20.7	NE, NE	19.9, 20.3
Median	20.0	20.0	20.0	20.0
Min, max	20, 20	20, 120	20, 20	20, 120
Day 29				
n ^c	178	168	180	348
GMT	21.0	113.4	149.3	130.8
95% CI ^b	19.7, 22.3	94.6, 136.0	126.5, 176.2	115.6, 147.9
Median	20.0	120.0	160.0	160.0
Min, max	20, 960	20, 1280	20, 1280	20, 1280
GMFR	1.05	5.59	7.46	6.49
95% CI ^b	0.99, 1.11	4.65, 6.71	6.32, 8.81	5.74, 7.34
Seroconversion ^d				
n ^e (%)	3 (1.7)	131 (78.0)	160 (88.9)	291 (83.6)
95% CI ^f	0.3, 4.8	70.9, 84.0	83.4, 93.1	79.3, 87.4
≥2-fold increase from baseline ^g				
n ^e (%)	3 (1.7)	132 (78.6)	160 (88.9)	292 (83.9)
95% CI ^f	0.3, 4.8	71.6, 84.5	83.4, 93.1	79.6, 87.6
≥3-fold increase from baseline ^g				
n ^e (%)	2 (1.1)	119 (70.8)	146 (81.1)	265 (76.1)
95% CI ^f	0.1, 4.0	63.3, 77.6	74.6, 86.5	71.3, 80.5
≥4-fold increase from baseline ^g				
n ^e (%)	2 (1.1)	110 (65.5)	130 (72.2)	240 (69.0)
95% CI ^f	0.1, 4.0	57.8, 72.6	65.1, 78.6	63.8, 73.8

Time Point Data Category Statistic	Overall			
	Placebo (N=181)	50 µg (N=179)	mRNA-1273 100 µg (N=186)	Total (N=365)
Day 43				
n ^c	175	141	150	291
GMT	20.4	1144.7	1179.4	1162.4
95% CI ^b	19.6, 21.4	1094.4, 1197.2	1130.5, 1230.5	1127.3, 1198.7
Median	20.0	1280.0	1280.0	1280.0
Min, max	20, 960	240, 1280	160, 1280	160, 1280
GMFR	1.02	56.23	58.97	57.63
95% CI ^b	0.98, 1.07	53.29, 59.34	56.52, 61.52	55.71, 59.62
Day 57				
n ^c	171	150	152	302
GMT	21.2	1091.0	1095.8	1093.4
95% CI ^b	19.8, 22.6	1035.5, 1149.5	1038.8, 1155.9	1053.5, 1134.8
Median	20.0	1280.0	1280.0	1280.0
Min, max	20, 640	240, 1280	200, 1280	200, 1280
GMFR	1.06	53.65	54.79	54.22
95% CI ^b	0.99, 1.13	50.54, 56.95	51.94, 57.80	52.11, 56.42
Seroconversion ^d				
n ^e (%)	3 (1.8)	150 (100)	152 (100)	302 (100)
95% CI ^f	0.4, 5.0	97.6, 100.0	97.6, 100.0	98.8, 100.0
≥2-fold increase from baseline ^g				
n ^e (%)	3 (1.8)	150 (100)	152 (100)	302 (100)
95% CI ^f	0.4, 5.0	97.6, 100.0	97.6, 100.0	98.8, 100.0
≥3-fold increase from baseline ^g				
n ^e (%)	3 (1.8)	150 (100)	152 (100)	302 (100)
95% CI ^f	0.4, 5.0	97.6, 100.0	97.6, 100.0	98.8, 100.0
≥4-fold increase from baseline ^g				
n ^e (%)	3 (1.8)	150 (100)	152 (100)	302 (100)
95% CI ^f	0.4, 5.0	97.6, 100.0	97.6, 100.0	98.8, 100.0

Abbreviations: GMT = geometric mean titer; GMFR = geometric mean fold-rise (post-baseline vs. baseline titers); LOD = limit of detection; LLOQ = lower limit of quantification; max = maximum; min = minimum; MN = microneutralization; NE = not evaluable ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values that were greater than the ULOQ are converted to the ULOQ. For MN endpoint titer: LLOQ=40 and ULOQ=1280.

For visit Day 29, visit window (−3/+7 days) was used to define per-protocol. If the visit (Day 29) was disrupted and could not be completed at Day 29 (−3/+7 days) as a result of the COVID-19 pandemic, the window was extended to Day 29 + 21 days.

Percentages were based on the number of participants in the Per-Protocol Set for SARS-CoV-2-specific nAb at the corresponding visit (n[3]).

- ^a Number of participants with nonmissing baseline.
- ^b 95% CI was 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.
- ^c Number of participants in the Per-Protocol Set for SARS-CoV-2-specific nAb at the corresponding visit.
- ^d Seroconversion at participant level is defined as a change of nAb titer from below the LLOQ to equal to LLOQ (respectively) or a 4-times or higher ratio in participants with pre-existing nAb titers.
- ^e Number of participants in the corresponding category at the corresponding time point.
- ^f 95% CI was calculated using the Clopper-Pearson method.
- ^g \geq z-fold increase from baseline at participant level was defined as a z-times or higher ratio in participants with pre-existing nAb titers.

Source: mRNA-1273-P201 [Table 14.2.2.1.1.1](#).

The numbers and titles of the mRNA-1273-P201 tables referenced in this section are as follows:

Table Number	Title
14.2.1.1.1	Summary of Binding Antibody Levels - Per-Protocol Set for SARS-CoV-2-specific bAb
14.2.2.1.1.1	Summary of Neutralizing Antibody Titers - Per-Protocol Set for SARS-CoV-2-specific nAb from the First Lot

2.5.4.2.4.2 Phase 1 Study 20-0003 Immunogenicity Results

[Table 11](#) and [Table 12](#) show the bAb concentrations for spike IgG as measured by ELISA at all dose levels in the 18 to 55 years of age stratum and for all 3 age strata at the 100-µg dose of mRNA-1273, respectively, in the Phase 1 study. [Table 13](#) and [Table 14](#) show the nAb titers as measured by PsVNA for the 18 to 55 years of age stratum across dose levels and for the 100-µg dose of mRNA-1273 across all 3 age strata, respectively. No formal statistical comparisons were prespecified in this study; thus, descriptive summaries are provided here.

Immunogenicity results in Study 20-0003 indicated that the 100-µg dose of mRNA-1273 administered as 2 injections 28 days apart resulted in the induction of nAbs in all participants by 1 week after the second injection ([Jackson et al 2020](#); [Anderson et al 2020](#)). After a single injection of 100 µg of mRNA-1273, bAbs for spike glycoprotein were detectable in all participants in all 3 age strata, with further increases observed at the second injection. The immune response was consistent across age groups and persisted 3 months after the second injection (20-0003 Immunogenicity Summary Report [29 Oct 2020]). A similar response was observed across all doses in all age cohorts, but higher responses were observed with the second injection in older adults at doses of 100 µg of mRNA-1273.

Pooled convalescent sera from patients recovered from COVID-19 were used as a clinically meaningful benchmark to assess the magnitude of the immune response to vaccination with mRNA-1273. Binding IgG antibodies against the spike protein (stabilized spike antigen, S-2P), as measured by ELISA, were observed to have higher median values at Day 43 and beyond in the mRNA-1273 groups than in the convalescent sera control group ([Table 11](#) and [Table 12](#)).

Neutralizing activity was observed for the 100-µg mRNA-1273 dose as of Day 36; the neutralizing activity was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata ([Table 13](#) and [Table 14](#)).

Study 20-0003 assessments of antibody responses focused on the initial Wuhan-1 strain sequence (614D), although the 614G polymorphism in SARS-CoV-2 spike has become the globally predominant isoform. An increase in neutralizing activity was observed on the pseudovirus neutralization assay when 614G was substituted for 614D ([Anderson et al 2020](#)). These data provide evidence that the immune response to mRNA-1273 may be sufficient to neutralize the current dominant circulating strain.

An intracellular cytokine stimulation assay was used to evaluate T-cell responses elicited by the mRNA-1273 vaccine. The 25-µg and 100-µg doses elicited CD4+ T-cell responses that upon stimulation by S-specific peptide pools were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. CD8+ T-cell responses to S-2P were detected at low levels after the second injection in the 100 µg dose group. This Th1-dominant profile adds to the body of nonclinical data suggesting that mRNA-1273 is unlikely to lead to enhanced disease following natural exposure to SARS-CoV-2 (20-0003 Immunogenicity Summary Report [24 Sep 2020]).

The 100-µg dose of mRNA-1273 was selected as the optimal dose for use in later-stage studies based on greater immunogenicity compared with the 25-µg dose. The observation that the Th1 phenotype of CD4+ T cells was induced was clinically reassuring in terms of the risk of developing vaccine-associated ERD.

Table 11: Serum IgG ELISA Endpoint Titer Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 20-0003 – Spike Stabilized Antigen (S-2P) – Age 18 to 55 Years

Time Point	Statistic	25 µg mRNA-1273 18-55 years (N=15)	50 µg mRNA-1273 18-55 years (N=15)	100 µg mRNA-1273 18-55 years (N=15)	250 µg mRNA-1273 18-55 years (N=15)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	15	15	15	41
	GMT	116	341	131	178	138901
	95% CI	72; 187	127; 914	65; 266	81; 392	82876; 232799
Day 29 Post Vaccination 1 (Pre-Vaccination 2)	n	15	15	15	14	NA
	GMT	40227	118294	109209	213526	NA
	95% CI	29094; 55621	71948; 194495	79051; 150874	128832; 353896	NA
Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)	n	13	14	14	14	NA
	GMT	379764	734025	811119	994629	NA
	95% CI	281597; 512152	588266; 915900	656336; 1002404	806189; 1227115	NA
Day 57 Post Vaccination 1 (28 Days Post Vaccination 2)	n	13	15	14	14	NA
	GMT	299751	562064	782719	1255376	NA
	95% CI	206070; 436020	407368; 775505	619310; 989244	969516; 1625521	NA
Day 119 Post Vaccination 1 (90 Days Post Vaccination 2)	n	13	ND	15	14	NA
	GMT	301540	ND	413971	604507	NA
	95% CI	217148; 418729	ND	322891; 530744	451387; 809568	NA

Abbreviations: GMT = geometric mean titer; n = number of participants with results available at time point; N = number of participants; NA = not available; ND = not determined.

Source: 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) Table 20.

Table 12: Serum IgG ELISA Endpoint Titer Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 20-0003 – Spike Stabilized Antigen (S-2P) – All Age Groups 100 µg mRNA-1273

Time Point	Statistic	100 µg mRNA-1273 18-55 years (N=15)	100 µg mRNA-1273 56-70 years (N=10)	100 µg mRNA-1273 ≥71 years (N=10)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	10	10	41
	GMT	131	655	953	138,901
	95% CI	65, 266	270, 1591	493, 1842	82876, 232799
Day 29 Post Vaccination 1 (Pre-Vaccination 2)	n	15	10	10	NA
	GMT	109209	115831	203365	NA
	95% CI	79051, 150874	73288, 183069	97384, 424686	NA
Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)	n	14	9	10	NA
	GMT	811119	1305996	8091439	NA
	95% CI	656336, 1002404	581138, 2934971	2546249, 25712881	NA
Day 57 Post Vaccination 1 (28 Days Post Vaccination 2)	n	14	9	10	NA
	GMT	782719	1183066	3638522	NA
	95% CI	619310, 989244	379698, 3686201	1316233, 10058130	NA
Day 119 Post Vaccination 1 (90 Days Post Vaccination 2)	n	15	9	10	NA
	GMT	413971	366252	195272	NA
	95% CI	322891, 530744	213031, 629675	117647, 324112	NA

Abbreviations: GMT = geometric mean titer; n = number of participants with results available at time point; N = number of participants; NA = not available.

Source: 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) Table 20, Table 21, and Table 22.

Table 13: Pseudovirus Neutralization Assay Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 20-0003 - ID50 – Age 18 to 55 Years

Time Point	Statistic	25 µg mRNA-1273	50 µg mRNA-1273	100 µg mRNA-1273	250 µg mRNA-1273	Convalescent Sera
		18-55 years (N=15)	18-55 years (N=15)	18-55 years (N=15)	18-55 years (N=15)	
Day 1 (Pre-Vaccination 1)	n	15	15	15	15	41
	GM	10	10	10	10	106
	95% CI	ND	ND	ND	ND	60, 189
Day 29 Post Vaccination 1 (Pre-Vaccination 2)	n	15	15	15	14	NA
	GM	12	14	18	21	NA
	95% CI	10, 14	9, 21	12, 27	13, 32	NA
Day 36 Post Vaccination 1 (7 Days Post Vaccination 2)	n	13	15	15	14	NA
	GM	106	294	263	378	NA
	95% CI	70, 160	178, 487	188, 368	306, 468	NA
Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)	n	13	14	14	14	NA
	GM	112	351	360	342	NA
	95% CI	71, 177	214, 575	273, 476	267, 438	NA
Day 57 Post Vaccination 1 (28 Days Post Vaccination 2)	n	13	15	14	14	NA
	GM	90	234	276	277	NA
	95% CI	57, 143	153, 358	193, 393	231, 332	NA
Day 119 Post Vaccination 1 (90 Days Post Vaccination 2)	n	13	ND	15	14	NA
	GM	54	ND	182	185	NA
	95% CI	29, 100	ND	112, 296	128, 269	NA

Abbreviations: GM = geometric mean; ID50 = 50% inhibitory dilution; n = number of participants with results available at time point; N = number of participants; NA = not available; ND = not determined.

Source: 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) Table 32.

Table 14: Pseudovirus Neutralization Assay Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 20-0003 – ID50 – All Age Groups 100 µg mRNA-1273

Time Point	Statistic	100 µg mRNA-1273 18-55 years (N=15)	100 µg mRNA-1273 56-70 years (N=10)	100 µg mRNA-1273 ≥71 years (N=10)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	10	10	41
	GM	10	10	10	106
	95% CI	ND	ND	ND	60, 189
Day 29 Post Vaccination 1 (Pre-Vaccination 2)	n	15	10	10	NA
	GM	18	11	20	NA
	95% CI	12, 27	10, 12	12, 33	NA
Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)	n	14	9	10	NA
	GM	360	404	317	NA
	95% CI	273, 476	292, 561	198, 508	NA
Day 57 Post Vaccination 1 (28 Days Post Vaccination 2)	n	14	9	10	NA
	GM	276	424	231	NA
	95% CI	193, 393	267, 673	150, 356	NA
Day 119 Post Vaccination 1 (90 Days Post Vaccination 2)	n	15	9	10	NA
	GM	182	167	109	NA
	95% CI	112, 296	88, 318	68, 175	NA

Abbreviations: GM = geometric mean; ID50 = 50% inhibitory dilution; n = number of participants with results available at time point; N = number of participants; NA = not available; ND = not determined.

Source: 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) Table 32, Table 33, and Table 34.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 Phase 3 Study mRNA-1273-P301

This section contains an overview of the key safety data for the ongoing study mRNA-1273-P301. Refer to IND 19745 (Module 5.3.5.1) for the comprehensive set of safety tables and listings.

In this study, the safety and reactogenicity of mRNA-1273 100 µg compared with placebo administered 28 days apart were assessed in participants 18 years of age and older at increased risk for acquiring COVID-19 based on occupation or location and living circumstances. Reactogenicity (solicited local and/or systemic ARs) was observed in the majority of participants in the mRNA-1273 group and generally increased after the second injection. The rates of local and systemic ARs were higher in the mRNA-1273 group than in the placebo group after each injection. The majority of solicited ARs in the mRNA-1273 group were grade 1 to grade 2 in severity and generally resolved within 3 days or less. The incidence of unsolicited TEAEs, severe TEAEs, and MAAEs during the 28 days after injection was also generally similar in participants who received mRNA-1273 and those who received placebo.

Deaths and SAEs were generally reported at a similar incidence in the mRNA-1273 and placebo groups. There was no evidence of enhanced disease, as fewer cases of severe COVID-19 and COVID-19 were observed in participants who received mRNA-1273 than in those who received placebo.

2.5.5.1.1 Solicited Adverse Reactions

Solicited local and systemic ARs with an onset within 7 days after each injection (ie, the day of dosing and 6 subsequent days) were assessed. Solicited ARs were recorded daily using eDiaries. The solicited ARs assessed included pain, erythema, swelling, and lymphadenopathy as well as fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. The eDiary solicited daily participant reporting of ARs using a structured checklist. Participants recorded such occurrences in an eDiary on the day of each IP injection and for the 6 days after the day of dosing (Day 1 through Day 7). If an AR persisted beyond Day 7, the participant was prompted to continue to record until resolution. Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to grading scales (grade 0 to grade 4) modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials ([DHHS 2007](#)).

Refer to the mRNA-1273-P301 study protocol for additional details on the collection of ARs.

2.5.5.1.1.1 Solicited Local Adverse Reactions

Solicited local ARs were reported by a majority of participants in the mRNA-1273 group and were reported at a higher incidence in the mRNA-1273 group than in the placebo group after each injection ([Table 15](#) and mRNA-1273-P301 [Table 14.3.1.1.3](#)). In the mRNA-1273 group, the most common solicited local AR was pain, and the incidence was similar after the first and second injection (83.7% versus 88.4%, respectively). The majority of solicited local ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, grade 3 solicited local ARs were more common after the second injection than after the first injection (7.0% versus 3.5%); the most common grade 3 solicited local AR after the second injection was pain (575 [4.1%] participants). No grade 4 solicited local ARs were reported, and only grade 3 pain was reported at a frequency > 2% after either injection.

The majority of the solicited local ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after injection (mRNA-1273-P301 [Table 14.3.1.3.1](#) and [Table 14.3.1.3.2](#)) and generally persisted for a median of 1 to 3 days (mRNA-1273-P301 [Table 14.3.1.4.1](#) and [Table 14.3.1.4.2](#)). There was a higher incidence of participants who reported solicited local ARs that persisted beyond 7 days in the mRNA-1273 group than in the placebo group after the first injection (2.2% versus 0.7%, respectively) and after the second injection (2.0% versus 0.8%), with no notable difference between the first and second injection (mRNA-1273-P301 [Table 14.3.1.6.1](#), [Table 14.3.1.6.2](#), and [Table 14.3.1.6.3](#)).

Table 15: Summary of Participants With Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade in Study mRNA-1273-P301 (Solicited Safety Set)

Category Grade	First Injection ^a			Second Injection ^a		
	Placebo (N=15154) n (%)	mRNA-1273 (N=15167) n (%)	Total (N=30322) n (%)	Placebo (N=13870) n (%)	mRNA-1273 (N=13947) n (%)	Total (N=27817) n (%)
Solicited local adverse reactions – N1	15150	15163	30314	13866	13944	27810
Any solicited local adverse reactions, n (%)	2998 (19.8)	12765 (84.2)	15763 (52.0)	2607 (18.8)	12381 (88.8)	14988 (53.9)
95% CI	19.2, 20.4	83.6, 84.8	51.4, 52.6	18.2, 19.5	88.3, 89.3	53.3, 54.5
Grade 1	2839 (18.7)	10728 (70.8)	13567 (44.8)	2459 (17.7)	8375 (60.1)	10834 (39.0)
Grade 2	81 (0.5)	1508 (9.9)	1589 (5.2)	78 (0.6)	3028 (21.7)	3106 (11.2)
Grade 3	78 (0.5)	529 (3.5)	607 (2.0)	70 (0.5)	978 (7.0)	1048 (3.8)
Grade 4	0	0	0	0	0	0
Pain - N1	15150	15163	30314	13866	13944	27810
Any	2660 (17.6)	12690 (83.7)	15350 (50.6)	2363 (17.0)	12325 (88.4)	14688 (52.8)
Grade 3	55 (0.4)	417 (2.8)	472 (1.6)	38 (0.3)	575 (4.1)	613 (2.2)
Erythema (redness) - N1 ^b	15150	15162	30313	13866	13944	27810
Any	65 (0.4)	431 (2.8)	496 (1.6)	55 (0.4)	1193 (8.6)	1248 (4.5)
Grade 3	13 (<0.1)	42 (0.3)	55 (0.2)	15 (0.1)	281 (2.0)	296 (1.1)
Swelling (hardness) - N1	15150	15162	30313	13866	13944	27810
Any	52 (0.3)	934 (6.2)	986 (3.3)	48 (0.3)	1695 (12.2)	1743 (6.3)
Grade 3	6 (<0.1)	82 (0.5)	88 (0.3)	11 (<0.1)	245 (1.8)	256 (0.9)
Lymphadenopathy - N1 ^c	15150	15162	30313	13866	13944	27810
Any	722 (4.8)	1553 (10.2)	2275 (7.5)	534 (3.9)	1956 (14.0)	2490 (9.0)
Grade 3	27 (0.2)	48 (0.3)	75 (0.2)	18 (0.1)	66 (0.5)	84 (0.3)

Abbreviations: Any = grade 1 or higher; eDiary = electronic diary; N1 = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Note: Percentages were based on the number of exposed participants who submitted any data for the event (N1). 95% CI was calculated using the Clopper-Pearson method.

^a The First and Second Injection Solicited Safety Set consist of all participants in the Solicited Safety Set who received the first or second study injection and contributed any SAR data (eDiary) from the time of first or second study injection through the following 6 days.

^b Toxicity grade for erythema (redness) is defined as: grade 3 = ≥ 100 mm.

^c Lymphadenopathy = localized axillary swelling or tenderness ipsilateral to the vaccination arm.

Source: mRNA-1273-P301 [Table 14.3.1.1.1](#) and [Table 14.3.1.1.2](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.1.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.1.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.1.3	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Grade - Solicited Safety Set
14.3.1.3.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Onset Day - First Injection Solicited Safety Set
14.3.1.3.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Onset Day - Second Injection Solicited Safety Set
14.3.1.4.1	Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection - First Injection Solicited Safety Set
14.3.1.4.2	Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection - Second Injection Solicited Safety Set
14.3.1.6.1	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.6.2	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.6.3	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Any Injection by Grade - Solicited Safety Set

2.5.5.1.1.2 Solicited Systemic Adverse Reactions

Solicited systemic ARs were reported by the majority of participants in the mRNA-1273 group and were more prevalent in the mRNA-1273 group than in the placebo group after each IP injection ([Table 16](#) and mRNA-1273-P301 [Table 14.3.1.1.3](#)). In the mRNA-1273 group, the incidence and severity of solicited systemic ARs appeared to increase after the second injection. In the mRNA-1273 group, the most common solicited systemic ARs after the first injection were fatigue and headache, and the frequency of reported events increased after the second injection. Frequently reported events after the second injection also included myalgia, arthralgia, and chills. The majority of solicited systemic ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, the most common grade 3 solicited systemic ARs after the second injection included fatigue, myalgia, headache, and arthralgia.

The majority of the solicited systemic ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after IP injection (mRNA-1273-P301 [Table 14.3.1.3.1](#) and [Table 14.3.1.3.2](#)) and generally persisted for a median of 1 to 2 days (mRNA-1273-P301 [Table 14.3.1.4.1](#) and [Table 14.3.1.4.2](#)). The incidence of participants who reported solicited systemic ARs that persisted beyond 7 days was similar between the mRNA-1273 and placebo groups (9.7% versus 8.7%, respectively), with no notable difference between the first and second injection (mRNA-1273-P301 [Table 14.3.1.6.1](#), [Table 14.3.1.6.2](#), and [Table 14.3.1.6.3](#)).

Table 16: Summary of Participants With Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade in Study mRNA-1273-P301 (Solicited Safety Set)

Category Grade	First Injection ^a			Second Injection ^a		
	Placebo (N=15154) n (%)	mRNA-1273 (N=15167) n (%)	Total (N=30322) n (%)	Placebo (N=13870) n (%)	mRNA-1273 (N=13947) n (%)	Total (N=27817) n (%)
Solicited systemic adverse reactions – N1	15154	15166	30321	13869	13947	27816
Any solicited systemic adverse reactions, n (%)	6398 (42.2)	8321 (54.9)	14719 (48.5)	5069 (36.5)	11064 (79.3)	16133 (58.0)
95% CI	41.4, 43.0	54.1, 55.7	48.0, 49.1	35.7, 37.4	78.6, 80.0	57.4, 58.6
Grade 1	4345 (28.7)	5370 (35.4)	9715 (32.0)	3373 (24.3)	3563 (25.5)	6936 (24.9)
Grade 2	1738 (11.5)	2499 (16.5)	4237 (14.0)	1420 (10.2)	5301 (38.0)	6721 (24.2)
Grade 3	309 (2.0)	447 (2.9)	756 (2.5)	273 (2.0)	2188 (15.7)	2461 (8.8)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)	3 (<0.1)	12 (<0.1)	15 (<0.1)
Fever – N1 ^b	15152	15163	30316	13864	13939	27803
Any	46 (0.3)	115 (0.8)	161 (0.5)	43 (0.3)	2172 (15.6)	2215 (8.0)
Grade 3	2 (<0.1)	11 (<0.1)	13 (<0.1)	1 (<0.1)	186 (1.3)	187 (0.7)
Grade 4	6 (<0.1)	4 (<0.1)	10 (<0.1)	3 (<0.1)	11 (<0.1)	14 (<0.1)
Headache – N1	15149	15162	30312	13866	13944	27810
Any	4027 (26.6)	4952 (32.7)	8979 (29.6)	3252 (23.5)	8165 (58.6)	11417 (41.1)
Grade 3	196 (1.3)	271 (1.8)	467 (1.5)	156 (1.1)	622 (4.5)	778 (2.8)
Fatigue – N1	15149	15162	30312	13864	13944	27808
Any	4133 (27.3)	5635 (37.2)	9768 (32.2)	3225 (23.3)	9096 (65.2)	12321 (44.3)
Grade 3	106 (0.7)	150 (1.0)	256 (0.8)	101 (0.7)	1347 (9.7)	1448 (5.2)
Grade 4	0	1 (<0.1)	1 (<0.1)	0	0	0
Myalgia – N1	15149	15162	30312	13865	13944	27809
Any	2069 (13.7)	3441 (22.7)	5510 (18.2)	1697 (12.2)	8036 (57.6)	9733 (35.0)
Grade 3	47 (0.3)	90 (0.6)	137 (0.5)	49 (0.4)	1233 (8.8)	1282 (4.6)

Category Grade	First Injection ^a			Second Injection ^a		
	Placebo (N=15154) n (%)	mRNA-1273 (N=15167) n (%)	Total (N=30322) n (%)	Placebo (N=13870) n (%)	mRNA-1273 (N=13947) n (%)	Total (N=27817) n (%)
Arthralgia – N1	15149	15162	30312	13864	13944	27808
Any	1783 (11.8)	2510 (16.6)	4293 (14.2)	1468 (10.6)	5937 (42.6)	7405 (26.6)
Grade 3	37 (0.2)	60 (0.4)	97 (0.3)	43 (0.3)	725 (5.2)	768 (2.8)
Grade 4	0	1 (<0.1)	1 (<0.1)	0	0	0
Nausea/vomiting – N1	15149	15162	30312	13864	13944	27808
Any	1074 (7.1)	1263 (8.3)	2337 (7.7)	883 (6.4)	2634 (18.9)	3517 (12.6)
Grade 3	12 (<0.1)	10 (<0.1)	22 (<0.1)	11 (<0.1)	18 (0.1)	29 (0.1)
Grade 4	0	0	0	0	1 (<0.1)	1 (<0.1)
Chills – N1	15149	15162	30312	13864	13944	27808
Any	878 (5.8)	1253 (8.3)	2131 (7.0)	755 (5.4)	6100 (43.7)	6855 (24.7)
Grade 3	14 (<0.1)	24 (0.2)	38 (0.1)	16 (0.1)	178 (1.3)	194 (0.7)

Abbreviations: Any = grade 1 or higher; eDiary = electronic diary; N1 = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Note: Percentages were based on the number of exposed participants who submitted any data for the event (N1). 95% CI was calculated using the Clopper-Pearson method.

^a The First and Second Injection Solicited Safety Set consist of all participants in the Solicited Safety Set who received the first or second study injection and contributed any SAR data (eDiary) from the time of first or second study injection through the following 6 days.

^b Toxicity grade for fever is defined as: grade 3 = 39°C to 40°C; grade 4 = >40°C.

Source: mRNA-1273-P301 [Table 14.3.1.1.1](#) and [Table 14.3.1.1.2](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.1.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.1.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.1.3	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Grade - Solicited Safety Set
14.3.1.3.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Onset Day - First Injection Solicited Safety Set
14.3.1.3.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Onset Day - Second Injection Solicited Safety Set
14.3.1.4.1	Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection - First Injection Solicited Safety Set
14.3.1.4.2	Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection - Second Injection Solicited Safety Set
14.3.1.6.1	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.6.2	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.6.3	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Any Injection by Grade - Solicited Safety Set

2.5.5.1.1.3 Subgroup Analyses of Solicited Adverse Reactions

2.5.5.1.1.3.1 Age Group

Local ARs were more commonly reported by younger adults (≥ 18 to < 65 years; 87.4% and 90.5% after the first and second injection of mRNA-1273, respectively) than older adults (≥ 65 years; 74.6% and 83.9% after the first and second injection of mRNA-1273, respectively) (mRNA-1273-P301 [Table 14.3.1.1.4](#), [Table 14.3.1.1.5](#), and [Table 14.3.1.1.6](#)). Systemic ARs were also more commonly reported by younger adults (≥ 18 to < 65 years; 57.0% and 81.9% after the first and second injection of mRNA-1273, respectively) than older adults (≥ 65 years; 48.3% and 71.9% after first and second injection of mRNA-1273, respectively) (mRNA-1273-P301 [Table 14.3.1.1.4](#) and [Table 14.3.1.1.5](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.1.4	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Age Group and Grade - First Injection Solicited Safety Set
14.3.1.1.5	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Age Group and Grade - Second Injection Solicited Safety Set
14.3.1.1.6	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade - Solicited Safety Set

2.5.5.1.1.3.2 Baseline SARS-CoV-2 Status

The incidence of solicited local ARs after the first injection in participants baseline negative for SARS-CoV-2 at baseline was 84.5% in the mRNA-1273 group and 19.7% in the placebo group. In baseline positive participants, the incidence was 71.8% and 17.4%, respectively (mRNA-1273-P301 [Table 14.3.1.1.7](#)). After the second injection, in baseline negative participants, the incidence of solicited local ARs was 89.0% in the mRNA-1273 group and 18.7% in the placebo group. In baseline positive participants at baseline, the incidence was 74.4% and 17.5%, respectively (mRNA-1273-P301 [Table 14.3.1.1.8](#)). The incidence of solicited systemic ARs after the first injection in participants baseline negative for SARS-CoV-2 at baseline was 54.6% in the mRNA-1273 group and 42.2% in the placebo group. In baseline positive participants, the incidence was 61.2% and 35.3%, respectively (mRNA-1273-P301 [Table 14.3.1.1.7](#)). After the second injection, the incidence of solicited systemic ARs in baseline negative participants was 79.5% in mRNA-1273 group and 36.5% in the placebo group, and in baseline positive participants, the incidence was 66.5% and 31.0%, respectively (mRNA-1273-P301 [Table 14.3.1.1.8](#)).

Overall, the frequency or severity of solicited local and systemic ARs was not higher in baseline positive participants than in baseline negative participants.

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.1.7	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Baseline SARS-CoV-2 Status and Grade – First Injection Solicited Safety Set
14.3.1.1.8	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Baseline SARS-CoV-2 Status and Grade – Second Injection Solicited Safety Set

2.5.5.1.2 Unsolicited Adverse Events

Unsolicited AEs observed or reported during the 28 days after each IP injection (ie, the day of dosing and 27 subsequent days) were collected. A TEAE is defined as any event occurring during the study and not present before exposure to the IP or any event already present that worsened after exposure to IP. Adverse events leading to discontinuation from dosing and/or study participation, SAEs, and MAAEs are being collected through completion of the study or until withdrawal from the study. The determination of severity for all unsolicited AEs was made by

the investigator based upon medical judgment and the definitions of severity as mild, moderate, or severe.

Refer to the mRNA-1273-P301 study protocol for additional details on the collection of unsolicited AEs.

2.5.5.1.2.1 Summary of Unsolicited Adverse Events

The incidences of unsolicited TEAEs, severe TEAEs, and MAAEs during the 28 days after any injection were generally similar in participants who received mRNA-1273 and those who received placebo ([Table 17](#)). The majority of unsolicited TEAEs were considered not related to the IP; treatment-related TEAEs were reported in 7.4% and 4.0% of participants in the mRNA-1273 and placebo groups, respectively. The difference appears to result from solicited ARs that were assessed as severe (grade 3) or required medical attention.

The incidence of severe TEAEs during the 28 days after any injection was low (1.3% overall), with no notable differences across treatments (1.4% for mRNA-1273 and 1.3% for placebo; [Table 17](#)). The majority of severe TEAEs were not related to IP.

The incidence of MAAEs during the 28 days after injection was generally similar in the mRNA-1273 and placebo groups (8.0% versus 8.4%, respectively; [Table 17](#)). Treatment-related MAAEs were reported in 0.8% and 0.5% of participants in the mRNA-1273 and placebo groups, respectively.

The incidence of SAEs during the 28 days after injection was low (0.6% overall), with no notable differences between treatment groups (0.5% for mRNA-1273 and 0.6% for placebo). Few participants (< 0.1% for mRNA-1273 and placebo groups) reported treatment-related SAEs ([Table 17](#)).

Deaths were reported in 4 participants in the mRNA-1273 group and 4 participants in the placebo group during the overall stage as of 11 Nov 2020 (data snapshot date), and none were considered related to the IP (mRNA-1273-P301 [Table 14.3.1.7.3](#)). Two deaths occurred in the mRNA-1273 group and 3 deaths occurred in the placebo group within 28 days after any injection ([Table 17](#); [Section 2.5.5.1.2.6.1](#)). The safety narratives are provided in [Appendix 3](#) ([Section 2.5.8.3](#)).

The incidence of participants who discontinued IP due to TEAEs during the 28 days after injection was low (0.4% overall), and discontinuations of IP due to TEAEs were less frequent in

the mRNA-1273 group than in the placebo group (0.3% for mRNA-1273 and 0.5% for placebo). No participants discontinued from participation in the study due to a TEAE ([Table 17](#)).

Table 17: Summary of Unsolicited TEAEs up to 28 Days After Any Injection in Study mRNA-1273-P301 (Safety Set)

	Placebo (N=15165) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30350) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination			
All	2949 (19.4)	3325 (21.9)	6274 (20.7)
Serious	86 (0.6)	82 (0.5)	168 (0.6)
Fatal	3 (<0.1)	2 (<0.1)	5 (<0.1)
Medically attended	1276 (8.4)	1215 (8.0)	2491 (8.2)
Leading to discontinuation from study vaccine	71 (0.5)	41 (0.3)	112 (0.4)
Leading to discontinuation from participation in the study	0	0	0
Severe	190 (1.3)	216 (1.4)	406 (1.3)
Unsolicited TEAEs related to study vaccination			
All	609 (4.0)	1127 (7.4)	1736 (5.7)
Serious	4 (<0.1)	5 (<0.1)	9 (<0.1)
Fatal	0	0	0
Medically attended	73 (0.5)	122 (0.8)	195 (0.6)
Leading to discontinuation from study vaccine	13 (<0.1)	15 (<0.1)	28 (<0.1)
Leading to discontinuation from participation in the study	0	0	0
Severe	29 (0.2)	70 (0.5)	99 (0.3)

Note: 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 were based on the number of safety participants.

Source: mRNA-1273-P301 [Table 14.3.1.7.1](#).

The numbers and titles of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days After Any Injection - Safety Set
14.3.1.7.3	Summary of Unsolicited TEAE in Overall Stage - Safety Set

2.5.5.1.2.2 Most Common Unsolicited Adverse Events

The incidence of unsolicited TEAEs in the 28 days after injection was generally similar between participants who received mRNA-1273 (3325 [21.9%] participants) and those who received

placebo (2949 [19.4%] participants; [Table 18](#)). Overall, the most commonly reported unsolicited TEAE in all participants in the 28 days after injection by PT was headache (844 [2.8%] participants). In the mRNA-1273 group, unsolicited TEAEs reported in $\geq 2\%$ of participants in the 28 days after injection by PT included headache and fatigue.

Similar results were noted during the overall study period as of 11 Nov 2020 (data snapshot date) (mRNA-1273-P301 [Table 14.3.1.8.3](#)).

Table 18: Summary of Most Common Unsolicited TEAE Reported by at Least 1% of Participants in Any Treatment Group up to 28 Days After Any Injection in Study mRNA-1273-P301 (Safety Set)

System Organ Class Preferred Term	Placebo (N=15165) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30350) n (%)
Number of participants reporting unsolicited AEs	2949 (19.4)	3325 (21.9)	6274 (20.7)
Number of unsolicited AEs	5348	6157	11505
Nervous system disorders	552 (3.6)	624 (4.1)	1176 (3.9)
Headache	409 (2.7)	435 (2.9)	844 (2.8)
Respiratory, thoracic and mediastinal disorders	522 (3.4)	480 (3.2)	1002 (3.3)
Cough	143 (0.9)	148 (1.0)	291 (1.0)
Oropharyngeal pain	184 (1.2)	137 (0.9)	321 (1.1)
Gastrointestinal disorders	387 (2.6)	426 (2.8)	813 (2.7)
Diarrhoea	147 (1.0)	178 (1.2)	325 (1.1)
Musculoskeletal and connective tissue disorders	521 (3.4)	586 (3.9)	1107 (3.6)
Arthralgia	152 (1.0)	174 (1.1)	326 (1.1)
Myalgia	138 (0.9)	172 (1.1)	310 (1.0)
General disorders and administration site conditions	560 (3.7)	894 (5.9)	1454 (4.8)
Fatigue	307 (2.0)	344 (2.3)	651 (2.1)
Injection site pain	49 (0.3)	147 (1.0)	196 (0.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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 were based on the number of safety participants. All AEs were coded using MedDRA Version 23.0.

Uncoded AEs (from 397 participants) are reported at this interim database lock; however, all AEs will be coded by the time of final database lock and clinical study report submission.

Source: mRNA-1273-P301 [Table 14.3.1.8.1](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.8.1	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.8.3	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set

2.5.5.1.2.3 Treatment-Related Unsolicited Adverse Events

Treatment-related TEAEs were reported by 1127 (7.4%) participants who received mRNA-1273 and 609 (4.0%) participants who received placebo (mRNA-1273-P301 [Table 14.3.1.11.1](#)). In the mRNA-1273 group, treatment-related TEAEs reported in $\geq 1\%$ of participants in the 28 days after any injection by PT included fatigue (198 [1.3%] participants in the mRNA-1273 group and 159 [1.0%] participants in the placebo group) and headache (191 [1.3%] participants in the mRNA-1273 group and 122 [0.8%] participants in the placebo group).

The number and title of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.3.1.11.1	Subject Incidence of Unsolicited Treatment-Related TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set

2.5.5.1.2.4 Unsolicited Severe Adverse Events

Severe AEs were defined as AEs that prevented the participant's daily activity and required intensive therapeutic intervention.

The incidence of unsolicited severe TEAEs in the 28 days after injection was low (406 [1.3%] participants overall), with no notable differences noted between treatment groups (216 [1.4%] participants for mRNA-1273 and 190 [1.3%] participants for placebo; [Table 19](#)).

The majority of severe TEAEs were not assessed as related to the IP. Treatment-related severe TEAEs were reported by 70 participants (0.5%) who received mRNA-1273 and 29 (0.2%) participants who received placebo (mRNA-1273-P301 [Table 14.3.1.18.1](#)).

Table 19: Summary of Unsolicited Severe TEAEs Reported by at Least 5 Participants in Any Treatment Group up to 28 Days After Any Injection in Study mRNA-1273-P301 (Safety Set)

System Organ Class Preferred Term	Placebo (N=15165) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30350) n (%)
Number of participants reporting unsolicited severe AEs	190 (1.3)	216 (1.4)	406 (1.3)
Number of unsolicited severe AEs	225	275	500
Nervous system disorders	21 (0.1)	27 (0.2)	48 (0.2)
Headache	13 (<0.1)	19 (0.1)	32 (0.1)
Cardiac disorders	13 (<0.1)	11 (<0.1)	24 (<0.1)
Bradycardia	5 (<0.1)	3 (<0.1)	8 (<0.1)
Vascular disorders	39 (0.3)	28 (0.2)	67 (0.2)
Hypertension	29 (0.2)	22 (0.1)	51 (0.2)
Musculoskeletal and connective tissue disorders	18 (0.1)	24 (0.2)	42 (0.1)
Myalgia	0	11 (<0.1)	11 (<0.1)
Arthralgia	2 (<0.1)	10 (<0.1)	12 (<0.1)
Back pain	5 (<0.1)	1 (<0.1)	6 (<0.1)
General disorders and administration site conditions	13 (<0.1)	43 (0.3)	56 (0.2)
Fatigue	7 (<0.1)	12 (<0.1)	19 (<0.1)
Injection site erythema	0	11 (<0.1)	11 (<0.1)
Injection site pain	1 (<0.1)	6 (<0.1)	7 (<0.1)
Investigations	13 (<0.1)	22 (0.1)	35 (0.1)
Blood pressure increased	7 (<0.1)	10 (<0.1)	17 (<0.1)
Blood pressure systolic increased	6 (<0.1)	8 (<0.1)	14 (<0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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 were based on the number of safety participants. All AEs were coded using MedDRA Version 23.0.

Uncoded AEs (from 16 participants) are reported at this interim database lock; however, all AEs will be coded by the time of final database lock and clinical study report submission.

Source: mRNA-1273-P301 [Table 14.3.1.17.1](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.17.1	Subject Incidence of Unsolicited Severe TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.18.1	Subject Incidence of Unsolicited Treatment-Related Severe TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set

2.5.5.1.2.5 Unsolicited Medically Attended Adverse Events

An MAAE was an AE that led to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (including unscheduled visits to the study site).

The incidence of MAAEs within 28 days of injection was generally similar between participants who received mRNA-1273 (1215 [8.0%] participants) and those who received placebo (1276 [8.4%] participants; mRNA-1273-P301 [Table 14.3.1.19.1](#)).

The incidence of MAAEs was similar in the mRNA-1273 and placebo groups (9.3% and 10.1%, respectively) during the overall study period as of 11 Nov 2020 (data snapshot date) (mRNA-1273-P301 [Table 14.3.1.19.3](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.19.1	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.19.3	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set

2.5.5.1.2.6 Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

2.5.5.1.2.6.1 Deaths

A total of 8 deaths were reported in Study mRNA-1273-P301 through 11 Nov 2020 (data snapshot date), with 4 occurring in the mRNA-1273 group and 4 occurring in the placebo group (mRNA-1273-P301 [Table 14.3.1.7.3](#)). A summary of participants with SAEs resulting in death is presented in [Table 20](#). None were considered related to IP or were due to COVID-19. Details for each participant are available in mRNA-1273-P301 Listing 16.2.12 (details of death), Listing 16.2.7.9 (details of SAE), and [Appendix 3](#) ([Section 2.5.8.3](#), safety narratives).

Table 20: Participants with SAEs Resulting in Death in Study mRNA-1273-P301

Treatment Assignment	Preferred Term(s)
mRNA-1273	Cardio-respiratory arrest
mRNA-1273	Completed suicide
mRNA-1273	Head injury
mRNA-1273	Myocardial infarction
Placebo	Systemic inflammatory response syndrome; Dermatitis bullous
Placebo	Myocardial infarction
Placebo	Abdominal injury (intra-abdominal perforation)
Placebo	Cardio-respiratory arrest

Source: mRNA-1273-P301 Listing 16.2.7.9.

The number and title of the mRNA-1273-P301 table referenced in this section are as follows:

Table Number	Title
14.3.1.7.3	Summary of Unsolicited TEAE in Overall Stage - Safety Set

2.5.5.1.2.6.2 Other Serious Adverse Events

The incidence of other SAEs in the 28 days after IP injection was similar between treatment groups ([Table 21](#)).

The incidence of treatment-related SAEs in the 28 days after IP injection was similar between treatment groups (mRNA-1273-P301 [Table 14.3.1.14.1](#)).

The incidence of SAEs was similar in the mRNA-1273 and placebo groups during the overall study period as of 11 Nov 2020 (data snapshot date) (mRNA-1273-P301 [Table 14.3.1.13.3](#) and [Table 14.3.1.14.3](#)).

Table 21: Summary of Serious TEAEs Reported by at Least 2 Participants in Any Treatment Group up to 28 Days After Any Injection in Study mRNA-1273-P301 (Safety Set)

System Organ Class Preferred Term	Placebo (N=15165) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30350) n (%)
Number of participants reporting serious TEAEs	86 (0.6)	82 (0.5)	168 (0.6)
Number of serious TEAEs	111	109	220
Infections and infestations	16 (0.1)	10 (<0.1)	26 (<0.1)
Pneumonia	3 (<0.1)	3 (<0.1)	6 (<0.1)
Appendicitis	3 (<0.1)	1 (<0.1)	4 (<0.1)
COVID-19	3 (<0.1)	0	3 (<0.1)
Urinary tract infection	2 (<0.1)	0	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (<0.1)	6 (<0.1)	10 (<0.1)
Prostate cancer	2 (<0.1)	2 (<0.1)	4 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)	2 (<0.1)	3 (<0.1)
Dehydration	1 (<0.1)	2 (<0.1)	3 (<0.1)
Psychiatric disorders	6 (<0.1)	3 (<0.1)	9 (<0.1)
Depression	2 (<0.1)	0	2 (<0.1)
Nervous system disorders	6 (<0.1)	7 (<0.1)	13 (<0.1)
Syncope	2 (<0.1)	2 (<0.1)	4 (<0.1)
Cardiac disorders	11 (<0.1)	12 (<0.1)	23 (<0.1)
Atrial fibrillation	2 (<0.1)	3 (<0.1)	5 (<0.1)
Myocardial infarction	0	3 (<0.1)	3 (<0.1)
Cardiac failure congestive	1 (<0.1)	2 (<0.1)	3 (<0.1)
Coronary artery disease	2 (<0.1)	1 (<0.1)	3 (<0.1)
Vascular disorders	8 (<0.1)	4 (<0.1)	12 (<0.1)
Hypertension	1 (<0.1)	2 (<0.1)	3 (<0.1)
Hypertensive emergency	2 (<0.1)	0	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	11 (<0.1)	5 (<0.1)	16 (<0.1)
Pulmonary embolism	3 (<0.1)	2 (<0.1)	5 (<0.1)
Chronic obstructive pulmonary disease	2 (<0.1)	0	2 (<0.1)
Gastrointestinal disorders	6 (<0.1)	11 (<0.1)	17 (<0.1)
Colitis	1 (<0.1)	2 (<0.1)	3 (<0.1)
Nausea	1 (<0.1)	2 (<0.1)	3 (<0.1)
Abdominal pain	2 (<0.1)	0	2 (<0.1)
Musculoskeletal and connective tissue disorders	4 (<0.1)	8 (<0.1)	12 (<0.1)
Renal and urinary disorders	1 (<0.1)	4 (<0.1)	5 (<0.1)
Nephrolithiasis	0	4 (<0.1)	4 (<0.1)

System Organ Class Preferred Term	Placebo (N=15165) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30350) n (%)
General disorders and administration site conditions	6 (<0.1)	5 (<0.1)	11 (<0.1)
Swelling face	1 (<0.1)	2 (<0.1)	3 (<0.1)
Chest pain	2 (<0.1)	1 (<0.1)	3 (<0.1)
Injury, poisoning and procedural complications	8 (<0.1)	8 (<0.1)	16 (<0.1)
Cervical vertebral fracture	0	2 (<0.1)	2 (<0.1)
Road traffic accident	0	2 (<0.1)	2 (<0.1)
Hip fracture	2 (<0.1)	1 (<0.1)	3 (<0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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 were based on the number of safety participants. All AEs were coded using MedDRA Version 23.0.

^a Uncoded AEs (from 10 participants) are reported at this interim database lock; however, all AEs will be coded by the time of final database lock and clinical study report submission.

Source: mRNA-1273-P301 [Table 14.3.1.13.1](#).

Details for each participant with an SAE are available in mRNA-1273-P301 Listing 16.2.7.9 and [Appendix 3 \(Section 2.5.8.3, safety narratives\)](#).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.13.1	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.13.3	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set
14.3.1.14.1	Subject Incidence of Serious Treatment-Related TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.14.3	Subject Incidence of Serious Treatment-Related TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set

2.5.5.1.2.6.3 Other Clinically Meaningful Unsolicited Adverse Events

2.5.5.1.2.6.3.1 Discontinuation From Investigational Product or Study Participation

The incidence of participants reporting TEAEs leading to discontinuation from the IP in the overall study period as of 11 Nov 2020 (data snapshot date) was low (0.4% overall), and TEAEs leading to discontinuation from the IP occurred less frequently in the mRNA-1273 group (45 [0.3%] participants for mRNA-1273 group and 85 [0.6%] participants for placebo group; mRNA-1273-P301 [Table 14.3.1.15.1](#)). Of the TEAEs leading to discontinuation of IP in

≥ 2 participants in the mRNA-1273 group, those with a higher incidence in the mRNA-1273 group than the placebo group included injection site erythema and urticaria (3 [$< 0.1\%$] participants each).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.15.1	Subject Incidence of Unsolicited TEAE Leading to Discontinuation from Study Vaccine by System Organ Class and Preferred Term - Safety Set

2.5.5.1.2.6.3.2 Delayed Injection Site Reactions

During the study, several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritis. A review of these events showed that the vast majority of the unsolicited TEAEs categorized as local injection or vaccination site reactions in the second week after immunization were a subset of the solicited local AR with a duration beyond Day 7 (mRNA-1273-P301 [Table 14.3.1.6.1](#) and [Table 14.3.1.6.2](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.6.1	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.6.2	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set

2.5.5.1.2.6.3.3 Vaccine Harm: COVID-19 and Severe COVID-19

Vaccine harm was monitored by the DSMB, which received unblinded case counts on a continuous basis, and prespecified rules based on an imbalance in the number of severe COVID-19 cases and all COVID-19 cases starting at the time of randomization were described in the DSMB analysis plan. The prespecified criteria for harm have not been met at any time from study onset through the interim analysis. There were fewer cases of severe COVID-19 (0 cases in the mRNA-1273 group versus 16 cases in the placebo group) or COVID-19 of any severity (7 cases in the mRNA-1273 group versus 128 cases in the placebo group) from time of randomization in participants who received mRNA-1273 than in those who received placebo; thus, there was no evidence of ERD (mRNA-1273-P301 [Table 14.2.2.1.2.5.1](#) and [Table 14.2.2.2.2.5.1](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.2.2.1.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - Per-Protocol Set
14.2.2.2.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting After Randomization - Per-Protocol Set

2.5.5.1.2.7 Subgroup Analyses of Unsolicited Adverse Reactions

2.5.5.1.2.7.1 Age Group

The incidence of unsolicited TEAEs within 28 days after any IP injection regardless of relationship was similar in younger adults (≥ 18 to < 65 years of age) and older participants (≥ 65 years of age) who received mRNA-1273 (21.5% versus 23.1%, respectively). The incidence of unsolicited TEAEs assessed as treatment-related was also similar in younger and older adults (7.6% versus 6.9%, respectively). As noted in the overall population, the incidences of MAAEs and severe TEAEs were higher in the mRNA-1273 group than in the placebo group regardless of age (mRNA-1273-P301 [Table 14.3.1.7.1](#), [Table 14.3.1.7.3](#), and [Table 14.3.1.7.4](#)). There was no apparent effect of age on the relative incidence of these TEAEs by a vaccine group (mRNA-1273-P301 [Table 14.3.1.7.4](#), [Table 14.3.1.7.6](#), [Table 14.3.1.8.4](#), and [Table 14.3.1.8.6](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days After Any Injection - Safety Set
14.3.1.7.3	Summary of Unsolicited TEAE in Overall Stage - Safety Set
14.3.1.7.4	Summary of Unsolicited TEAE by Age Group up to 28 Days After Any Injection - Safety Set
14.3.1.7.6	Summary of Unsolicited TEAE by Age Group in Overall Stage - Safety Set
14.3.1.8.4	Subject Incidence of Unsolicited TEAE by Age Group, System Organ Class and Preferred Term up to 28 Days after Any Injection - Safety Set
14.3.1.8.6	Subject Incidence of Unsolicited TEAE by Age Group, System Organ Class, and Preferred Term in Overall Stage - Safety Set

2.5.5.1.2.7.2 Baseline SARS-CoV-2 Status

In the overall stage as of 11 Nov 2020 (data snapshot date), the incidence of unsolicited TEAEs among participants with positive baseline status for SARS-CoV-2 was 16.1% in the mRNA-1273 group and 20.4% in the placebo group. Among participants with negative baseline status for SARS-CoV-2, the incidence of unsolicited TEAEs was 24.0% in the mRNA group and 22.0% in

the placebo group (mRNA-1273-P301 [Table 14.3.1.7.7](#), [Table 14.3.1.7.9](#), [Table 14.3.1.8.7](#), and [Table 14.3.1.8.9](#)).

The numbers and titles of the mRNA-1273-P301 tables referenced in this section are as follows:

Table Number	Title
14.3.1.7.7	Summary of Unsolicited TEAE by Baseline SARS-CoV-2 Status up to 28 Days After Any Injection - Safety Set
14.3.1.7.9	Summary of Unsolicited TEAE by Baseline SARS-CoV-2 Status in Overall Stage - Safety Set
14.3.1.8.7	Subject Incidence of Unsolicited TEAE by Baseline SARS-CoV-2 Status, System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.8.9	Subject Incidence of Unsolicited TEAE by Baseline SARS-CoV-2 Status, System Organ Class and Preferred Term in Overall Stage - Safety Set

2.5.5.1.3 Other Safety Data

2.5.5.1.3.1 Pregnancies

Details of all pregnancies in female participants are being collected from first day of dosing until study completion. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs.

Twelve pregnancies have been reported in Study mRNA-1273-P301; 6 in the mRNA-1273 group and 6 in the placebo group ([Table 22](#)). As of 11 Nov 2020 (data snapshot date), 9 of the 12 pregnancies were ongoing with no reported complications. One participant (placebo group) experienced spontaneous abortion at approximately 7 gestation weeks; this SAE was considered not related to the IP. One participant in the placebo group had an elective abortion at approximately 6 gestation weeks; this SAE was considered not related to the IP. One participant in the placebo group was lost to follow-up, and the pregnancy outcome is unknown.

Table 22: Pregnancies in Female Participants in Study mRNA-1273-P301

Treatment Group	Expected Due Date (calculated by LMP)	Previous Pregnancies	Date of First Dose	Date of Second Dose (if applicable)	Outcome
Placebo	Mar 17, 2021	3 Previous pregnancies: 2 live births and 1 abortion	Aug 3, 2020	N/A	Ongoing
Placebo	Jun 1, 2021	13 Previous pregnancies: 11 abortions (all induced), 2 live births	Aug 26, 2020	N/A	Spontaneous abortion
Placebo	Jun 7, 2021	None reported	Aug 28, 2020	N/A	Elective termination
Placebo	Jun 2, 2021	1 Live birth	Aug 24, 2020	N/A	Ongoing
Placebo	May 26, 2021	2 Live births	Aug 4, 2020	Sep 1, 2020	Ongoing
Placebo	Jun 6, 2021	None reported	Sep 9, 2020	Oct 7, 2020	Unknown (participant was lost to follow-up)
mRNA-1273	May 18, 2021	1 Previous pregnancy	Aug 7, 2020	Sep 4, 2020	Ongoing
mRNA-1273	Apr 1, 2021	None reported	Aug 10, 2020	N/A	Ongoing
mRNA-1273	May 19, 2021	None reported	Aug 14, 2020	N/A	Ongoing
mRNA-1273	Jun 7, 2021	2 Previous pregnancies: 1 spontaneous abortion and 1 ectopic pregnancy	Aug 24, 2020	N/A	Ongoing
mRNA-1273	Unknown	5 Previous pregnancies: 2 live births, 2 spontaneous abortions, and 1 elective termination	Aug 13, 2020	Sep 10, 2020	Ongoing
mRNA-1273	Jul 2, 2021	2 Live births	Aug 9, 2020	Sep 11, 2020	Ongoing

Abbreviations: LMP = last menstrual period; N/A = not applicable.

Note: Pregnancies are only collected in the Pharmacovigilance Global Database. Data in this table reflects pregnancies during the study as of 11 Nov 2020 (data snapshot date).

2.5.5.2 Phase 2a Study mRNA-1273-P201

This section contains an overview of the key safety data for ongoing Study mRNA-1273-P201. Refer to IND 19745 (Module 5.3.5.1) for the comprehensive set of safety tables and listings.

In this study, 2 mRNA-1273 dose levels (50 and 100 µg) or placebo administered 28 days apart were assessed in participants ≥ 18 to < 55 years and ≥ 55 years of age. No protocol-specified

pause rules (mRNA-1273-P201 Protocol Section 3.4.2.1) were met during the study. In addition, the study initiated with a sentinel group of 50 participants ≥ 55 years of age; after review of the safety data by the independent SMC, the cohort was expanded to include the remaining 250 participants ≥ 55 years of age. The overall safety profile in Study mRNA-1273-P201, as evaluated by solicited local and systemic ARs was similar to that observed in Study mRNA-1273-P301 ([Section 2.5.5.1](#)).

2.5.5.2.1 Solicited Adverse Reactions

Solicited local and systemic ARs were collected via eDiaries during the 7 days after each IP injection (ie, the day of dosing and 6 subsequent days). Refer to the mRNA-1273-P201 study protocol for additional details on the collection of unsolicited AEs.

The solicited AR profile of mRNA-1273 at 100 μg was similar to that observed in Study mRNA-1273-P301.

The majority of solicited ARs were grade 1 or grade 2 in severity; no grade 4 solicited ARs were reported after any injection (mRNA-1273-P201 [Table 14.3.1.1.3](#)). Solicited ARs generally resolved within 1 to 3 days (mRNA-1273-P201 [Table 14.3.1.4.1](#) and [Table 14.3.1.4.2](#)).

The numbers and titles of the mRNA-1273-P201 tables referenced in this section are as follows:

Table Number	Table Title
14.3.1.1.3	Summary of Solicited Adverse Reactions within 7 Days After Any Injection by Grade - Solicited Safety Set
14.3.1.4.1	Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection -First Injection Solicited Safety Set
14.3.1.4.2	Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection - Second Injection Solicited Safety Set

2.5.5.2.2 Unsolicited Adverse Events

Unsolicited AEs were collected during the 28 days after each IP injection (ie, the day of dosing and 27 subsequent days). Adverse events leading to discontinuation from IP and/or study participation, SAEs, and MAAEs are being collected through completion of the study or until withdrawal from the study. Refer to the mRNA-1273-P201 study protocol for additional details on the collection of unsolicited AEs.

Unsolicited TEAEs were reported by 113 (28.3%) participants who received mRNA-1273 (regardless of dose level) and 51 (25.5%) participants who received placebo (mRNA-1273-P201

[Table 14.3.1.8.1](#)). The most commonly reported unsolicited TEAEs (in $\geq 2\%$ of participants) in the 28 days after any injection by PT in the mRNA-1273 100 μg group included headache, arthralgia, and injection site swelling (mRNA-1273-P201 [Table 14.3.1.9.1](#)). The most commonly reported treatment-related TEAEs (in $\geq 2\%$ of participants) in the 28 days after any injection by PT in the mRNA-1273 100 μg group included headache and injection site swelling (mRNA-1273-P201 [Table 14.3.1.12.1](#)).

The incidence of severe TEAEs was low with no notable differences across treatment groups (12 [3.0%] participants for mRNA-1273 and 4 [2.0%] participants for placebo) (mRNA-1273-P201 [Table 14.3.1.16.1](#)). No individual severe PT was reported by more than 2 participants in any treatment group. Treatment-related severe TEAEs in the mRNA-1273 100 μg group included headache and rhinorrhea (mRNA-1273-P201 [Table 14.3.1.17.1](#)).

Medically attended AEs were reported by 39 (9.8%) participants who received mRNA-1273 and 17 (8.5%) participants who received placebo (mRNA-1273-P201 [Table 14.3.1.18.1](#)). Medically attended AEs reported by ≥ 2 participants in the mRNA-1273 100 μg group included headache, arthralgia, and axillary pain (2 participants each).

No noteworthy differences by age cohort (≥ 18 to < 55 years or ≥ 55 years) were observed in the unsolicited AE profile across treatment groups (mRNA-1273-P201 [Table 14.3.1.7.1](#)).

The numbers and titles of the mRNA-1273-P201 tables referenced in this section are as follows:

Table Number	Table Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days after Any Vaccination - Safety Set
14.3.1.8.1	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.9.1	Subject Incidence of Unsolicited TEAE by Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.12.1	Subject Incidence of Unsolicited Treatment-Related TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Any Vaccination - Safety Set
14.3.1.16.1	Subject Incidence of Unsolicited Severe TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.17.1	Subject Incidence of Unsolicited Treatment-Related Severe TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.18.1	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set

2.5.5.2.2.1 Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

No deaths, SAEs, or TEAEs leading to discontinuation from the study IP or from study participation occurred in the 28 days after any injection (mRNA-1273-P201 [Table 14.3.1.7.1](#), [Table 14.3.1.13.1](#), and [Table 14.3.1.15.1](#)).

One SAE has been reported as of 06 Nov 2020. One participant who received mRNA-1273 50 µg experienced an SAE of pneumonia; this SAE was considered not related to IP (mRNA-1273-P201 [Table 14.3.1.7.2](#) and [Table 14.3.1.13.2](#)).

The numbers and titles of the mRNA-1273-P201 tables referenced in this section are as follows:

Table Number	Table Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days after Any Vaccination - Safety Set
14.3.1.7.2	Summary of Unsolicited TEAE from Day 1 to Day 57 Visit - Safety Set
14.3.1.13.1	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.13.2	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term from Day 1 to Day 57 Visit - Safety Set
14.3.1.15.1	Subject Incidence of Unsolicited TEAE Leading to Discontinuation from Participation in the Study by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set

2.5.5.3 Phase 1 Study 20-0003

This section contains an overview of the key safety data for ongoing Study 20-0003. Refer to the 20-0003 Safety Summary Report (dated 26 Oct 2020) (IND 19745 Module 1.11.3) for the comprehensive safety analysis.

In this study, 3 mRNA-1273 dose levels (25, 100, and 50 µg) administered 28 days apart were assessed in participants 18 to 55 years, 56 to 70 years, and ≥ 71 years of age. The mRNA-1273 250-µg dose was not evaluated in participants 56 to 70 years and ≥ 71 years of age due to reactogenicity observed in 4 participants in the 250 µg (18 to 55 years) dose cohort.

Reactogenicity was measured by the occurrence of solicited local (injection site) and systemic ARs during the 7 days after each injection (ie, the day of dosing and 6 subsequent days). Refer to the 20-0003 study protocol for additional details on the collection of ARs.

Across all age groups, solicited ARs were predominantly mild or moderate in severity and most commonly included fatigue, chills, headache, myalgia, and pain at the injection site. The incidence and severity of solicited ARs were generally dose dependent and increases in incidence

and severity were generally observed after the second injection. The incidence of systemic reactions increased after the second injection, particularly at the highest (250 µg) dose. Four (27%) participants in the 250 µg dose cohort reported at least 1 severe solicited AR after the second injection, including feverishness, fatigue, fever, headache, myalgia, nausea, and erythema/redness.

No SAEs have been reported through Day 119, and no pause rules were triggered during the study.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 Benefits

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study mRNA-1273-P301. The primary efficacy endpoint in Study mRNA-1273-P301 was met: mRNA-1273 prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the mRNA-1273 group and 90 cases in the placebo group). The VE was 94.5% (95% CI: 86.5%, 97.8%; one-sided p value < 0.0001), rejecting the null hypothesis of $VE \leq 30\%$ and achieving the prespecified efficacy boundary based on the 1-sided nominal alpha of 0.0047 using the Lan-DeMets O'Brien-Fleming spending function.

The vaccine was effective in preventing severe COVID-19, with 11 cases in the placebo group and 0 cases in the mRNA-1273 group. In addition, the vaccine was efficacious in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second injection (VE of 93.5% based on HR).

The mRNA-1273-P301 study population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of mRNA-1273 was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females, and in White participants and those from communities of color. There was a limited number of participants in each ethnic group in the subgroup analysis who contributed to the primary efficacy endpoint, and therefore efficacy analyses were not performed for each specific racial and ethnic subgroup.

The efficacy of mRNA-1273 in the PPS was consistent across several sensitivity analyses, including those using the mITT population and FAS populations, as well as COVID-19 cases from randomization and 14 days after the first injection. The vaccine efficacy to prevent COVID-19 starting 14 days after the first dose of vaccine was 95.4%, and to prevent COVID-19 after randomization was 94.6%. However, these analyses must be interpreted with caution because the follow-up period was limited (approximately 28 days), the vast majority (>90%) of participants received a second dose, and cases were not censored from the analysis if they occurred after the second dose.

The immunogenicity of the mRNA-1273 vaccine was evaluated in Studies DMID 20-0003 and mRNA-1273-P201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal Phase 3 study. In Study 20 0003 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of neutralizing or binding antibody and this observation was the basis for selecting the 100-µg dose for use in the pivotal Phase 3 study. Importantly, the antibody levels after 2 doses of mRNA 1273 exceeded those in a pool of convalescent sera. Neutralizing activity was observed for the 100 µg mRNA-1273 dose as of Day 36, which was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. Additionally, in Study 20-0003, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response and similar responses were observed among all age groups for the 100-µg dose. In the dose-confirming study, mRNA-1273-P201, generally comparable neutralizing and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of mRNA-1273 administered 28 days apart.

2.5.6.2 Risks

The safety of mRNA-1273 is largely based on data from the pivotal Phase 3 study using an 11 Nov 2020 data snapshot taken at the time of the interim analysis. The safety analysis set included 30,350 study participants: 15,184 received mRNA-1273 and 15,165 received placebo. The median study duration from first injection was 78 days (range: 1 to 108 days or more) for 30,350 participants and the median study duration from second injection was 49 days (range: 0 to 83 days or more).

Solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and systemic ARs were more common after the second injection. The most common solicited local AR was pain and the incidence was similar between the first and second injections of mRNA-1273. The majority of the solicited local ARs occurred within the

first 1 to 2 days after administration of mRNA-1273 and generally persisted for a median of 1 to 3 days. Solicited systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and the majority of these solicited systemic ARs were mild to moderate in severity. The most common solicited systemic ARs were headache and fatigue after the first injection and, headache and fatigue, myalgia, arthralgia and chills after second injection. The majority of solicited systemic reactions also occurred within the first 1 to 2 days after administration of IP and persisted for a median of 3 days or less.

Solicited local and systemic ARs were more commonly reported by younger adults (18 to < 65 years) compared with older adults (\geq 65 years) after the first and second injections. There was no difference in the incidence of solicited local and systemic ARs based on baseline SARS-CoV-2 status. The solicited AR profile in the pivotal Study mRNA-1273-P301 was similar to the profile observed in the 100- μ g mRNA-1273 treatment group in Study mRNA-1273-P201.

The overall incidence of unsolicited TEAEs and MAAEs reported up to 28 days after vaccination were comparable in participants who received mRNA-1273 or placebo. The overall incidence of related TEAEs was higher in participants who received mRNA-1273 compared with placebo. This difference is a consequence of more frequently reported solicited adverse reactions by participants who received mRNA-1273 either persisting beyond Day 7 or were severe reactions and/or required medical attention, since these were also reported as unsolicited AE. The incidence of unsolicited TEAEs leading to discontinuation from study vaccine was greater in participants who received placebo compared with mRNA-1273 (85 participants [0.6%] vs 45 participants [0.3%], respectively), largely due to a diagnosis of COVID-19 prior to Day 29 which rendered them ineligible to receive the second injection.

The incidence of unsolicited TEAEs within 28 days after any injection regardless of relationship was comparable in adults 18 to <65 years of age compared with participants 65 years of age and older who received mRNA-1273 (21.5% versus 23.1%, respectively). There was no apparent effect of age on the relative incidence of these TEAEs by vaccine group. There was no difference in the incidence of unsolicited TEAEs based on SARS-CoV-2 serology at baseline.

The incidence and absolute number of SAEs and treatment-related SAEs in the 28 days after vaccination was comparable between mRNA-1273 and placebo groups. A total of 8 deaths occurred in Study mRNA-1273-P301, with 4 deaths occurring in the mRNA-1273 group and 4 deaths occurring in the placebo group. None were attributed to COVID-19 nor considered related to study product. The causes of death were consistent those that are expected in the population enrolled in the study.

There were fewer cases of severe COVID-19 or COVID-19 from the time of randomization amongst participants who received mRNA-1273 compared with placebo, and thus no evidence of vaccine-associated enhanced respiratory disease.

In the Phase 2a Study mRNA-1273-P201, the incidence of unsolicited TEAEs, related unsolicited TEAEs, and MAAEs were comparable between the mRNA-1273 and placebo groups. One SAE was reported and assessed as unrelated to IP in Study mRNA-1273-P201 and no SAEs have been reported through Day 119 in Study 20-0003.

2.5.6.3 Risk-Benefit Assessment

There is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Based on the interim results from the pivotal Phase 3 study, mRNA-1273 prevents COVID-19 and severe COVID-19. The demonstrated clinical benefit of mRNA-1273 is supported by evidence of a robust immune response both in terms of bAbs and nAbs as well as the induction of CD4+ T-cells with a Th-1 dominant phenotype. Based on administration of mRNA-1273 to 15,693 adults across all 3 clinical studies to date, there have been no emergent safety concerns and the AE profile is manifested largely by mild to moderate reactogenicity lasting 2 to 3 days.

Statistically significant vaccine efficacy to prevent COVID-19 was demonstrated in adults ≥ 18 years of age during the ongoing pandemic. The clinical benefit was consistent in older and younger adults, with or without risk factors for complications of COVID-19, in males and females, and in participants who were white as compared to those from communities of color. Importantly, mRNA-1273 was demonstrated to be effective in preventing severe COVID-19. The efficacy of mRNA-1273 to prevent COVID-19 and severe COVID-19 demonstrated in the study to date also mitigates concern about the risk of enhanced disease during the 28- day period following 2 doses of vaccine. The results from the pivotal efficacy study are supported by the substantial immune response observed in the Phase 1 and Phase 2 studies that was consistent across age groups and persisted over 3 months after the second injection of mRNA-1273.

Vaccination with mRNA-1273 generally results in transient local injection site and systemic reactions. The incidence of local and systemic ARs was lower in older adults compared with younger adults. The incidence of unsolicited TEAEs, MAAEs, and TEAEs leading to discontinuation of IP, were similar between the treatment groups but unsolicited related TEAEs were more common in participants who received mRNA-1273. This difference is explained by an increase in local and systemic ARs which were assessed as severe or persisted beyond 7 days. Less common but clinically significant AEs, such as SAE and deaths were reported at

comparable rates for placebo and IP recipients. The overall safety profile observed in the Phase 3 large-scale safety and efficacy study was generally consistent with the safety profile observed to date in the Phase 1 and Phase 2 studies.

Based on the data presented in this submission, mRNA-1273 administered as two 100 µg doses 28 days apart is an effective vaccine with an acceptable safety profile for the prevention of COVID-19 in adults 18 years of age and older. The safety and immunogenicity data from the Phase 1 study and the safety data from the Phase 3 and Phase 2a studies support the use of the 100-µg dose of mRNA-1273. Considering the ongoing public health emergency due to SARS-CoV-2, the lack of approved preventative vaccines, as well as the available safety and efficacy data from the 3 clinical studies presented herein, the Sponsor considers that the known and potential benefits of the IP outweigh the known and potential risks for mRNA-1273 and warrant consideration for EUA under Section 564 (b)(1)(C) of the FD&C Act.

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2.5.8 APPENDICES

2.5.8.1 APPENDIX 1: mRNA-1273-P301 - Interim Analysis 1 Tables

2.5.8.1.1 Demographic, Background, and Disposition Data

Disposition and Baseline Characteristics in Study mRNA-1273-P301

Table Number	Title
14.1.1.1.1.1	Subject Disposition by Baseline SARS-CoV-2 Status - Randomization Set
14.1.2.3	Number of Subjects in Each Analysis Set by Randomization Stratum - Randomization Set
14.1.3.1.3	Baseline Demographics and Characteristics by Randomization Stratum - Full Analysis Set
14.1.6.2	Summary of Study Duration - Safety Set

2.5.8.1.2 Efficacy Data

Summary of Efficacy Analysis Results in Study mRNA-1273-P301

Table Number	Title
14.2.1.1.1.1.1	Summary of Primary and Secondary Efficacy Endpoint Analysis Results - Per-Protocol Set
14.2.2.2.2.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.2.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Starting After Randomization - Per-Protocol Set

Analysis of Primary Efficacy Endpoint (COVID-19) per Adjudication Committee Assessments in Study mRNA-1273-P301

Table Number	Title
14.2.2.1.1.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection – Per-Protocol Set
14.2.2.1.1.1.2	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - mITT Set
14.2.2.1.1.6.1.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Age Group (≥ 18 and < 65 Years, ≥ 65 Years) - Per-Protocol Set
14.2.2.1.1.6.3.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Age and Health Risk for Severe COVID-19 - Per-Protocol Set
14.2.2.1.1.6.4.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Sex - Per-Protocol Set
14.2.2.1.1.6.7.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Risk for Severe COVID-19 at Screening - Per-Protocol Set
14.2.2.1.1.6.10.1	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection by Race and Ethnicity Group (White, Communities of Colors) - Per-Protocol Set

Analysis of Primary Efficacy Endpoint (COVID-19) in Study mRNA-1273-P301

Table Number	Title
14.2.2.1.2.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.1.2.3.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After First Injection - Per-Protocol Set
14.2.2.1.2.5.1	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - Per-Protocol Set
14.2.2.1.2.5.2	Sensitivity Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting After Randomization - mITT Set

Analysis of Severe COVID-19 Based on Adjudication Committee Assessments in Study mRNA-1273-P301

Table Number	Title
14.2.2.2.1.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.2.1.1.2	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - mITT Set

Analysis of Secondary Definition of COVID-19 in Study mRNA-1273-P301

Table Number	Title
14.2.2.4.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Secondary Definition of COVID-19 Starting 14 Days After Second Injection - Per-Protocol Set

Analysis of COVID-19 Regardless of Prior SARS-CoV-2 Infection Based on Adjudication Committee Assessments in Study mRNA-1273-P301

Table Number	Title
14.2.2.7.1.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set
14.2.2.7.1.6.10	Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection by Baseline SARS-CoV-2 Status - Full Analysis Set

Analysis of COVID-19 Regardless of Prior SARS-CoV-2 Infection in Study mRNA-1273-P301

Table Number	Title
14.2.2.7.2.1	Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set

Efficacy Figures in Study mRNA-1273-P301

Figure Number	Title
14.2.2.1.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.1.1.2.3	Forest Plot of Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.2.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection - Per-Protocol Set
14.2.2.7.1.1.1	Kaplan-Meier Estimates of Time to First Occurrence of COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection - Full Analysis Set

2.5.8.1.3 Safety Data

Solicited Adverse Reactions in Study mRNA-1273-P301

Table Number	Title
14.3.1.1.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.1.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.1.3	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Grade - Solicited Safety Set
14.3.1.1.4	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Age Group and Grade - First Injection Solicited Safety Set
14.3.1.1.5	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Age Group and Grade - Second Injection Solicited Safety Set
14.3.1.1.6	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade - Solicited Safety Set
14.3.1.1.7	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Baseline SARS-CoV-2 Status and Grade - First Injection Solicited Safety Set
14.3.1.1.8	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Baseline SARS-CoV-2 Status and Grade - Second Injection Solicited Safety Set
14.3.1.3.1	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Onset Day - First Injection Solicited Safety Set
14.3.1.3.2	Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Onset Day - Second Injection Solicited Safety Set
14.3.1.4.1	Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection - First Injection Solicited Safety Set
14.3.1.4.2	Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection - Second Injection Solicited Safety Set
14.3.1.6.1	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After First Injection by Grade - First Injection Solicited Safety Set
14.3.1.6.2	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Second Injection by Grade - Second Injection Solicited Safety Set
14.3.1.6.3	Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Any Injection by Grade - Solicited Safety Set

Unsolicited Adverse Events up to 28 Days After Any Injection in Study mRNA-1273-P301

Table Number	Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days After Any Injection - Safety Set
14.3.1.7.4	Summary of Unsolicited TEAE by Age Group up to 28 Days After Any Injection - Safety Set
14.3.1.7.7	Summary of Unsolicited TEAE by Baseline SARS-CoV-2 Status up to 28 Days After Any Injection - Safety Set
14.3.1.8.1	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.8.4	Subject Incidence of Unsolicited TEAE by Age Group, System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.8.7	Subject Incidence of Unsolicited TEAE by Baseline SARS-CoV-2 Status, System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.11.1	Subject Incidence of Unsolicited Treatment-Related TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.13.1	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.14.1	Subject Incidence of Serious Treatment-Related TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.17.1	Subject Incidence of Unsolicited Severe TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.18.1	Subject Incidence of Unsolicited Treatment-Related Severe TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set
14.3.1.19.1	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days After Any Injection - Safety Set

Unsolicited Adverse Events - Overall Stage in Study mRNA-1273-P301

Table Number	Title
14.3.1.7.3	Summary of Unsolicited TEAE in Overall Stage - Safety Set
14.3.1.7.6	Summary of Unsolicited TEAE by Age Group in Overall Stage - Safety Set
14.3.1.7.9	Summary of Unsolicited TEAE by Baseline SARS-CoV-2 Status in Overall Stage - Safety Set
14.3.1.8.3	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set
14.3.1.8.6	Subject Incidence of Unsolicited TEAE by Age Group, System Organ Class, and Preferred Term in Overall Stage - Safety Set
14.3.1.8.9	Subject Incidence of Unsolicited TEAE by Baseline SARS-CoV-2 Status, System Organ Class and Preferred Term in Overall Stage - Safety Set
14.3.1.13.3	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set
14.3.1.14.3	Subject Incidence of Serious Treatment-Related TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set
14.3.1.15.1	Subject Incidence of Unsolicited TEAE Leading to Discontinuation from Study Vaccine by System Organ Class and Preferred Term - Safety Set
14.3.1.19.3	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term in Overall Stage - Safety Set

2.5.8.2 APPENDIX 2: Study mRNA-1273-P201 - Day 57 Tables

2.5.8.2.1 Demographic, Background, and Disposition Data

Disposition and Demographics in Study mRNA-1273-P201

Table Number	Table Title
14.1.1.1	Subject Disposition - Randomized Set
14.1.2	Number of Subjects in Each Analysis Set - Randomized Set
14.1.3.2	Baseline Demographics - Randomized Set

2.5.8.2.2 Immunogenicity Data

Immunogenicity in Study mRNA-1273-P201

Table Number	Table Title
14.2.1.1.1	Summary of Binding Antibody Levels - Per-Protocol Set for SARS-CoV-2-specific bAb
14.2.2.1.1.1	Summary of Neutralizing Antibody Titers - Per-Protocol Set for SARS-CoV-2-specific nAb from the First Lot

2.5.8.2.3 Safety Data

Solicited Adverse Reactions in Study mRNA-1273-P201

Table Number	Table Title
14.3.1.1.3	Summary of Solicited Adverse Reactions within 7 Days After Any Injection by Grade - Solicited Safety Set
14.3.1.4.1	Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection - First Injection Solicited Safety Set
14.3.1.4.2	Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection - Second Injection Solicited Safety Set

Unsolicited Adverse Events in Study mRNA-1273-P201

Table Number	Table Title
14.3.1.7.1	Summary of Unsolicited TEAE up to 28 Days after Any Vaccination - Safety Set
14.3.1.7.2	Summary of Unsolicited TEAE from Day 1 to Day 57 Visit - Safety Set
14.3.1.8.1	Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.9.1	Subject Incidence of Unsolicited TEAE by Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.12.1	Subject Incidence of Unsolicited Treatment-Related TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Any Vaccination - Safety Set
14.3.1.13.1	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set

Table Number	Table Title
14.3.1.13.2	Subject Incidence of Serious TEAE by System Organ Class and Preferred Term from Day 1 to Day 57 Visit - Safety Set
14.3.1.15.1	Subject Incidence of Unsolicited TEAE Leading to Discontinuation from Participation in the Study by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.16.1	Subject Incidence of Unsolicited Severe TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.17.1	Subject Incidence of Unsolicited Treatment-Related Severe TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set
14.3.1.18.1	Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days after Any Vaccination - Safety Set

2.5.8.3 APPENDIX 3: Participant Safety Narratives for SUSARs, Deaths, and Related SAEs

Safety narratives for SUSARS, Deaths, and Related SAEs are provided in [Module 5.3.5.1](#).