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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
AR	adverse reaction
bAb	binding antibody
BOD	burden of disease
BOI	burden of infection
CDC	US Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CSR	clinical study report
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FRNT-mNG	focus-reduction neutralization test against mNeonGreen live virus
GISAID	Global Initiative on Sharing All Influenza Data
GM	geometric mean
GMFR	geometric mean fold-rise
GMT	geometric mean titer
ID_{50}	serum dilution required to achieve 50% neutralization
ID_{80}	serum dilution required to achieve 80% neutralization
IM	intramuscular
IP	investigational product
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
mITT	modified intent-to-treat
MN	microneutralization
nAb	neutralizing antibody
NP	nasopharyngeal
PP	per-protocol
PRNT	plaque reduction neutralization test using a wild-type SARS-CoV-2 virus
PsVNA	pseudovirus neutralization assay
RBD	receptor binding domain
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike

Abbreviation	Definition
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCE	Summary of Clinical Efficacy
SMC	safety monitoring committee
ULOQ	upper limit of quantitation
VE	vaccine efficacy

2.7.3.1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

ModernaTX, Inc. (Sponsor) is developing mRNA-1273 as a vaccine to prevent coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). An overview of the development program is presented in Module 2.2 of this Application, with greater detail provided in Module 2.5.

This Summary of Clinical Efficacy (SCE) summarizes data from the following 3 studies as evidence of the clinical efficacy and immunogenicity of mRNA-1273 in the prevention of COVID-19:

- Study mRNA-1273-P301 (hereafter, Study 301) is a Phase 3 study that provides the clinical evidence of vaccine efficacy (VE) (Section 2.7.3.2.1.1) and immunogenicity (Section 2.7.3.2.1.2) and the majority of the clinical safety data for this Application (Section 2.7.4). The Study 301 Part A CSR (primary efficacy analysis) is located in Module 5, and a tabular overview is provided in Table 1. Primary analysis results were reported on 30 Dec 2020 (Baden et al 2021). Additional data on persistence of protection including the Participant Decision Visit (PDV) and up to the data cutoff date (26 Mar 2021) are provided in the Study 301 CSR Addendum 1 (Part B) and summarized in this SCE.

- Study mRNA-1273-P201 (hereafter, Study 201) is a Phase 2a study that provides confirmation of the dose selected from the Phase 1 study and includes immunogenicity data (Section 2.7.3.2.2) and safety data (Section 2.7.4). The original Part A CSR includes the results from the primary analysis of immunogenicity and safety data through Day 57, and the Study 201 CSR Addendum 1 (End of Part A) includes results from the analysis of immunogenicity and safety data through Day 209. Both the Study 201 Primary Analysis CSR and the Study 201 CSR Addendum 1 (End of Part A) are located in Module 5 and a tabular overview of the study design is provided in Table 1. The interim analysis of the immunogenicity and safety data through Day 57 has been published (Chu et al 2021).

- Study 20-0003 (hereafter, Study 101) is a Phase 1 dose-finding study of immunogenicity (Section 2.7.3.2.3) and safety (Section 2.7.4) that provided support for dose selection for Study 201 and Study 301. The Study 101 Day 119 CSR and the Study 101 CSR Addendum 1 (Day 209) are located in Module 5, and a tabular overview of the study design is provided in Table 1. Durability of responses through 90 days after the second vaccination dose were reported on 03 Dec 2020 (Widge et al 2021) and through 180 days after dose 2 on 06 Apr 2021 (Doria-Rose et al 2021). Safety and immunogenicity results

in older adults were reported on 29 Sep 2020 (Anderson et al 2020) and in adults 18 to 55 years old on 14 Jul 2020 (Jackson et al 2020).

This Application includes no analysis of pooled data from these 3 studies. Efficacy was only studied in Study 301, which also provided the vast predominance of immunogenicity and safety data.

The Summary of Clinical Safety is located in Section 2.7.4.

2.7.3.1.1 Overview of the Design of the Clinical Studies

mRNA-1273 is being evaluated in 3 ongoing clinical studies in adult participants. Commonalities of design among the 3 studies include the following:

- The study population included men and nonpregnant women at least 18 years of age.
- The study population included older adults, given that they are at higher risk for complications of COVID-19.
- mRNA-1273 or placebo (as applicable) was administered as 2 intramuscular (IM) doses, 28 days apart, as a 0.5-mL injection in the deltoid muscle, preferably in the nondominant arm. It was recommended that the Day 1 and Day 29 vaccinations be administered in the same arm.

A tabular listing of the 3 studies is provided in Table 1. Each of the 3 study designs are described in additional detail in Section 2.7.3.1.1.1 (Study 301), Section 2.7.3.1.1.2 (Study 201), and Section 2.7.3.1.1.3 (Study 101).

Table 1: Clinical Studies Included in the Summary of Clinical Efficacy

Study Number (Country)	Study Population	Study Design	Dose, Schedule, and Number of Participants Exposed	Key Efficacy and Immunogenicity Objectives[a]	Study Status
mRNA-1273-301 Part A (US)	Men and nonpregnant women at least 18 years of age, at appreciable risk of SARS-CoV-2 infection, with a negative history for SARS-CoV-2 infection	Phase 3, case-driven, randomized, stratified, observer-blind, placebo-controlled Randomization was stratified by a combination of age and health risk for COVID-19: • ≥18 to < 65 years old, not at risk for severe COVID-19 • ≥18 to < 65 years old, at risk for severe COVID-19 • ≥ 65 years old	100 µg of mRNA-1273 or placebo 2 doses, 28 days apart 100 µg (n=15,180) placebo (n=15,166)	• Efficacy of mRNA-1273 to prevent COVID-19 (primary) • Efficacy of mRNA-1273 to prevent severe COVID-19 • Efficacy of mRNA-1273 to prevent SARS-CoV-2 infection regardless of symptomatology or severity • Efficacy of mRNA-1273 to prevent COVID-19 regardless of prior SARS-CoV-2 infection • Immunogenicity of 2 doses of mRNA-1273	Ongoing
mRNA-1273-201 (US)	Men and nonpregnant women, at least 18 years of age, in good health	Phase 2a, randomized, observer-blind, placebo-controlled Age cohorts: • ≥ 18 to < 55 years old • ≥ 55 years old	50 or 100 µg mRNA-1273 or placebo 2 doses, 28 days apart 50 µg (n=200) 100 µg (n=200) placebo (n=200)	• Immunogenicity of 2 dose levels of mRNA-1273 by measure of specific bAb levels • Immunogenicity of 2 dose levels of mRNA-1273 by measure of specific nAb levels	Ongoing

20-0003 (US)	Men and nonpregnant women at least 18 years of age, in good health	Phase 1, open-label, dose-finding study. Age cohorts: • ≥ 18 to < 56 years old • ≥ 56 to < 71 years old • ≥ 71 years old	10 (not enrolled), 25, 50, 100, or 250 µg of mRNA-1273 2 doses, 28 days apart 25 µg (n=35) 50 µg (n=35) 100 µg (n=35) 250 µg (n=15)	Immunogenicity of mRNA-1273 measured by IgG ELISA to SARS-CoV-2 S protein Immunogenicity of mRNA-1273 measured by nAb levels against SARS-CoV-2 pseudovirus and wild-type virus. SARS-CoV-2 protein-specific T-cell responses in a subset of participants	Ongoing

Abbreviations: bAb = binding antibody; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; nAb = neutralizing antibody; S = spike

[a] Key safety endpoints for these studies are presented in Section 2.7.4.1.1.2.

2.7.3.1.1.1 Study 301 (Phase 3)

This is a 2-part Phase 3 study. The study was designed as a randomized, observer-blind, placebo-controlled study of the efficacy, safety, and immunogenicity of mRNA-1273 compared to placebo (Part A). Sample size was driven by the total number of cases required to demonstrate the VE of mRNA-1273 to prevent COVID-19. Vaccine efficacy was demonstrated based on the prespecified efficacy success criterion at the interim analysis (11 Nov 2020 dataset), based on a total of 95 adjudicated cases. The subsequent primary analysis of efficacy was performed with a total of 196 adjudicated COVID-19 cases (25 Nov 2020 dataset) and was consistent with the interim analysis (Section 2.7.3.2.1.1). After Emergency Use Authorization (EUA) in the United States was granted for mRNA-1273 and another mRNA COVID-19 vaccine, Part B, the open-label observational phase of the study, was initiated. All participants in Part A were invited to proceed to Part B, starting with a PDV, at which participants were given the option to be unblinded to their original group assignment or remain blinded. Unblinded participants who had received placebo in Part A had the choice to be vaccinated with mRNA-1273 in Part B (Study 301 Protocol)

This Application contains the completed analyses of Part A, both formal hypothesis testing and descriptive or confirmatory analyses, as presented in the Study 301 Part A CSR, including the following endpoints:

- Primary and secondary efficacy, primary safety, immunogenicity, and selected exploratory endpoints (04 May 2021 dataset)

- Primary efficacy and safety endpoints from the primary analysis (25 Nov 2020 dataset)
- Primary efficacy and safety endpoints from the interim analysis (11 Nov 2020 dataset)

Additional unblinded safety data and VE data from Part B are presented in the Study 301 CSR Addendum 1 (Part B). Participants will continue to be followed until Day 759 (Month 25) to assess long-term safety of mRNA-1273 and the durability of VE. Additional immunogenicity data, as well as additional effectiveness and safety data from continued participant follow-up, will be reported in the end-of-study CSR for Study 301.

Part A is a Phase 3, randomized, parallel, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who had no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or asymptomatic SARS-CoV-2 infection.

Approximately 30,000 participants were planned to be randomly assigned to receive either 100 µg of mRNA-1273 or placebo using a 1:1 randomization ratio with stratification by age group and health risk (< 65 years old and not at risk for severe COVID-19, < 65 years old and at risk for severe COVID-19, ≥ 65 years old). This was a case-driven study, and the planned sample size was driven by the total number of cases required to demonstrate VE (mRNA-1273 vs. placebo) to prevent COVID-19.

The primary efficacy endpoint was the VE of mRNA-1273 to prevent the first adjudicated occurrence of COVID-19 starting 14 days after the second dose of investigational product (IP), where COVID-19 was defined as symptomatic disease based on the following case definition:

- The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38°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 nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR).

Only COVID-19 cases that had been positively adjudicated by an independent, expert committee contributed to the analysis of the primary efficacy endpoint.

Secondary efficacy endpoints included the following:

- The VE of mRNA-1273 to prevent severe COVID-19, defined as first occurrence of COVID-19 starting 14 days after the second injection of IP (as per the primary endpoint) AND any of the following:
    - Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or the ratio of the oxygen pressure in arterial blood to the fraction of inspired oxygen < 300 mm Hg, OR
    - Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors), OR
    - Significant acute renal, hepatic, or neurologic dysfunction, OR
    - Admission to an intensive care unit or death.
- The VE of mRNA-1273 to prevent the first occurrence of either COVID-19 or asymptomatic SARS-CoV-2 infection starting 14 days after the second IP dose
- The VE of mRNA-1273 to prevent the secondary case definition of COVID-19 starting 14 days after the second injection of IP, where the secondary case definition was the presence of at least one US Centers for Disease Control and Prevention (CDC)-specified systemic symptom (fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, diarrhea) AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR
- The VE of mRNA-1273 to prevent death due to a cause directly attributed to a complication of COVID-19, starting 14 days after the second injection of IP

- The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the first injection of IP
- The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second injection of IP regardless of evidence of prior SARS-CoV-2 infection determined by serologic titer against SARS-CoV-2 nucleocapsid (full analysis set)
- The VE of mRNA-1273 to prevent the first occurrence of SARS-CoV-2 infection in the absence of symptoms defining COVID-19 starting 14 days after the second injection of IP

The immunogenicity endpoints reported in the Study 301 Part A CSR included the following:

- Geometric mean (GM) levels of S protein-specific binding antibody (bAb) on Day 1, Day 29, and Day 57
- Geometric mean fold-rise (GMFR) of S protein-specific bAb relative to Day 1 on Day 29 and Day 57
- Seroresponse of S protein-specific bAb relative to Day 1 on Day 29 and Day 57
- Geometric mean titer (GMT) of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29, and Day 57
- GMFR of SARS-CoV-2-specific nAb relative to Day 1 on Day 29 and Day 57
- Seroresponse of SARS-CoV-2-specific nAb relative to Day 1 on Day 29 and Day 57

The primary safety endpoints include the following (results presented in Section 2.7.4):

- Solicited local and systemic adverse reactions (ARs) through 7 days after each dose of IP
- Unsolicited AEs through 28 days after each dose of IP
- AEs leading to withdrawal throughout the entire study period
- MAAEs throughout the entire study period
- Serious adverse events (SAEs) throughout the entire study period
- Pregnancies and perinatal outcomes

Exploratory assessments reported in the Study 301 Part A CSR and this SCE include the following:

- VE of mRNA-1273 to reduce duration and presence/severity of COVID-19 symptoms
- VE of mRNA-1273 against burden of disease (BOD)
- VE of mRNA-1273 against burden of infection (BOI)
- Efficacy against viral load
- VE to prevent all-cause mortality after randomization
- Genotypic analysis of SARS-CoV-2 identified in NP swab samples and efficacy against variants

Part A was designed to include up to 7 scheduled in-clinic study site visits (Screening, Days 1, 29, 57, 209, 394, and 759), with additional safety surveillance by telephone calls and electronic diary (eDiary) throughout the Part A study period. All participants were assessed for efficacy, immunogenicity, and safety endpoints according to the applicable schedule of events. Unscheduled visits included Illness Visits (for identification of COVID-19 cases) and Convalescent Visits (scheduled at Day 28 relative to an Illness Visit at nominal Day 1), as well as the PDV for participants eligible to enter into Part B.

Participants received an IM injection (0.5 mL) of either mRNA-1273 (100 µg) or saline placebo on Day 1 and Day 29: an NP swab sample was collected on each day prior to injection, for evaluation by RT-PCR. To preserve observer blinding, only delegated unblinded study personnel responsible for study vaccine preparation, administration, and/or accountability had knowledge of study treatment assignment. Participant blinding was maintained by using a shielded syringe for injection.

Participants were given an eDiary to report solicited ARs for 7 days after each dose of IP and to prompt an unscheduled clinic visit for clinical evaluation and NP swab sample if a participant experienced any symptoms of COVID-19. Participants used the eDiary to report solicited ARs for 7 days and beyond, if present on day 7 and until resolution after each dose of IP. Weekly eDiary prompts (every 7 days) were sent to the participants to elicit an unscheduled Illness Visit if the participant experienced COVID-19 symptoms. All participants received safety calls from study personnel on Day 8, Day 15, Day 22, Day 36, and Day 43 that served both to monitor for unsolicited AEs and to monitor for symptoms of COVID-19.

Safety telephone calls and eDiary safety prompts were performed in conjunction with surveillance for COVID-19 according to the schedules of events and were intended to capture SAEs, MAAEs, AEs leading to withdrawal, concomitant medications associated with these events, receipt of nonstudy vaccinations, and pregnancy. If an eDiary prompt resulted in identification of a relevant safety event, a follow-up safety call was triggered.

Surveillance for COVID-19 was performed through weekly contacts with the participant via a combination of telephone calls and completion of an eDiary starting from Day 1 and continuing through the end of the study. Participants with at least 1 systemic symptom (secondary case definition) of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) returned to the clinic or were visited at home by medically qualified study site personnel within 72 hours to collect an NP swab sample for RT-PCR testing for SARS-CoV-2 and other respiratory pathogens, or alternatively, if a clinic or home visit was not possible, submitted a saliva (or nasal swab) sample for SARS-CoV-2 RT-PCR testing.

All study participants who experienced COVID-19 symptoms and subsequently presented for an Illness Visit (in-clinic or at home) were given an instruction card listing symptoms and the severity grading system along with a thermometer, an oxygen saturation monitor, and saliva collection tubes. Study participants were contacted by the investigator (or appropriately delegated study site personnel) daily with telemedicine visits through Day 14 or until symptoms had resolved, whichever was later. During the telemedicine visit (preferably done in the evening), the participant was asked to verbally report the severity of each symptom in addition to their highest body temperature and lowest oxygen saturation for that day. The investigator determined if medical attention was required due to worsening of COVID-19 symptoms. Study participants collected their own saliva (or nasal swab) samples 3, 5, 7, 9, 14, and 21 days after the initial Illness Visit if they met the case definition for COVID-19 (defined as the date of onset of symptoms and positive virologic test). Finally, a Convalescent Visit was scheduled approximately 28 days after the initial Illness Visit. At this visit, a saliva (or nasal swab) sample was collected, and a blood sample was drawn for immunologic assessment of SARS-CoV-2 infection.

At each injection visit, participants were instructed (Day 1) or reminded (Day 29) on how to document and report solicited ARs in the eDiary provided. Solicited ARs were assessed for 7 days after each IP dose, and unsolicited AEs were assessed for 28 days after each IP dose; SAEs, MAAEs, and AEs leading to withdrawal were assessed throughout the study.

Participants were scheduled for blood sampling for immunological assessments at Days 1, 29, 57, 209, 394, and 759. Immunological assessments are reported in this Application for Days 1,

29, and 57, including assessments for vaccine immunogenicity and SARS-CoV-2 infection. Vaccine immunogenicity is assessed by measurement of serum bAb specific to the SARS-CoV-2 S protein by enzyme-linked immunosorbent assay (ELISA) and by measurement of serum nAb by pseudovirus neutralization. Asymptomatic SARS-CoV-2 infection is identified by seroconversion against SARS-CoV-2 nucleocapsid protein or detection of SARS-CoV-2 by RT-PCR in the absence of COVID-19 symptoms.

2.7.3.1.1.2 Study 201 (Phase 2a)

Study 201 is an ongoing Phase 2a randomized, parallel, observer-blind and placebo-controlled dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in adults at least 18 years of age. The Study 201 Primary Analysis CSR provided the primary analysis of safety and immunogenicity data through Day 57 (data cutoff 05 Nov 2020), and the Study 201 CSR Addendum 1 (End of Part A) includes results from the analysis of immunogenicity and safety data through Day 209. The Study 201 CSR Addendum 1 (End of Part A) includes the analyses of validated immunoassay results from Day 1 through Day 209 that are reported in this SCE. After the primary analysis was completed, Study 201 was amended to include an open-label interventional phase Part B and an additional open-label interventional phase Part C. Part B provides the opportunity for study participants who previously received placebo to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine. In addition, all participants who previously received 1 or 2 injections of mRNA-1273 (50 µg or 100 µg) vaccine will be able to receive a single booster dose of mRNA-1273 (50 µg). Part C was prompted by the need to pro-actively prepare for vaccination strategies that induce broader protection, including against variants of SARS-CoV-2 such as B.1.351.

Two mRNA-1273 dose levels, 50 µg and 100 µg, were evaluated. The study included 2 age cohorts: Cohort 1, ≥ 18 to < 55 years of age (300 participants planned), and Cohort 2, ≥ 55 years of age (300 participants planned). Eligible participants (approximately 600 planned) received either mRNA-1273 (50 or 100 µg per vaccination) or saline placebo control according to a 1:1:1 randomization ratio within each age cohort.

Immunogenicity endpoints presented in the Study 201 Primary Analysis CSR and in this SCE include the following:

- Level of SARS-CoV-2-specific bAb (IgG specific to SARS-CoV-2 spike [S] protein) measured by ELISA on Day 1, Day 29, Day 43, and Day 57

- Titer of SARS-CoV-2-specific nAb (by microneutralization [MN] assay against SARS-CoV-2 virus on confluent VERO E6 cells) on Day 1, Day 29, Day 43, and Day 57
- Seroconversion on Day 29, Day 43, and Day 57 as measured by an increase of SARS-CoV-2-specific nAb titer either from below the lower limit of quantitation (LLOQ) to equal to or above LLOQ or a 4-times higher titer in participants with pre-existing nAb titer

Safety endpoints presented in the Study 201 Primary Analysis CSR and in Section 2.7.4 include the following:

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

The primary analysis CSR comprises 8 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, and Day 57.

The study was initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving vaccine or placebo. Before initiating administration of IP to the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 were reviewed by the safety monitoring committee (SMC). No safety concerns were found, and Cohort 2 enrollment continued.

Participants received an IM injection (0.5 mL) of either mRNA-1273 or placebo on Day 1 and Day 29: an NP swab sample was collected on each vaccination visit prior to injection, to test for the presence of SARS-CoV-2 by RT-PCR. An additional NP swab sample was scheduled for collection on Day 57. During the course of the study, participants meeting prespecified disease criteria that suggested possible SARS-CoV-2 infection were asked to contact the study site to arrange for a prompt, thorough, and careful assessment.

All participants were monitored for safety and reactogenicity, starting with the first dose. An SMC met regularly to assess safety throughout the study and could have convened on an ad hoc basis if study pause rules were met. No study pause rules were met during the vaccination phase of the study.

At each injection visit, participants were instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within an eDiary application and/or device provided to them. Solicited ARs were assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs were assessed for 28 days after each injection; SAEs and MAAEs were assessed throughout the study.

Participants provided blood samples for the assessment of immunogenicity (Days 1, 15, 29, 57, and 209 and safety (Screening and Days 29 and 57 for participants in Cohort 2 [≥ 55 years old] only). Blood samples were drawn from participants in case of any medical concerns, according to the investigator's judgment.

Vaccine immunogenicity was assessed by measurement of serum bAb specific to the SARS-CoV-2 S protein by ELISA and by measurement of serum nAb by pseudovirus and/or live wild-type virus neutralization assays.

2.7.3.1.1.3 Study 101 (Phase 1)

This is an ongoing Phase 1, open-label, dose-finding study in healthy men and nonpregnant women at least 18 years of age. This clinical study was designed to assess the safety, reactogenicity, and immunogenicity of mRNA-1273.

Up to 155 participants were planned to be enrolled in up to 13 cohorts (Table 2), with participants receiving an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29 and then followed through 12 months after the second vaccination (Day 394). The immunogenicity control group in this study is a serologic panel obtained from 41 participants convalescing from COVID-19. There was no safety control group in this study.

Table 2: Planned Study Cohorts

Cohort	Stratum (age in years)	mRNA-1273 Dose (µg) on Day 1 and Day 29
1	18 to 55	25
2	18 to 55	100
3	18 to 55	250
4	56 to 70	25
5	56 to 70	100
6	56 to 70	250
7	≥ 71	25
8	≥ 71	100
9	≥ 71	250
10	18 to 55	50
11	56 to 70	50
12	≥ 71	50
13	18 to 55	10

The Study 101 Day 119 CSR provides the interim analysis of safety and immunogenicity data through Day 119 for Cohorts 1 through 5, 7 and 8 and through Day 57 for Cohorts 10, 11, and 12; no participants were enrolled in Cohorts 6, 9, and 13 based on review of available interim safety and/or immunogenicity data. The Study 101 CSR Addendum 1 (Day 209) provides additional safety and immunogenicity data collected through Day 209. The Study 101 Day 119 CSR and the Study 101 CSR Addendum 1 (Day 209) together comprise the Phase 1 study data for this SCE and Application. The full overview of the Study 101 design is presented in the Study 101 Day 119 CSR.

Binding antibody titers were measured against SARS-CoV-2 S protein with 2 proline residues introduced for stability in a prefusion conformation (S-2P) using an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibody titers were assessed using the following viral neutralization assays: pseudovirus neutralization assay (PsVNA), plaque reduction neutralization test (PRNT) against wild-type SARS-CoV-2, and a focus-reduction neutralization test against mNeonGreen (FRNT-mNG) live virus.

Immunogenicity endpoints presented from the Study 101 CSR Addendum 1 (Day 209) in this SCE include the following:

- GMT and GMFR of SARS-CoV-2 S-2P-specific bAb titers through Day 209
- GMT and GMFR of SARS-CoV-2 receptor binding domain (RBD)-specific bAb titers through Day 209

- GMT and GMFR of nAb by PsVNA through Day 209 and by PRNT assay through Day 119

Safety endpoints presented in the Study 101 Day 119 CSR and the Day 209 CSR Addendum and in this Application include the following:

- Solicited local and systemic ARs through 7 days after each injection
- Unsolicited AEs through 28 days after each injection
- MAAEs
- SAEs
- New onset of chronic medical condition(s)

The Study 101 Day 119 CSR and Day 209 CSR Addendum include safety and immunogenicity data from the following 9 scheduled study site visits: Screening, Day 1, Day 8 (no immunogenicity), Day 15, Day 29, Day 36, Day 43, Day 57, Day 119 (3 months after the second injection), and Day 209 (6 months after the second injection). The immunogenicity results are summarized in Section 2.7.3.2.3 and the safety results are summarized in Section 2.7.4 of this Application.

All participants were monitored for safety and reactogenicity at each visit, starting with the first dose at Day 1. Additional safety and reactogenicity data were solicited via telephone calls to participants 1 and 2 days after each vaccination (Days 2, 3, 30, and 31).

Reactogenicity was assessed by the occurrence of solicited local (injection site) and systemic adverse reactions (ARs) from the time of each vaccination through 7 days after each vaccination. Unsolicited nonserious AEs were collected from the time of each vaccination through 28 days after each vaccination. Serious AEs, new onset of chronic medical conditions, and MAAEs are being collected throughout the study.

Clinical safety laboratory evaluations were performed at screening, immediately before each vaccination, and 7 days after each vaccination.

Evaluation of immunogenicity in serum included quantitation of bAb to the SARS-CoV-2 S protein at multiple time points after vaccination as measured by ELISA and by quantitation of nAb as measured by PsVNA, PRNT, and FRNT-mNG assays. T-cell responses to vaccination

were assessed using multiparametric flow cytometry of CD4+ and CD8+ T-cells in blood samples stained for intracellular cytokines on Days 1, 29, and 43.

2.7.3.2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Further details of the results of each study are provided in Module 5, in the respective CSRs. Of note, clinical efficacy of mRNA-1273 was not evaluated in either Study 201 or Study 101. Study 201 and Study 101 contribute immunogenicity data to this SCE.

2.7.3.2.1 Narrative of Study 301 (Phase 3)

The overview of the design of Study 301, including endpoints, is presented in Section 2.7.3.1.1.1. Three analyses of efficacy data have been performed on data from Part A of Study 301: the interim (efficacy) analysis, the primary (efficacy) analysis, and the final (efficacy) analysis. Unless stated otherwise, all results in this narrative are presented from the final efficacy analysis of Part A, based on the 04 May 2021 dataset. Results based on analyses of 2 earlier datasets of Study 301 are also briefly summarized. A tabular description of the analyses and corresponding datasets are presented in Table 3. Further details of the datasets and study results are found in the Study 301 Part A CSR.

Table 3: Description of Data Used to Analyze Efficacy and Safety for Study 301, Part A

Analysis Name	Efficacy Data Cutoff Date	Safety Data Cutoff Date	Dataset Date
Interim Analysis	07 Nov 2020	11 Nov 2020	11 Nov 2020
Primary Analysis	21 Nov 2020	25 Nov 2020	25 Nov 2020
Final Analysis	26 Mar 2021[a]	26 Mar 2021[a]	04 May 2021[b]

[a] Part A presents available data from the randomized, placebo-controlled, blinded phase of the study based on the database lock of 04 May 2021 and includes available participant level date up to early unblinding, study discontinuation, the Part B PDV or data cutoff date (26 Mar 2021), whichever was earlier. The results of Elecsys and RT-PCR assays for asymptomatic SARS-CoV-2 infection (obtained at the PDV) are included in the final analysis.

[b] Dataset date for final analysis reflects extensive cleaning of dataset prior to database lock.

In the 04 May 2021 dataset, a total of 30,351 participants were randomized and received at least 1 dose of investigational product (IP): 15,180 in the mRNA-1273 group and 15,166 in the placebo group. There were no obvious imbalances between treatment groups in demographic or other baseline characteristics. The median duration of follow-up from randomization to PDV

(ie, Part A) for participants who had a PDV before the data cutoff date was 148 days. Demography of the study is more fully summarized in Section 2.7.4.1.3.1.1, and exposure is summarized in Section 2.7.4.1.2.

2.7.3.2.1.1 Efficacy Results of Study 301

The primary efficacy endpoint of final analysis was the VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second injection, based on adjudication committee assessments (adjudicated COVID-19 cases). Sample size was driven by the total number of cases to demonstrate the VE (mRNA-1273 versus placebo) to prevent COVID-19 with the null hypothesis H_0: VE ≤ 30%.

At the interim analysis (11 Nov 2020 dataset), VE was demonstrated based on the prespecified success criterion for efficacy based on a total of 95 adjudicated cases (5 cases in the mRNA-1273 group and 90 cases in the placebo group). The VE for the primary efficacy endpoint at the interim analysis was 94.5% (95% CI: 86.5%, 97.8%; p <0.0001), based on the hazard ratio. The subsequent primary analysis of efficacy was performed on the 25 Nov 2020 dataset, with a total of 196 adjudicated COVID-19 cases for the primary efficacy endpoint. The VE for the primary efficacy endpoint at the primary analysis was 94.1% (95% CI: 89.3%, 96.8%; p < 0.0001), based on the hazard ratio.

Analysis of the primary efficacy endpoint on the 04 May 2021 dataset showed that the VE was 93.2% (95% CI: 91.0%, 94.8%; p <0.0001), based on the hazard ratio (Table 4) for a total of 799 adjudicated COVID-19 cases (55 cases in the mRNA-1273 group and 744 cases in the placebo group). The point estimate of the VE based on the incidence rate (95% CI) was 93.0% (90.8%, 94.8%). The point estimates of VE for the primary efficacy endpoint were consistent across analyses as the time on study and number of accrued cases increased, confirming persistent, high efficacy over a substantially larger case database and over the median 5.3-month blinded observation period from randomization in Part A.

For the 67 days (median) from the PDV through the data cutoff date (26 Mar 2021) covered in the Study 301 CSR Addendum 1 (Part B), cases of adjudicated COVID-19 were reported, and incidence rates were calculated for those participants remaining in their originally randomized groups beyond the PDV in Part B (Study 301 CSR Addendum 1 [Part B] Section 6.1.1). In the mRNA-1273 group, of 13,704 participants at risk, 19 (0.1%) adjudicated COVID-19 cases were detected in the per-protocol (PP) set. The corresponding incidence rate for the mRNA-1273 group remained low (7.961 cases per 1000 person-years; 95% CI: 4.793, 12.432). These results are consistent with Part A, where the incidence rate in the mRNA-1273 group was 9.599 cases

per 1000 person-years (95% CI: 7.231, 12.494). In the placebo group, of 1,175 participants at risk, 3 (0.3%) adjudicated COVID-19 cases were detected. The incidence rate for the placebo group was 77.378 cases per 1000 person-years; (95% CI: 15.957, 226.131), which was 10-fold higher than in the mRNA-1273 group. These Part B data confirmed the persistence of vaccine-induced protection for a total median observation period of 7.6 months from randomization or a median of 6.5 months after the second injection across Part A and Part B up to database lock for the analysis.

Sensitivity analyses based on the modified intent-to-treat (mITT) Set of the 04 May 2021 dataset gave results consistent with the primary analysis: VE based on hazard ratio for the mITT Set was 92.8% (95% CI: 90.6%, 94.5%).

Table 4: Primary Efficacy Endpoint Analyses of Study 301, Part A, Starting 14 Days After Second Injection (11 Nov 2020, 25 Nov 2020, and 04 May 2021 Datasets; Adjudicated Cases, Per-Protocol Sets)

	11 Nov 2020 Dataset, Interim Analysis		25 Nov 2020 Dataset, Primary Analysis		04 May 2021 Dataset, Final Analysis	
	Placebo (N=13,883)	**mRNA-1273 (N=13,934)**	**Placebo (N=14,073)**	**mRNA-1273 (N=14,134)**	**Placebo (N=14,164)**	**mRNA-1273 (N=14,287)**
Number of participants with COVID-19, n (%)	90 (0.6)	5 (<0.1)	185 (1.3)	11 (< 0.1)	744 (5.3)	55 (0.4)
Vaccine efficacy based on hazard ratio (95% CI)[a]		0.945 (0.865, 0.978)		0.941 (0.893, 0.968)		0.932 (0.910, 0.948)
p value[b]		<.0001		<.0001		<.0001
Person-years[c]	2697.5	2716.9	3273.7	3304.9	5445.2	5729.9
Incidence rate per 1,000 person-years (95% CI)[d]	33.365 (26.829, 41.011)	1.840 (0.598, 4.295)	56.510 (48.660, 65.266)	3.328 (1.662, 5.955)	136.633 (126.991, 146.814)	9.599 (7.231, 12.494)
Vaccine efficacy based on incidence rate (95% CI)[e]		0.945 (0.87, 0.98)		0.941 (0.892, 0.971)		0.930 (0.908, 0.948)

[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 ≤ 0.3.

[c] Person-years is defined as the total years from randomization date to the date of COVID-19, last date of study participation, or efficacy cutoff date, 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.

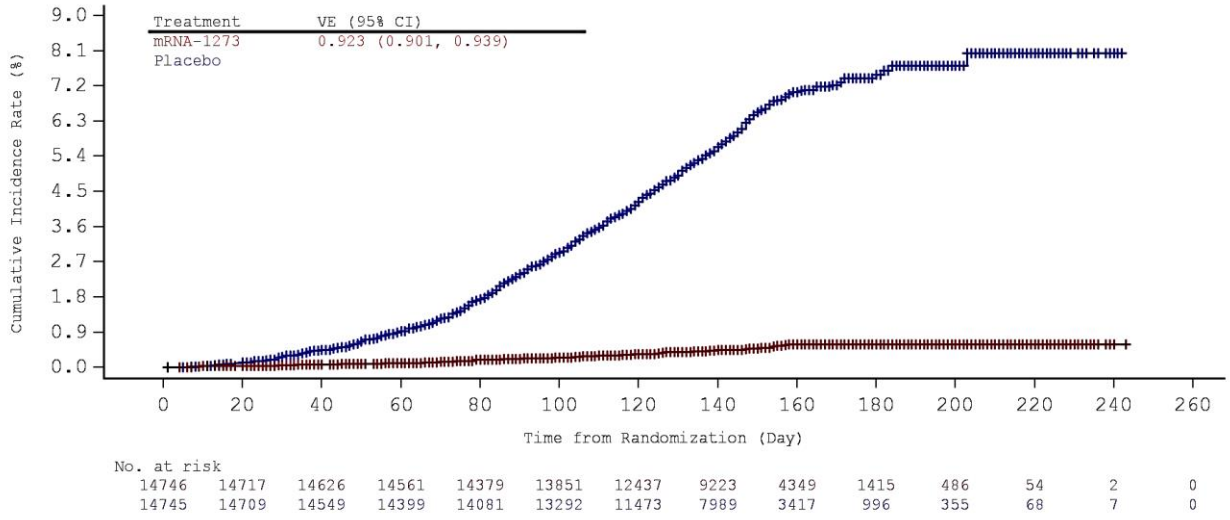
[e] Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Sources: Study 301 Part A CSR Table 6-1 and Table 6-2.

Analysis of adjudicated COVID-19 cases after randomization by time period in the mITT Set revealed that the number of cases starts to diverge between placebo and mRNA-1273 groups in the time period from randomization to 14 days after the first injection (Study 301 Part A CSR, Table 6-3). The cumulative incidence rate curves for adjudicated COVID-19 cases starting after randomization in the mITT Set (Figure 1) present a consistent picture, indicating early onset of protection. Thereafter, for the remainder of the 5.3-month median observation period for Part A, the cumulative incidence rate for the placebo group increased steadily while it remained stable and low in the mRNA-1273 group.

The mITT Set provides a more conservative estimate of VE and incidence rates than the PP Set by including participants who may have received only 1 dose of IP or who might have had a major protocol deviation, thereby including a broader population than the PP Set. Results were consistent with those observed for the PP Set: the VE point estimate (95% CI) based on the hazard ratio was 92.8% (90.6%, 94.5%).

Figure 1: Cumulative Incidence Rate Curves of COVID-19* Based on Adjudication Committee Assessments Starting After Randomization (mITT Set; 04 May 2021 Dataset)



Abbreviations: CI = confidence interval.

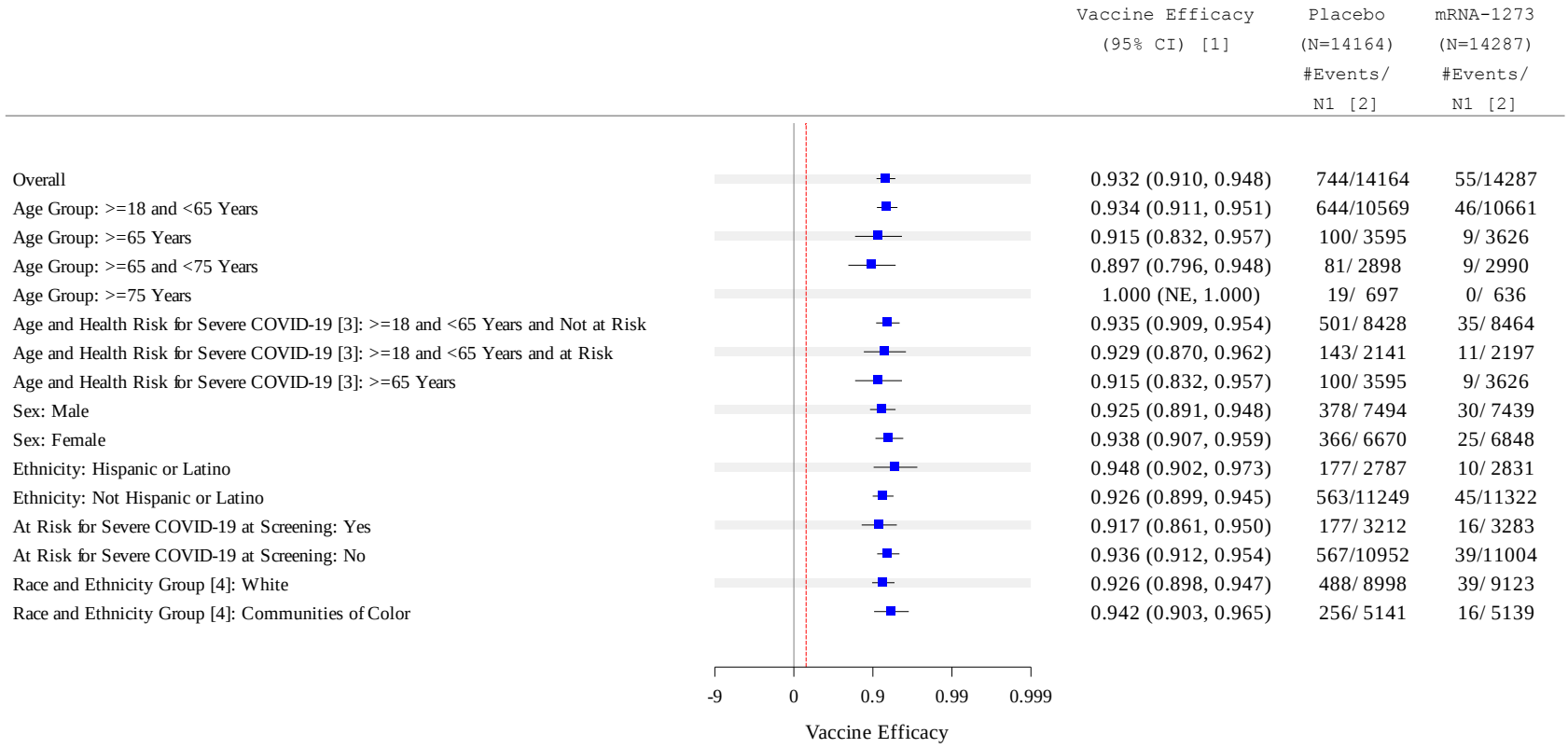
* With the censoring rules for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a subject had positive RT-PCR at pre-dose 2 visit (Day 29) without eligible symptoms within 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19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

Vaccine efficacy (VE) 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.

Source: Study 301 Part A CSR Figure 6-1.

The efficacy of mRNA-1273 for the primary efficacy endpoint based on the final analysis of the 04 May 2021 dataset was consistent across major demographic and baseline characteristic subgroups. The subgroup analysis results for the primary efficacy endpoint are presented in Figure 2.

Figure 2: **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 (Final Analysis, Per-Protocol Set)**



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

Note: The dotted red reference line indicates vaccine efficacy of 0.3, the acceptable lower bound for the 95% CI of the primary endpoint for the interim efficacy analysis.

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

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

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

[3] Age and health risk for severe COVID-19 are derived from age and risk factor collected on case report form (CRF).

[4] White is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported or missing.

Source: Study 301 Part A CSR Figure 6-2.

The VE of mRNA-1273 for the secondary endpoints based on the final Part A analyses of the 04 May 2021 dataset was consistent with the VE for the primary endpoint, with point estimates of VE in the range from 92.8% to 100% based on hazard ratios, with the exception of VE to prevent asymptomatic infection (63.0%) and VE to prevent SARS-CoV-2 infection regardless of symptomatology and severity (82.0%), which were anticipated to be lower given the inclusion of milder disease in the endpoints (Table 5).

Table 5: Summary of Primary and Secondary Efficacy Endpoint Analysis Results in Study 301 (Final Analysis, Per-Protocol Set)

	Placebo (N=14164)	mRNA-1273 (N=14287)
COVID-19* based on adjudication committee assessments starting 14 days after second injection		
Number of events	744	55
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.932 (0.910, 0.948)
p-value [b]		<.0001
COVID-19* starting 14 days after second injection		
Number of events	751	55
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.932 (0.911, 0.949)
Severe COVID-19* based on adjudication committee assessments starting 14 days after second injection		
Number of events	106	2
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.982 (0.928, 0.996)
Severe COVID-19* starting 14 days after second injection		
Number of events	118	3
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.976 (0.924, 0.992)
SARS-CoV-2 infection regardless of symptomatology and severity starting 14 days after second injection [c]		
Number of events	1339	280
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.820 (0.795, 0.842)
Secondary definition of COVID-19* starting 14 days after second injection		
Number of events	807	58
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.934 (0.914, 0.949)

	Placebo (N=14164)	mRNA-1273 (N=14287)
Death caused by COVID-19 starting 14 days after second injection		
Number of events	3	0
Vaccine efficacy based on hazard ratio (95% CI) [a]		1.000 (NE, 1.000)
COVID-19* based on adjudication committee assessments starting 14 days after first injection		
Number of events	769	56
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.933 (0.911, 0.949)
COVID-19* starting 14 days after first injection		
Number of events	782	58
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.931 (0.910, 0.947)
Asymptomatic SARS-CoV-2 infection starting 14 days after second injection [c]		
Number of events	498	214
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.630 (0.566, 0.685)
COVID-19* based on adjudication committee assessments starting 14 days after second injection regardless of prior SARS-CoV-2 infection, n/N [d]		
Number of events	754/15166	58/15180
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.928 (0.906, 0.945)
COVID-19* starting 14 days after second injection regardless of prior SARS-CoV-2 infection, n/N [d]		
Number of events	762/15166	58/15180
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.929 (0.907, 0.946)

Abbreviations: CI = confidence interval; RT-PCR = reverse transcription polymerase chain reaction.

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

[a] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor. For asymptomatic SARS-CoV-2 infection, VE and 95% CI are estimated using Fine and Gray's sub-distribution hazard model with disease cases as competing events and with the treatment group as a covariate, adjusting for stratification factor.

[b] 1-sided p-value from stratified Cox proportional hazard model to test the null hypothesis VE <= 0.3.

[c] Including participant decision visit.

[d] n and N are based on the number of subjects in the full analysis set.

Source: Study 301 Part A CSR Table 14.2.1.1.1.1.1.2.

The VE of mRNA-1273 to prevent adjudicated severe COVID-19 cases starting 14 days after second injection was consistent with the VE for the primary endpoint, confirming and extending the primary analysis of 25 Nov 2020. The analysis of adjudicated severe COVID-19 cases after randomization by time period revealed that the number of cases starts to diverge between placebo and mRNA-1273 groups in the time period of 7 to 14 days after the second injection (Study 301 Part A CSR, Table 6-5). Subgroup analyses of VE to prevent adjudicated severe COVID-19 were performed and the observed efficacy in each subgroup was consistent with the high efficacy observed across all cases of adjudicated severe COVID-19. As anticipated, participants at risk had a higher overall frequency of severe COVID-19 (1.4% and < 0.1% in the placebo and mRNA-1273 groups, respectively) compared with participants not at risk (0.6% and <0.1%, respectively). The VE point estimates (95% CI) based on the hazard ratio for at risk and no risk subgroups were similar at 97.9% (84.6%, 99.7%) and 98.5% (88.9%, 99.8%). Consistent VE point estimates were observed in subgroup analyses of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and human immunodeficiency virus infection.

For the less restrictive, secondary definition of COVID-19 (presence of at least one CDC-specified systemic symptom of COVID-19 AND a SARS-CoV-2-positive RT-PCR sample), the VE was consistent with the VE for the primary endpoint, indicating that mRNA-1273 is efficacious even against mild COVID-19.

The VE to prevent asymptomatic SARS-CoV-2 infection was analyzed in the PP Set and the mITT Set from randomization through the PDV. The sensitivity of the detection of asymptomatic infection was limited by the infrequency of assessment of seroconversion to anti-nucleoprotein positive (at Day 29, Day 57, and PDV) and the kinetics of seroconversion, which may take one to two weeks after the initial infection. A total of 712 participants had an asymptomatic SARS-CoV-2 infection starting 14 days after randomization in the PP Set (498 cases in the placebo group and 214 cases in the mRNA-1273 group); the VE point estimate (95% CI) based on the hazard ratio was 63.0% (56.6%, 68.5%; Table 5). The VE (95% CI) against all infections, symptomatic and asymptomatic, was 82.0% (79.5%, 84.2%; Table 5). It is notable that the lower bound of the 95% CI of VE to prevent asymptomatic SARS-CoV-2 infection exceeds 55%. This analysis confirms that vaccination with mRNA-1273 even protects against asymptomatic infection (albeit at a lower VE than for symptomatic cases).

The VE of mRNA-1273 to prevent SARS-CoV-2 infection, regardless of COVID-19 symptomatology and severity and starting 14 days after second injection, was consistent with the VE for the primary endpoint. The incidence of SARS-CoV-2 infection regardless of COVID-19 symptomatology and severity was higher in the placebo group over each time period starting in

the period from randomization up to 14 days after the first injection (Study 301 Part A CSR, Table 6-7), consistent with the corresponding analysis for COVID-19 cases.

Viral load during infection was assessed in adjudicated COVID-19 cases in the PP Set during Part A, from the Illness Visit (Day 1 of the convalescent period) through Day 28 of the convalescent period. From Day 1 through Day 9 of the convalescent period, the mean number of viral copies detected in the placebo arm was significantly higher than those in the mRNA-1273 arm, with the number being 100-fold lower among mRNA-1273 cases at Day 1 and 10-fold lower at Day 9 (Study 301 Part A CSR, Appendix 16.5)

Sequence information was obtained from all available SARS-CoV-2 PCR positive NP samples collected from July 2020 through May 2021 from participants in Part A (Study 301 Part A CSR, Appendix 16.5). Sequence data of the S protein gene were generated from 832 different samples, corresponding to 791 trial participants (720 from placebo recipients, 71 from mRNA-1273 recipients). To assess the relative prevalence of key variant lineages detected in the clinical dataset, Pango lineages were inferred for each isolate based on amino acid mutations detected in the S protein gene. The prevalences of selected lineages were then compared to those from a United States time-matched subset of the Global Initiative on Sharing All Influenza Data (GISAID) database. This comparison revealed that the sequences detected in adjudicated case samples were essentially a representation of the circulating strains in the US during the trial, with similar frequencies between the Part A and GISAID sample populations.

Of the total adjudicated COVID-19 cases starting 14 days after the second injection in the PP Set with sequence data during Part A, 18 were attributed to variants of concern or variants of interest in the placebo group and 3 in the mRNA-1273 group (Study 301 Part A CSR Ad Hoc Table 14.2.2.6.2.1.3 and Ad Hoc Table 14.2.2.6.2.1.4). For variants of concern detected at the time the exploratory analysis was conducted (B.1.427, B.1.429, P1), the VE point estimate (95% CI) based on the hazard ratio for 16 participants in the placebo group and 3 in the mRNA-1273 group was 82.4% (40.4%, 94.8%) (Ad Hoc Table 14.2.2.6.2.1.3). For the California variants of concern B.1.427 and B.1.429 combined, the VE point estimate (95% CI) based on the hazard ratio for 15 participants in the placebo group and 3 in the mRNA-1273 group was 81.2% (36.1%, 94.5%) (Ad Hoc Table 14.2.2.6.2.1.1). These results should be interpreted with caution given the low case numbers in both the mRNA-1273 and placebo groups.

2.7.3.2.1.2 Immunogenicity Results of Study 301

The results for the immunogenicity endpoints are presented through Day 57 (1 month after the second injection).

mRNA-1273 was highly immunogenic as measured by both bAb and nAb in both SARS-CoV-2 baseline-negative and baseline-positive individuals, as indicated by increased bAb and nAb levels 1 month after first injection (Day 29) and 1 month after second injection (Day 57).

Antibody levels at Day 29 in baseline-positive participants were similar to those observed at Day 57 in baseline-negative participants, indicating that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection. Among SARS-CoV-2 baseline-negative mRNA-1273 treated participants, seroresponse by bAb assay exceeded 99% at both Day 29 and Day 57 (Study 301 Part A CSR Table 6-12), while seroresponse by nAb assay was 81.4% at Day 29 and 98.9% at Day 57 (Study 301 Part A CSR Table 6-16). Similar results were observed for subgroups stratified by age (≥ 18 to < 65 years and ≥ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive participants.

While vaccination with mRNA-1273 was highly immunogenic and protective against COVID-19, breakthrough cases occurred and there was no apparent bAb level or nAb titer through Day 57 that was predictive of the presence or absence of COVID-19 cases.

2.7.3.2.1.2.1 SARS-CoV-2 Spike Protein-Specific Binding Antibodies as Measured by MesoScale Discovery Assay

As expected, the baseline GM level of SARS-CoV-2 S-protein IgG antibodies, as measured by MSD Multiplex assay, was higher at baseline in participants positive for SARS-CoV-2 (approximately 7000 AU/mL in both treatment groups) than in those who were negative for SARS-CoV-2 at baseline (approximately 115 AU/mL in both treatment groups) (Table 6).

mRNA-1273 is highly immunogenic in SARS-CoV-2 baseline-negative participants, as indicated by increased GM levels of anti-SARS-CoV-2 S-protein IgG antibodies on Day 29 (28 days after the first injection), which were further increased on Day 57 (28 days after the second injection) (Table 6 and Figure 3).

In SARS-CoV-2 baseline-positive mRNA-1273 treated participants, the GM levels on Day 29 were higher than those observed in baseline-negative mRNA-1273 treated participants, and were similar to those observed on Day 57 in baseline-negative mRNA-1273 treated participants, indicating that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection (Table 6 and Figure 3). mRNA-1273 is highly immunogenic in SARS-CoV-2 baseline-positive participants as measured by the MSD assay.

Table 6: Summary of Binding Antibody Specific to SARS-CoV-2 Spike Protein by MesoScale Discovery Assay by Baseline SARS-CoV-2 Status (Per-Protocol Random Subcohort for Immunogenicity)

Timepoint Data Category Statistic	Placebo (N=142)	mRNA-1273 (N=1055)
Baseline SARS-CoV-2 Status: Negative **Antibody: SARSCOV2S2P IgG Antibody (AU/mL) by MSD MULTIPLEX (LLOQ: 199.64, ULOQ: 1128438.87)**		
Baseline (day 1)		
n [a]	139	1046
GM level	114.514	114.842
95% CI [b]	(105.36, 124.46)	(110.82, 119.01)
Median	99.820	99.820
Min, Max	99.82, 4219.35	99.82, 686841.33
Day 29		
n [a]	139	1040
GM level	117.183	35752.817
95% CI [b]	(105.96, 129.59)	(33375.81, 38299.12)
Median	99.820	38717.833
Min, Max	99.82, 12742.93	99.82, 1064384.47
Day 57		
n [a]	141	1035
GM level	125.014	316448.298
95% CI [b]	(106.43, 146.84)	(300071.44, 333718.95)
Median	99.820	347458.394
Min, Max	99.82, 415541.60	99.82, 2020355.24

Timepoint Data Category Statistic	Placebo (N=130)	mRNA-1273 (N=130)
Baseline SARS-CoV-2 Status: Positive **Antibody: SARSCOV2S2P IgG Antibody (AU/mL) by MSD MULTIPLEX (LLOQ: 199.64, ULOQ: 1128438.87)**		
Baseline (day 1)		
n [a]	128	127
GM level	7126.943	6988.940
95% CI [b]	(4898.91, 10368.28)	(4832.11, 10108.48)
Median	11824.822	9198.493
Min, Max	99.82, 3729897.61	99.82, 1373004.50

Timepoint Data Category Statistic	Placebo (N=130)	mRNA-1273 (N=130)
Day 29		
n [a]	127	130
GM level	5672.206	410049.212
95% CI [b]	(3955.04, 8134.92)	(313904.05, 535642.52)
Median	8387.515	656888.423
Min, Max	99.82, 1279426.90	99.82, 6557162.89
Day 57		
n [a]	128	130
GM level	5185.775	668685.136
95% CI [b]	(3609.31, 7450.81)	(570883.47, 783241.82)
Median	7845.081	755936.141
Min, Max	99.82, 1161989.31	435.65, 5834191.86

Abbreviations: CI = confidence intervals; Min = minimum; Max = maximum; GM = geometric mean; MSD = MesoScale Discovery.

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

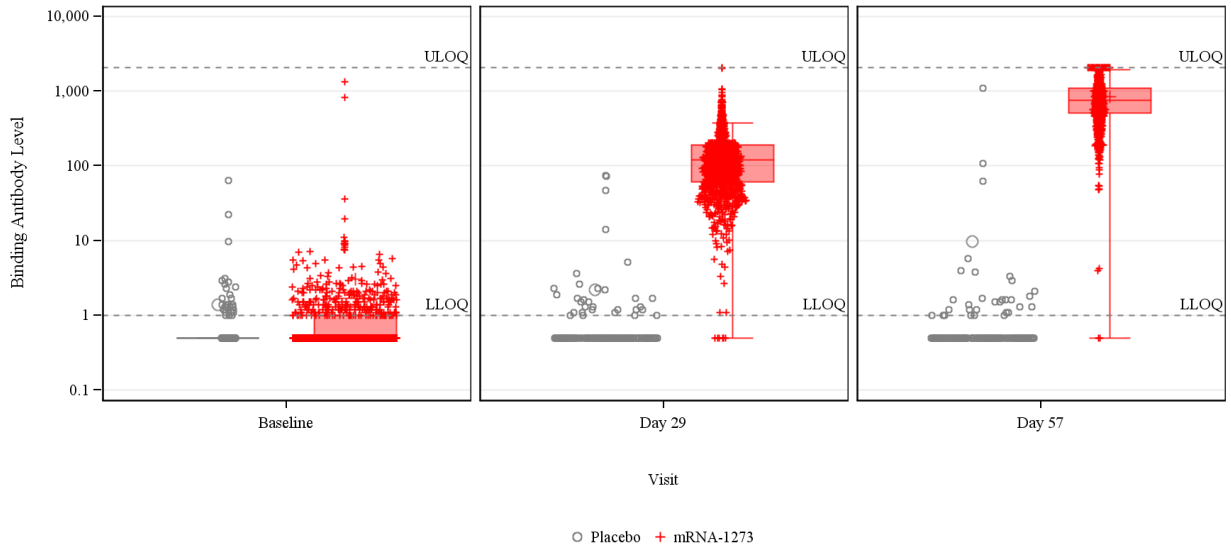
[a] Number of subjects with non-missing data at the corresponding timepoint.

[b] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value, then back transformed to the original scale for presentation.

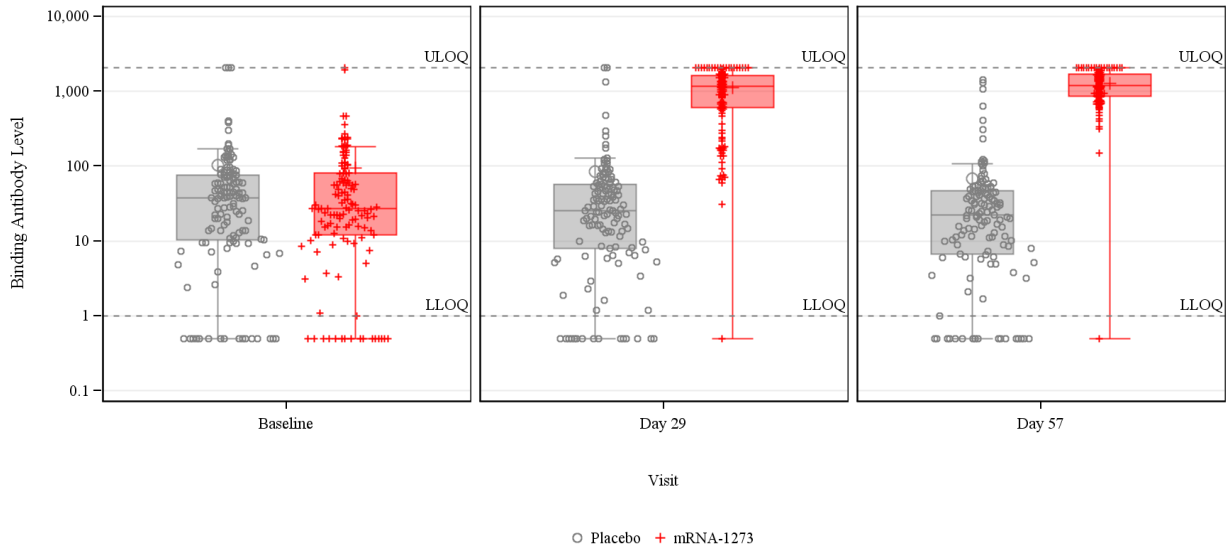
Source: Study 301 Part A CSR Table 6-12.

Figure 3 **Box Plots of Binding Antibody Specific to SARS-CoV-2 Spike Protein by MesoScale Discovery Assay by Baseline SARS-CoV-2 Status (Per-Protocol Random Subcohort for Immunogenicity)**

Baseline SARS-CoV-2 Status: negative
Antibody: SARS-COV-2 S2P IgG Antibody (AU/mL) by MSD MULTIPLEX (LLOQ: 199.64, ULOQ: 1128438.87)



Baseline SARS-CoV-2 Status: positive
Antibody: SARS-COV-2 S2P IgG Antibody (AU/mL) by MSD MULTIPLEX (LLOQ: 199.64, ULOQ: 1128438.87)



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

Source: Study 301 Part A CSR Figure 6-3.

Similar baseline results were observed for subgroups stratified by age (≥ 18 to < 65 years and ≥ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive participants (Study 301 Part A CSR Table 6-13 and Figure 6-4). In baseline-negative mRNA-1273 treated participants, the GM levels on Day 29 and Day 57 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years; however, seroresponse rates remained high (98.9% to 100%) across both age groups on Day 29 and Day 57. In baseline-positive mRNA-1273 treated participants, the GM levels on Day 29 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years, while Day 57 levels were similar between age groups; seroresponse rates ranged from 95.7% to 100% across both age groups on Day 29 and Day 57.

Overall, the results for SARS-CoV-2- S-2P protein IgG (VSDVAC65), as measured by ELISA assay were similar to those measured by MSD Multiplex assay (Study 301 Part A CSR Section 6.5.1.2).

2.7.3.2.1.2.2 SARS-CoV-2 Spike Protein-Specific Neutralizing Antibodies as Measured by Pseudotyped Virus Neutralization Assay

As expected, the baseline GM titers for the serum dilution required to achieve 50% neutralization (ID_{50}) neutralizing antibodies against SARS-CoV-2 S-protein, as measured by the PsVNA, were higher at baseline in participants who were positive for SARS-CoV-2 (approximately 83 for placebo group and 68 for mRNA-1273 treatment group) than in those who were negative for SARS-CoV-2 (approximately 9 and 10 for placebo and mRNA-1273 treatment groups, respectively; Table 7).

mRNA-1273 is highly immunogenic in SARS-CoV-2 baseline-negative participants, as indicated by increased ID_{50} GM titers on Day 29, which were further increased on Day 57 (Table 7 and Figure 4).

In SARS-CoV-2 baseline-positive mRNA-1273 treated participants, the ID_{50} GM titer levels on Day 29 were higher than those observed in baseline-negative participants, with titer levels that were similar to those observed on Day 57 in baseline-negative participants, supporting the observation that the first injection of mRNA1273 acts like a booster in participants with previous SARS-CoV-2 infection (Table 7 and Figure 4). mRNA-1273 is highly immunogenic in SARS-CoV-2 baseline-positive participants as measured by the PsVNA.

Table 7: Summary of Pseudovirus Neutralizing Antibody ID50 Titers by Baseline SARS-CoV-2 Status (Per-Protocol Random Subcohort for Immunogenicity)

Timepoint Data Category Statistic	Placebo (N=142)	mRNA-1273 (N=1055)
Baseline SARS-CoV-2 Status: Negative		
Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 4404)		
Baseline (day 1)		
n [a]	142	1052
GM titer	9.250	9.624
95% CI [b]	(NE, NE)	(9.35, 9.90)
Median	9.250	9.250
Min, Max	9.25, 9.25	9.25, 18997.56
Day 29		
n [a]	142	1055
GM titer	9.515	54.866
95% CI [b]	(9.00, 10.06)	(50.98, 59.04)
Median	9.250	55.527
Min, Max	9.25, 512.90	9.25, 26386.22
Day 57		
n [a]	142	1053
GM titer	9.903	1081.124
95% CI [b]	(8.99, 10.90)	(1019.80, 1146.14)
Median	9.250	1060.676
Min, Max	9.25, 2616.89	9.25, 63402.68

Timepoint Data Category Statistic	Placebo (N=130)	mRNA-1273 (N=130)
Baseline SARS-CoV-2 Status: Positive		
Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 4404)		
Baseline (day 1)		
n [a]	129	130
GM titer	82.519	68.117
95% CI [b]	(59.40, 114.64)	(49.88, 93.02)
Median	68.199	67.343
Min, Max	9.25, 135391.03	9.25, 258320.14
Day 29		
n [a]	129	130

Timepoint Data Category Statistic	Placebo (N=130)	mRNA-1273 (N=130)
GM titer	52.728	1478.910
95% CI [b]	(39.45, 70.48)	(1069.60, 2044.86)
Median	45.877	2485.351
Min, Max	9.25, 48317.06	9.25, 68671.79
Day 57		
n [a]	130	130
GM titer	47.708	3145.904
95% CI [b]	(35.41, 64.28)	(2539.80, 3896.66)
Median	37.961	3337.000
Min, Max	9.25, 49231.00	9.25, 54959.75

Abbreviations: CI = confidence intervals; Min = minimum; Max = maximum; GM = geometric mean.
Antibody values reported as below the lower limit of quantitation (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.

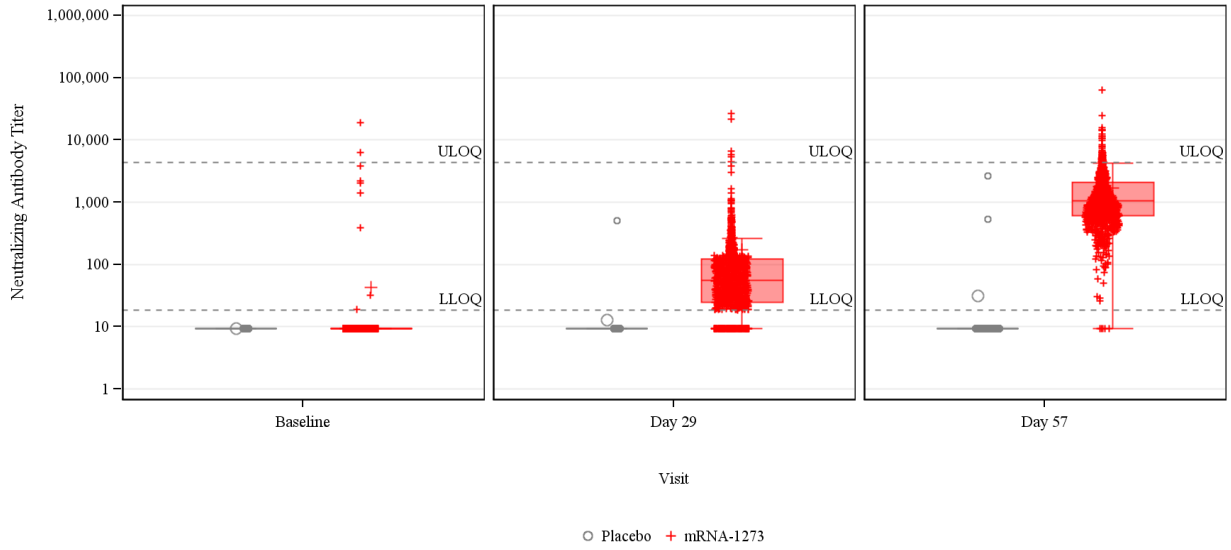
[a] Number of subjects with non-missing data at the corresponding timepoint.

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

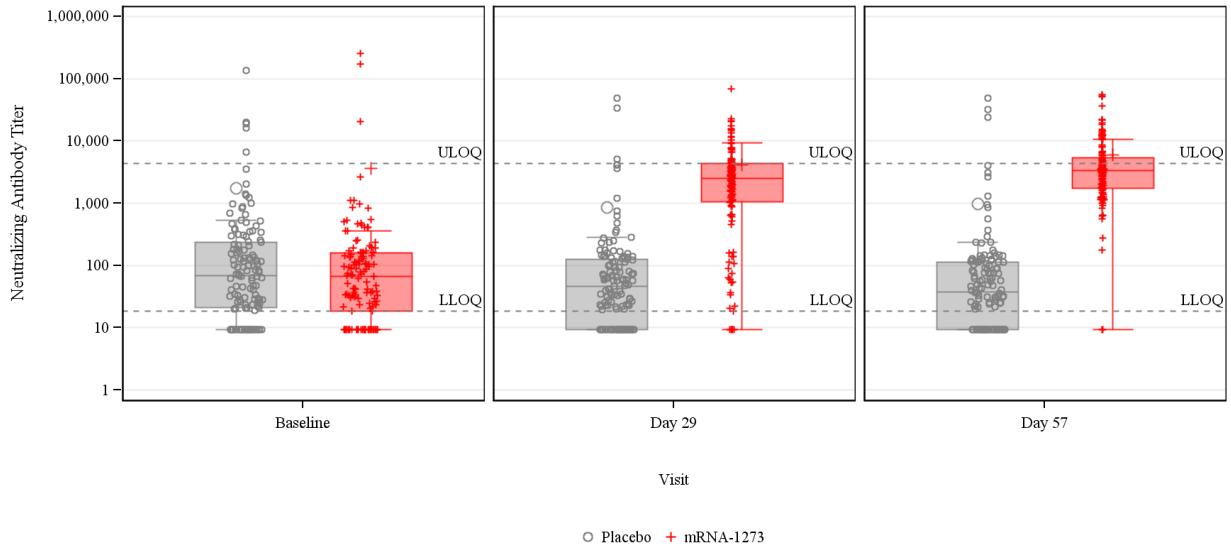
Source: Study 301 Part A CSR Table 6-16.

Figure 4: **Box Plots of Pseudovirus Neutralizing Antibody ID50 titers Neutralizing Specific to SARS-CoV-2 S-Protein by Pseudotyped Virus Neutralization Assay by Baseline SARS-CoV-2 Status (Per-Protocol Random Subcohort for Immunogenicity)**

Baseline SARS-CoV-2 Status: negative
Antibody: Pseudovirus Neutralizing Antibody ID_{50} Titers (LLOQ: 18.5, ULOQ: 4404)



Baseline SARS-CoV-2 Status: positive
Antibody: Pseudovirus Neutralizing Antibody ID_{50} Titers (LLOQ: 18.5, ULOQ: 4404)



Antibody values reported as below the lower limit of quantitation (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantitation (ULOQ) are replaced by ULOQ if actual values are not available.
Source: Study 301 Part A CSR Figure 6-7.

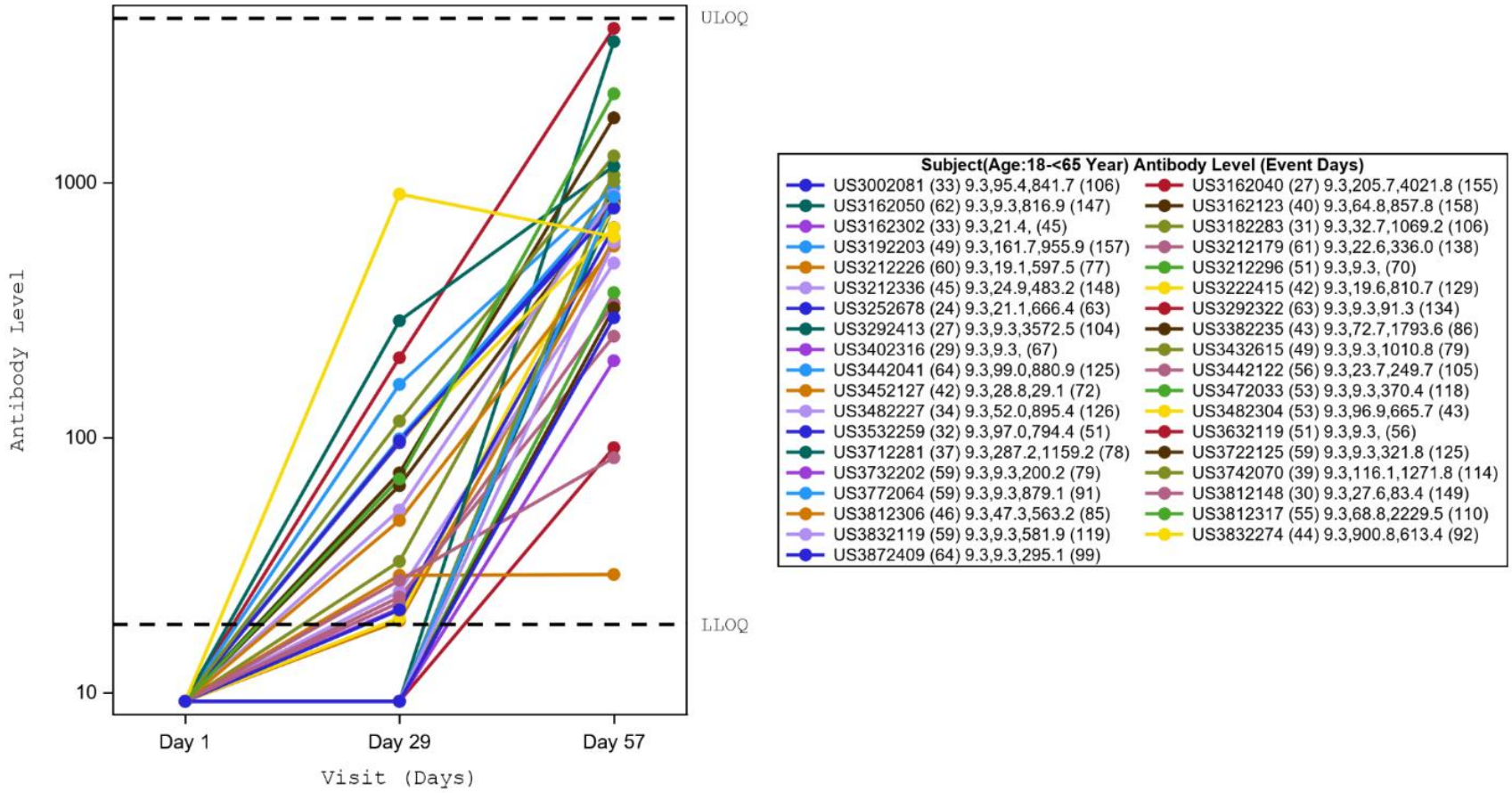
Similar baseline results were observed for both subgroups stratified by age (≥ 18 to < 65 years and ≥ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive participants (Study 301 CSR Part A Table 6-17 and Figure 6-8). In baseline-negative mRNA-1273 treated participants, the ID_{50} GM titers on Day 29 and Day 57 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years. The seroresponse rate was also lower in the older age group than in the younger age group on Day 29 (71.1% vs. 86.6%), with similar seroresponse rates observed in both age groups on Day 57 (99.4% vs. 98.6%). No notable differences were observed between age groups in SARS-CoV-2 baseline-positive participants. Similar results were observed for the serum dilution required to achieve 80% neutralization (ID_{80}) titers (Study 301 CSR Part A Section 6.5.1.3).

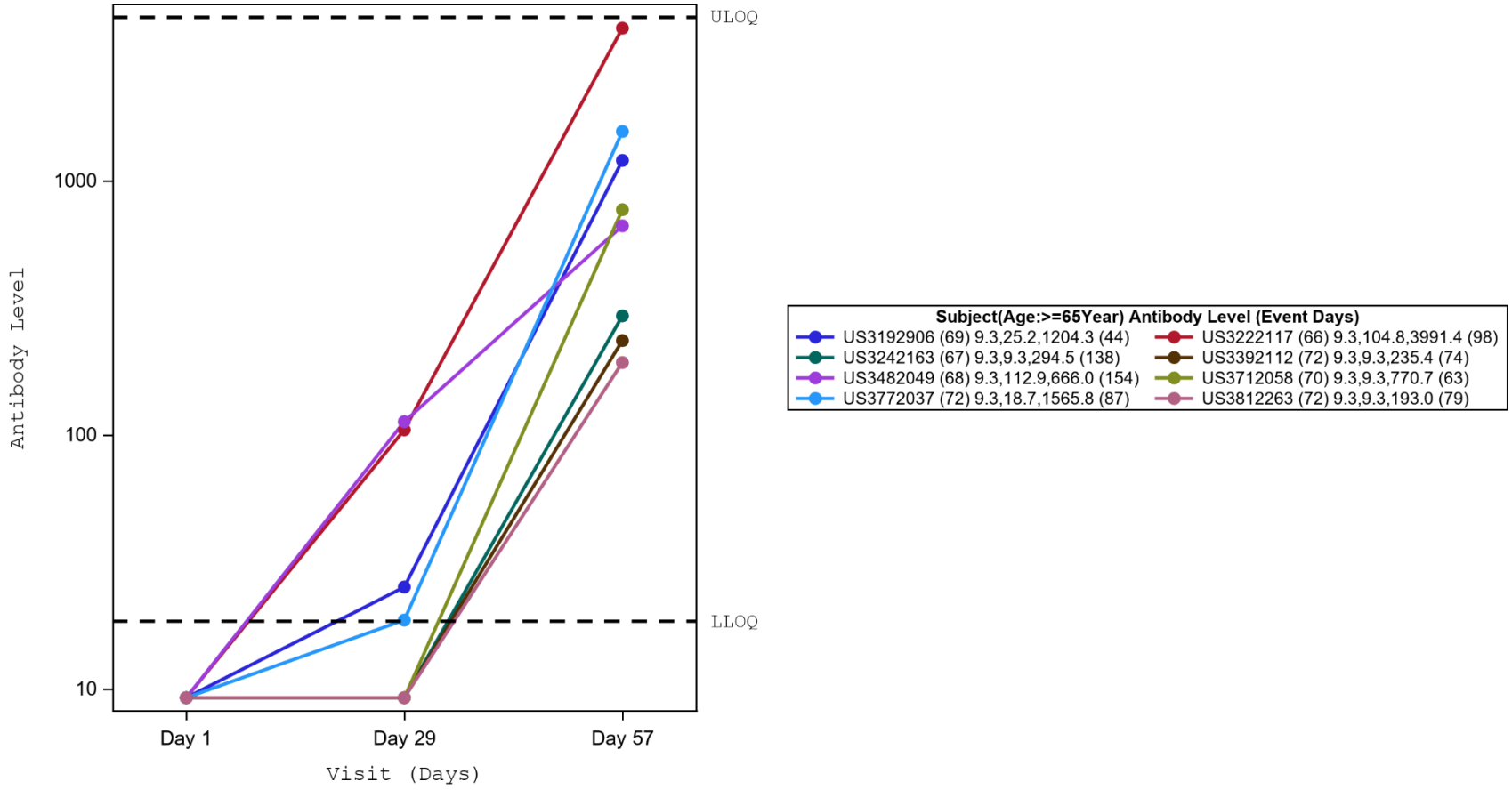
2.7.3.2.1.2.3 Analysis of Breakthrough COVID-19 Cases

Overall, while vaccination with mRNA-1273 was highly immunogenic and protective against COVID-19, there were still breakthrough cases of COVID-19 in the vaccinated group. There was no apparent bAb level or nAb titer through Day 57 that was predictive of the presence or absence of COVID-19 cases (Study 301 Part A CSR Section 6.5.2).

Available nAb data in mRNA-1273 participants who were adjudicated COVID-19 cases starting 14 days after second injection in the PP Set are presented in Figure 5. Similar results for bAb levels as measured by MSD assay or ELISA are presented in Study 301 Part A CSR Section 14 (Figure 16.2.2.1.3.1.1.3 and Figure 16.2.2.1.3.1.1.4, respectively).

Figure 5: **Plot of Pseudovirus Neutralizing Antibody ID50 in Participants on mRNA-1273 with COVID-19* Based on Adjudication Committee Assessments Starting 14 Days After Second Injection (Per-Protocol Set)**





COVID-19 cases with corresponding immunogenicity data available

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

Source: Study 301 Part A CSR Figure 6-9.

2.7.3.2.2 Narrative of Study 201 (Phase 2a)

Study 201 did not include any clinical efficacy endpoints, and immunogenicity was characterized by descriptive statistics, without formal statistical comparisons. The overview of the design of Study mRNA-1373-P201, including endpoints, is presented in Section 2.7.3.1.1.2. Further details of this study are found in the Study 201 Primary Analysis CSR and the Study 201 CSR Addendum 1 (End of Part A).

A total of 600 participants were randomly assigned to study treatment: 200 participants each in the placebo, mRNA-1273 50 µg, and mRNA-1273 100 µg groups. The participants in the Randomized Set were approximately two-thirds female (65.0%) and mostly White (94.8% and not Hispanic or Latino (92.0%), with a mean age of 50.8 years and an age range of 18 to 87 years (Study 201 Primary Analysis CSR Table 14.1.3.1). No apparent differences were observed in baseline demographics across treatment groups. With the exception of age and gender, baseline demographics in the younger cohort (Cohort 1; ≥ 18 to < 55 years) and the older cohort (Cohort 2; ≥ 55 years) were similar and generally consistent with the overall demographics for the total study population. The demography of the study is fully summarized in Section 2.7.4.1.3.2.1.

Immunogenicity was assessed by measurement of nAb against infective SARS-CoV-2 virus by MN assay and bAb against SARS-CoV-2 S-2P by enzyme-linked immunosorbent assay (ELISA). Levels of bAb and titers of nAb were capped at the upper limit of quantitation (ULOQ) for samples collected at Days 29, 43, and 57 for bAb (Table 8) and at Days 29, 43, 57, and 209 for nAb (Table 10).

2.7.3.2.2.1 Binding Antibody Response to Vaccination

The time course of bAb response to vaccination was similar between participants who received 100 µg doses of mRNA-1273 and those who received 50 µg doses, with the highest GM levels occurring at Day 43 for both dose levels (Table 8). The 100 µg dose group had numerically greater responses than the 50 µg dose group on Days 29, 43 (overlapping 95% CIs), 57, and 209 (Table 8). Interpretation of any apparent differences between bAb data from the 100 µg and 50 µg dose groups is limited by the capping of high levels, as demonstrated by the maximum of the range of GM levels at Days 29, 43, and 57. In the mRNA-1273 100 µg dose group, the GM level declined from the peak at Day 43 to Day 209. The Day 209 GM level remained higher than the GM level at Day 29, before the second injection.

Table 8: Summary of Binding Antibody Levels by Dose Group (Study 201, Per-Protocol Set for IgG Specific to SARS-CoV-2 Spike Protein)

		mRNA-1273	
Timepoint Statistic	**Placebo (N=186)**	**50 µg (N=185)**	**100 µg (N=189)**
Baseline			
n [a]	186	185	189
GM Value [b]	0.67	0.70	0.67
95% CI [b]	0.61, 0.73	0.63, 0.78	0.60, 0.73
Median	0.50	0.50	0.50
Min, Max	0.5, 20.4	0.5, 72.0	0.5, 135.5
Day 29			
n [c]	182	183	189
GM Value [b]	0.68	59.42	81.51
95% CI [b]	0.61, 0.76	52.05, 67.82	70.19, 94.67
Median	0.50	66.30	88.20
Min, Max	0.5, 144.4	5.8, 440.5	0.5, 2052.0
Day 43			
n [c]	180	176	180
GM Value [b]	0.65	720.85	834.66
95% CI [b]	0.59, 0.71	660.30, 786.96	765.28, 910.33
Median	0.50	765.25	896.20
Min, Max	0.5, 73.3	148.8, 2052.0	82.7, 2052.0
Day 57			
n [c]	174	176	174
GM Value [b]	0.67	519.48	647.22
95% CI [b]	0.60, 0.75	474.00, 569.33	588.98, 711.21
Median	0.50	577.80	709.15
Min, Max	0.5, 67.8	112.3, 2052.0	86.0, 2052.0
Day 209			
n [c]	154	170	174
GM Value [b]	0.91	97.02	128.00
95% CI [b]	0.73, 1.14	87.58, 107.47	114.44, 143.18
Median	0.50	94.80	128.15
Min, Max	0.5, 467.3	13.5, 854.2	19.5, 1362.4

Abbreviations: ANCOVA=analysis of covariance; AU=absorbance units; bAb=binding antibody; CI=confidence interval; GM=geometric mean; LLOQ=lower limit of quantitation; Max=maximum; Min=minimum; ULOQ=upper limit of quantitation.

Note: Units for antibody levels are AU/mL. Results are reported for the assay using the VAC65 IgG anti-spike antibody (LLOQ = 1, ULOQ = 2052).

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values that were greater than the ULOQ were converted to the ULOQ.

For visit Day 29, visit window (-3/+7 days) is 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 subjects with non-missing baseline.

[b] The GM values, GM fold-rise, and corresponding 95% CIs are estimated using ANCOVA model based on the log-transformed level with baseline level as a covariate for the post-baseline visits, then back transformed to the original scale for presentation. For Placebo, mRNA 50 ug and mRNA 100 ug, the ANCOVA model is based on Placebo, mRNA 50 ug and mRNA 100 ug.

[c] Number of subjects in the Per-Protocol Set for SARS-CoV-2-specific bAb at the corresponding visit.

Source: Study 201 CSR Addendum 1 (End of Part A) Table 8.

Comparing bAb GM levels between age cohorts, bAb GM levels were higher in the younger than in the older cohort for both 100 µg and 50 µg dose groups at all days postbaseline (Table 9). Within both age cohorts, GM levels were numerically higher in the 100 µg group than in the 50 µg group, although the difference was less pronounced in the older age cohort. Interpretation of any apparent differences between age cohorts is limited by the capping of high levels, as demonstrated by the maximum of GM levels at Days 29, 43, and 57. Within the 100 µg dose group, the bAb GM levels were numerically higher in the younger cohort than in the older cohort at Days 29, 43, 57, and 209 (Table 9).

Table 9: Summary of Binding Antibody Levels by Dose Group and Age Cohort (Study 201, Per-Protocol Set for SARS-CoV-2-Specific Antibody)

	Cohort 1 (Age ≥ 18 and Age < 55)			Cohort 2 (Age ≥ 55)		
		mRNA-1273			mRNA-1273	
Timepoint Statistic	Placebo (N=92)	50 µg (N=90)	100 µg (N=95)	Placebo (N=94)	50 µg (N=95)	100 µg (N=94)
Baseline						
n [a]	92	90	95	94	95	94
GM Value [b]	0.69	0.71	0.59	0.65	0.68	0.75
95% CI [b]	0.61, 0.79	0.60, 0.85	0.55, 0.64	0.58, 0.73	0.59, 0.78	0.63, 0.89
Median	0.50	0.50	0.50	0.50	0.50	0.50
Min, Max	0.5, 11.1	0.5, 72.0	0.5, 3.4	0.5, 20.4	0.5, 14.9	0.5, 135.5
Day 29						
n [c]	88	88	95	94	95	94
GM Value [b]	0.69	80.82	114.53	0.67	44.69	57.80
95% CI [b]	0.59, 0.82	69.20, 94.39	94.82, 138.34	0.57, 0.79	36.73, 54.36	46.67, 71.60
Median	0.50	80.65	134.90	0.50	46.70	63.15
Min, Max	0.5, 144.4	15.1, 338.7	0.5, 1666.1	0.5, 135.8	5.8, 440.5	0.5, 2052.0
Day 43						
n [c]	87	84	93	93	92	87
GM Value [b]	0.62	760.95	937.29	0.67	686.09	737.34
95% CI [b]	0.55, 0.70	678.54, 853.38	852.64, 1030.34	0.58, 0.79	600.95, 783.28	637.24, 853.16
Median	0.50	759.80	961.00	0.50	767.30	823.70
Min, Max	0.5, 8.5	164.3, 2052.0	199.5, 2052.0	0.5, 73.3	148.8, 2052.0	82.7, 2052.0
Day 57						
n [c]	83	84	85	91	92	89
GM Value [b]	0.68	566.56	772.04	0.66	479.93	546.89
95% CI [b]	0.57, 0.80	502.80, 638.40	694.74, 857.93	0.57, 0.77	418.32, 550.60	471.66, 634.13
Median	0.50	586.20	827.50	0.50	549.55	653.10
Min, Max	0.5, 67.8	165.7, 2052.0	135.3, 2052.0	0.5, 56.4	112.3, 2052.0	86.0, 1927.8
Day 209						
n [c]	74	80	90	80	90	84
GM Value [b]	0.96	104.13	132.94	0.86	91.11	122.92
95% CI [b]	0.69, 1.35	89.86, 120.66	113.31, 155.97	0.63, 1.17	78.93, 105.16	104.78, 144.19
Median	0.50	94.80	131.90	0.50	96.00	126.75
Min, Max	0.5, 467.3	29.0, 854.2	19.5, 1006.2	0.5, 446.9	13.5, 419.6	20.4, 1362.4

Note: Units for antibody levels are AU/mL. Results are reported for the assay using the VAC65 IgG anti-spike antibody (LLOQ = 1, ULOQ = 2052).

Abbreviations: ANCOVA=analysis of covariance; AU=absorbance units; bAb=binding antibody; CI=confidence interval; GM=geometric mean; LLOQ=lower limit of quantitation; Max=maximum; Min=minimum; ULOQ=upper limit of quantitation.

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values that were greater than the ULOQ were converted to the ULOQ.

For visit Day 29, visit window (-3/+7 days) is 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 subjects with non-missing baseline.

[b] The GM values, GM fold-rise, and corresponding 95% CIs are estimated using ANCOVA model based on the log-transformed level with baseline level as a covariate for the post-baseline visits, then back transformed to the original scale for presentation. For Placebo, mRNA 50 ug and mRNA 100 ug, the ANCOVA model is based on Placebo, mRNA 50 ug and mRNA 100 ug

[c] Number of subjects in the Per-Protocol Set for SARS-CoV-2-specific bAb at the corresponding visit.
Source: Study 201 CSR Addendum 1 (End of Part A) Table 9.

2.7.3.2.2.2 Neutralizing Antibody Response to Vaccination

The time course and magnitude of nAb response to vaccination was similar between participants who received 100 µg doses of mRNA-1273 and those who received 50 µg doses. Titers peaked at Day 43 and declined to Day 209 (Table 10). At Day 209, GMT remained higher than GMT observed at Day 29 for both 100 µg and 50 µg dose groups. While GMTs were numerically higher in the 100 µg dose group at each postbaseline time point, the 95% CIs were generally overlapping. Interpretation of any apparent differences between nAb data from the 100 µg and 50 µg dose groups is limited by the capping of high titers. Within the mRNA-1273 100 µg group, the nAb GMTs were numerically higher in the younger cohort than in the older cohort at Days 29, 43, 57, and 209 (Table 11).

Table 10: Summary of Neutralizing Antibody MN_{50} Titers by Dose Group (Study 201, Per-Protocol Set for SARS-CoV-2-Specific Antibody from All Lots)

Timepoint Statistic	Placebo (N=186)	mRNA-1273 50 µg (N=185)	mRNA-1273 100 µg (N=189)
Baseline			
n [a]	186	185	189
GMT [b]	47.109	46.500	46.684
95% CI [b]	45.745, 48.512	45.425, 47.600	44.957, 48.477
Median	45.550	45.550	45.550
Min, Max	45.55, 159.23	45.55, 169.71	45.55, 1357.65
Day 29			
n [c]	184	184	187
GMT [b]	49.231	173.750	227.433
95% CI [b]	46.355, 52.285	148.550, 203.225	194.207, 266.343
Median	45.550	169.706	254.559
Min, Max	45.55, 1357.65	45.55, 1810.19	45.55, 2031.87
Day 43			
n [c]	180	174	181
GMT [b]	48.059	1761.660	1813.480
95% CI [b]	45.820, 50.408	1690.216, 1836.124	1741.280, 1888.673
Median	45.550	2031.870	2031.870
Min, Max	45.55, 1357.65	339.41, 2031.87	226.27, 2031.87
Day 57			
n [c]	175	176	177
GMT [b]	49.141	1632.442	1656.064
95% CI [b]	46.267, 52.194	1550.245, 1718.998	1570.464, 1746.330
Median	45.550	1810.193	1917.830
Min, Max	45.55, 905.10	339.41, 2031.87	282.84, 2031.87
Day 209			
n [c]	153	171	174
GMT [b]	167.002	401.508	538.798
95% CI [b]	159.249, 175.133	350.667, 459.720	472.772, 614.045
Median	159.230	339.411	678.823
Min, Max	159.23, 1357.65	159.23, 1917.83	159.23, 1917.83

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean titer; LLOQ=lower limit of quantitation; Max=maximum; Min=minimum; MN=microneutralization; nAb=neutralizing antibody ULOQ=upper limit of quantitation.

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values that were greater than the ULOQ were converted to the ULOQ. For MN_{50} (the First Lot): LLOQ=91.10 and ULOQ=2031.87. For MN_{50} (the new Lot): LLOQ=318.46 and ULOQ=1917.83.

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

[a] Number of subjects with non-missing baseline.

[b] The GMT and corresponding 95% CIs are estimated using ANCOVA model based on the log-transformed titer with baseline titer as a covariate for the post-baseline visits, then back transformed to the original scale for presentation. For Placebo, mRNA 50 ug and mRNA 100 ug, the ANCOVA model is based on Placebo, mRNA 50 ug and mRNA 100 ug.

[c] Number of subjects in the Per-Protocol Set for SARS-CoV-2-specific nAb from All Lots at the corresponding visit.

Source: Study 201 CSR Addendum 1 (End of Part A) Table 10.

Table 11: Summary of Neutralizing Antibody MN_{50} Titers by Dose Group and Age Cohort (Study 201, Per-Protocol Set for SARS-CoV-2-Specific Antibody from All Lots)

	Cohort 1 (Age ≥ 18 and Age < 55)			Cohort 2 (Age ≥ 55)		
		mRNA-1273			mRNA-1273	
Timepoint Statistic	Placebo (N=92)	50 µg (N=90)	100 µg (N=95)	Placebo (N=94)	50 µg (N=95)	100 µg (N=94)
Baseline						
n [a]	92	90	95	94	95	94
GMT [b]	45.550	46.221	45.550	48.686	46.766	47.858
95% CI [b]	NE, NE	44.898, 47.582	NE, NE	45.950, 51.584	45.077, 48.519	44.348, 51.646
Median	45.550	45.550	45.550	45.550	45.550	45.550
Min, Max	45.55, 45.55	45.55, 169.71	45.55, 45.55	45.55, 159.23	45.55, 159.23	45.55, 1357.65
Day 29						
n [c]	90	89	94	94	95	93
GMT [b]	47.301	184.278	272.772	51.152	164.433	189.259
95% CI [b]	43.885, 50.982	147.555, 230.140	220.239, 337.837	46.555, 56.203	131.409, 205.756	150.303, 238.312
Median	45.550	226.274	339.411	45.550	159.230	169.706
Min, Max	45.55, 1357.65	45.55, 1357.65	45.55, 2031.87	45.55, 1357.65	45.55, 1810.19	45.55, 2031.87
Day 43						
n [c]	87	83	94	93	91	87
GMT [b]	45.550	1727.866	1902.388	50.532	1793.060	1722.081
95% CI [b]	NE, NE	1610.014, 1854.343	1844.760, 1961.817	46.091, 55.400	1710.583, 1879.514	1594.239, 1860.175
Median	45.550	2031.870	2031.870	45.550	2031.870	1917.830
Min, Max	45.55, 45.55	339.41, 2031.87	905.10, 2031.87	45.55, 1357.65	678.82, 2031.87	226.27, 2031.87
Day 57						
n [c]	84	84	87	91	92	90
GMT [b]	48.508	1584.249	1704.173	49.733	1677.724	1610.851
95% CI [b]	44.389, 53.009	1459.163, 1720.058	1602.726, 1812.040	45.745, 54.069	1571.714, 1790.885	1477.046, 1756.777
Median	45.550	1810.193	1917.830	45.550	1917.830	1917.830
Min, Max	45.55, 905.10	339.41, 2031.87	452.55, 2031.87	45.55, 905.10	452.55, 2031.87	282.84, 2031.87
Day 209						
n [c]	74	81	90	79	90	84
GMT [b]	167.803	435.677	558.848	166.255	373.053	518.114
95% CI [b]	155.864, 180.658	359.609, 527.836	468.470, 666.661	156.199, 176.960	307.612, 452.415	425.305, 631.174
Median	159.230	452.548	678.823	159.230	339.411	622.254
Min, Max	159.23, 1357.65	159.23, 1917.83	159.23, 1917.83	159.23, 1357.65	159.23, 1917.83	159.23, 1917.83

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean titer; LLOQ=lower limit of quantitation; Max=maximum; Min=minimum; MN=microneutralization; nAb=neutralizing antibody; NE=not estimated; ULOQ=upper limit of quantitation.

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values that were greater than the ULOQ were converted to the ULOQ. For MN_{50} (the First Lot): LLOQ=91.10 and ULOQ=2031.87. For MN_{50} (the new Lot): LLOQ=318.46 and ULOQ=1917.83.

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

[a] Number of subjects with non-missing baseline.

[b] The GMT and corresponding 95% CIs are estimated using ANCOVA model based on the log-transformed titer with baseline titer as a covariate for the post-baseline visits, then back transformed to the original scale for presentation. For Placebo, mRNA 50 ug and mRNA 100 ug, the ANCOVA model is based on Placebo, mRNA 50 ug and mRNA 100 ug.

[c] Number of subjects in the Per-Protocol Set for SARS-CoV-2-specific nAb from All Lots at the corresponding visit.

Source: Study 201 CSR Addendum 1 (End of Part A) Table 11.

2.7.3.2.3 Narrative of Study 101 (Phase 1)

The overview of the design of Study mRNA-1373-P101, including immunogenicity endpoints, is presented in Section 2.7.3.1.1.3. Immunogenicity was characterized by descriptive statistics, without formal statistical comparisons. Further details of the results of this study are found in the Study 101 Day 119 CSR and in the Study 101 CSR Addendum 1 (Day 209).

Of the participants 18 to 55 years of age, 15 received each of the following dose levels of mRNA-1273: 25 µg, 50 µg, 100 µg, and 250 µg. Of the participants 56 to 70 years of age, 10 participants received each of the following dose levels of mRNA-1273: 25 µg, 50 µg, and 100 µg. Of the participants ≥ 70 years of age, 10 received each of the following dose levels of mRNA-1273: 25 µg, 50 µg, and 100 µg. The mRNA-1273 250 µg dose was not evaluated in participants 56 to 70 years and ≥ 71 years of age due to increased reactogenicity of the 250 µg dose observed in 4 participants in the 18 to 55 year age group with similar immunogenicity compared to the 100 µg dose.

Immune responses from participants vaccinated in this study were compared to levels of antibodies in a panel of convalescent serum from 41 COVID-19 patients recovering from acute SARS-CoV-2 infection. The severity of COVID-19 was known for 38 of the serum donors and was classified as mild in 63% of the patients, moderate in 22% patients, and severe (defined as hospitalization requiring intensive care, ventilation, or both) in 15% patients. Time since diagnosis (onset of symptoms or positive PCR test) ranged from 23 to 54 days (median 34 days) for donors to the convalescent serum control panel. The age of serum donors ranged from 20 to 77 years (median 49); 19 were female and 22 were male.

mRNA-1273 administered in 2 doses separated by 28 days induced robust humoral responses compared to the panel of convalescent serum. Dose-dependent increases in bAb titers to both full-length S-2P and RBD were observed across age groups, and S-2P geometric mean titers were

generally higher for the 100 µg dose level than for either the 50 µg or 25 µg dose levels at all time points. Dose-dependent increases in nAb levels were detected across age groups by 3 neutralization assays (against a wild-type SARS-CoV-2 virus, a SARS-CoV-2 pseudovirus, and a high-throughput live SARS-CoV-2 reporter assay) but only after the second vaccination dose (Section 2.7.3.2.3.2). Binding antibody responses and nAb responses among all age groups for the 100 µg dose level persisted through Day 119 at levels that declined modestly relative to Day 57 but remained similar to or higher than responses in the panel of control convalescent serum. At Day 209, bAb and nAb responses appeared to have declined from Day 119 levels but remained within the respective 95% CIs of convalescent serum panel values.

Correlations were calculated within and between the values from binding antibody assays and nAb assays (Section 2.7.2). These correlations provide support for the use of each assay in characterizing the humoral response induced by mRNA-1273.

In assessments of cellular immune response at the 25 and 100 µg dose levels, mRNA-1273 elicited CD4+ T-cell responses after stimulation with S-specific peptide pools that were strongly biased toward expression of Th1 cytokines versus minimal Th2 cytokine expression; in contrast, CD8+ T-cell responses were below the LLOQ or detected at low levels (Section 2.7.3.2.3.3).

The accelerated development of mRNA-1273 during the pandemic was dependent on the availability of real-time data from the Phase 1 Study 101. The immune responses to the 25, 100, and 250 µg doses assessed by bAb against S-2P (Section 2.7.3.2.3.1) and by nAb in the PRNT against wild-type SARS-CoV-2 (Section 2.7.3.2.3.2) in adults 18 to 55 years of age were the essential data used to decide the dose of mRNA-1273 in the Phase 3 Study 301.

2.7.3.2.3.1 Binding Antibody Response to mRNA-1273 Vaccination

Binding antibody response to mRNA-1273 vaccination was assessed by S-2P ELISA and receptor binding domain (RBD) of S-2P ELISA. Focusing on the 25 µg, 100 µg, and 250 µg dose levels in the 18 to 55 year age group, the increase in bAb titer measured by S-2P ELISA was dose dependent, with geometric mean titer (GMT) increased with increased dose through Day 119 (Table 12). Immune response to mRNA-1273 vaccination was evident 2 weeks after the first vaccine dose (Day 15), and 1 week after the second vaccine dose (Day 36), GMT was higher than in the panel of convalescent serum (Table 12). These levels persisted through Day 119 at higher levels than in the panel of convalescent serum. In the 100 µg dose group, the GMT reached a peak at Day 43, followed by declines to Day 119 and then Day 209. At Day 209, bAb GMT levels had decreased to approximately 60% of the convalescent serum level but remained within the 95% CIs of the convalescent serum panel values.

In the 18 to 55 year age group, participants who received the 100 µg dose had higher levels of S-2P bAb than participants who received the 25 µg dose, and the 95% confidence intervals (CIs) did not overlap until Day 119 (Table 12). Similarly, participants who received the 250 µg dose had higher levels of S-2P bAb than participants who received the 100 µg dose, but the 95% CIs did overlap. In the 56 to 70 year and ≥ 71 year age groups, the results of the comparison between the 100 µg and 25 µg doses were similar to those from the 18 to 55 year age group, although with relatively wider CIs due to variability in immune response in a smaller number of participants (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 2 and Table 3).

Table 12: S-2P ELISA Geometric Mean Titer Results by Time Point and Treatment Group– Age 18-55, Per-Protocol Population

Time Point	Statistic	25 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 Serum
Day 1 (before injection 1)	n	15	15	15	41
	GMT	116	131	178	138901
	95% CI	72, 187	65, 266	81, 392	82876, 232799
Day 15 (14 days after injection 1)	n	15	15	15	
	GMT	32261	86291	163449	
	95% CI	18723, 55587	56403, 132016	102155, 261520	
Day 29 after injection 1 (before injection 2)	n	15	15	14	
	GMT	40227	109209	213526	
	95% CI	29094, 55621	79051, 150874	128832, 353896	
Day 36 after injection 1 (7 days after injection 2)	n	13	15	14	
	GMT	391018	781399	1261975	
	95% CI	267402, 571780	606247, 1007156	973972, 1635140	
Day 43 after injection 1 (14 Days after injection 2)	n	13	14	14	
	GMT	379764	811119	994629	
	95% CI	281597, 512152	656336, 1002404	806189, 1227115	
Day 57 after injection 1 (28 days after injection 2)	n	13	14	14	
	GMT	299751	782719	1255376	
	95% CI	206070, 436020	619310, 989244	969516, 1625521	
Day 119 after injection 1 (90 days after injection 2)	n	13	15	14	
	GMT	301540	413971	604507	
	95% CI	217148, 418729	322891, 530744	451387, 809568	

Time Point	Statistic	25 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 Serum
Day 209 after injection 1 (180 days after injection 2)	n	13	15	14	
	GMT	81697	84025	73802	
	95% CI	51860, 128702	60469, 116758	55937, 97372	

Abbreviations: CI=confidence interval; GMT=geometric mean titer; n=number of subjects with results available at a specified time point; N=number of subjects.
Source: Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 1.

The bAb results for the 50 µg dose level measured by the S-2P ELISA in Study 101 were not available before initiation of either Study 201 or Study 301 and thus did not contribute to the selection of dose levels for either subsequent study. In the 18 to 55 year age group, participants who received the 100 µg dose had higher levels of S-2P bAb than participants who received the 50 µg dose at Days 15, 43, 57, and 119, but lower levels at Days 29, 36, and 209 (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 1). The 95% CIs overlapped at each time point except Day 119. In the 56 to 70 and ≥ 71 year age groups, GMTs in the 100 µg dose group were higher from Day 15 through Day 209 (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 2 and Table 3).

The bAb results for the RBD ELISA were consistent with results obtained with the S-2P ELISA (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 4, Table 5, and Table 6).

2.7.3.2.3.2 Neutralizing Antibody Response to mRNA-1273 Vaccination

2.7.3.2.3.2.1 Plaque Reduction Neutralization Test

The PRNT assessed the neutralization titers against a wild-type SARS-CoV-2 infection of confluent monolayer cells, with neutralization titer expressed as the reciprocal of the highest serum dilution reducing virus infectivity by 80% ($PRNT_{80}$). These results were primary to deciding the dose of mRNA-1273 in the Phase 3 Study 301.

Comparing the results from the 25 µg and 100 µg dose groups, nAb titers were low prior to the first injection and had increased substantially by 14 days after the second injection (approximately 80-fold and 160-fold, respectively) in the 18 to 55 year age group (Table 13). Comparing results at Day 43 across age groups at the 100 µg dose level, the nAb titer was highest in the 56 to 70 year age group and lowest in the ≥ 71 year age group, with 95% CIs overlapping (Study 101 Day 119 CSR Section 14.2 Table 35, Table 36, and Table 37). At

Day 119 (90 days after the second injection), nAb titers persisted in all age groups, with persistence greatest in the 18 to 55 year age group and least in the ≥ 71 year age group (still approximately 40-fold higher than before the first injection).

Table 13: Plaque Reduction Neutralization Test Geometric Mean Titer by Treatment Group, Age Group, and Time Point – ID_{80} (Per-Protocol Population)

Time Point	Statistic	25 µg mRNA-1273 18-55 Years (N=15)	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)
Day 1 (before vaccination 1)	n	15	15	10	10
	GMT	4	4	4	4
	95% CI	NE	NE	NE	NE
Day 43 after vaccination 1 (14 days after vaccination 2)	n	13	14	9	10
	GMT	340	654	878	317
	95% CI	184, 627	460, 930	516, 1494	181, 557
Day 119 after vaccination 1 (90 days after vaccination 2)	n		15	9	10
	GMT		430	269	165
	95% CI		277, 667	134, 542	82, 332

Abbreviations: CI = confidence interval; GMT = geometric mean titer; N = number of subjects; n = number of subjects with results available at indicated time point; NE = not estimable.
Source: Study 101 Day 119 CSR Section 14.2 Table 35, Table 36, and Table 37.

2.7.3.2.3.2.2 Pseudovirus Neutralization Assay

The PsVNA assessed neutralization titers against a virus pseudotyped to SARS-CoV-2 infecting a confluent cell monolayer, with neutralization titer expressed as the reciprocal of the highest serum dilution reducing virus infectivity by 50% (50% inhibitory dilution, ID_{50}) or 80% (80% inhibitory dilution, ID_{80}).

Focusing on the 25 µg, 100 µg, and 250 µg dose levels in the 18 to 55 year age group, PsVNA titers of nAb (both ID_{50} and ID_{80}) were undetectable before the first injection, were marginally higher on Day 15 and Day 29 (before the second injection), and substantially increased after the second injection, starting with Day 36 (Table 14 [ID_{50} results] and Study 101 CSR Addendum 1 [Day 209] Section 14.2 Table 16 [ID_{80} results]). In all 3 dose groups, the GMTs at Day 36, Day 43, and Day 57 were similar to or higher than the GMT of the panel of convalescent serum. The GMTs of the 100 µg and 250 µg dose groups were approximately 2- to 3-fold higher than the GMT of the 25 µg dose group from Day 36 through Day 119, and the 95% CIs were not overlapping between the 25 µg dose group and the 100 µg and 250 µg dose groups. At Day 119, the GMTs of the 100 µg and 250 µg dose groups (182 and 185, respectively) remained above the GMT of the panel of convalescent serum (106), although the GMT of the 25 µg dose group (54) did not. At Day 209, the GMT of the 100 µg dose group had decreased approximately 56% from the Day 119 GMT, to approximately 75% of the convalescent serum panel (overlapping 95% CIs).

Compared to the 18 to 55 year age group results for the 100 µg and 25 µg dose levels, results for the ID_{50} in the 56 to 70 and ≥ 71 year age groups were similar (Study 101 CSR Addendum 1 [Day 209] Section 14.2 Table 14 and Table 15). At the 100 µg dose level, results for the ID_{50} for the 56 to 70 and ≥ 71 year age groups were similar to the results in the 18 to 55 year age group.

Compared to the ID_{50} results, the ID_{80} results were qualitatively similar in comparisons among age groups and dose groups with ID_{80} GMTs and 95% CIs lower by approximately 50% to 60% than the corresponding ID_{50} values (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 16, Table 17, and Table 18).

Table 14: Pseudovirus Neutralization Geometric Mean Titer Results by Time Point and Treatment Group – ID_{50} - Age 18-55, Per-Protocol Set

Time Point	Statistic	25 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 Serum Panel
Day 1 (before injection 1)	n	15	15	15	41
	GMT	10	10	10	106
	95% CI	NE	NE	NE	60, 189
Day 15 (14 days after injection 1)	n	15	15	15	
	GMT	14	24	26	
	95% CI	10, 21	13, 42	14, 48	
Day 29 after injection 1 (before injection 2)	n	15	15	14	
	GMT	12	18	21	
	95% CI	10, 14	12, 27	13, 32	
Day 36 after injection 1 (7 days after injection 2)	n	13	15	14	
	GMT	106	263	378	
	95% CI	70, 160	188, 368	306, 468	
Day 43 after injection 1 (14 Days after injection 2)	n	13	14	14	
	GMT	112	360	342	
	95% CI	71, 177	273, 476	267, 438	
Day 57 after injection 1 (28 days after injection 2)	n	13	14	14	
	GMT	90	276	277	
	95% CI	57, 143	193, 393	231, 332	
Day 119 after injection 1 (90 days after injection 2)	n	13	15	14	
	GMT	54	182	185	
	95% CI	29, 100	112, 296	128, 269	
Day 209 after injection 1 (180 days after injection 2)	n	13	15	14	
	GMT	25	80	59	
	95% CI	15, 40	48, 135	34, 103	

Abbreviations: CI = confidence interval; GMT = geometric mean titer; N = number of subjects; n = number of subjects with results available at indicated time point; NE = not estimable.

Source: Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 13.

The nAb results for the 50 µg dose level measured by the PsVNA in Study 101 were not available before initiation of either Study 201 or Study 301 and thus did not contribute to the selection of dose levels for either subsequent study.

In the 18 to 55 year age group, ID_{50} GMT values were similar between the 50 µg and 100 µg dose groups at all measured time points from Day 36 through Day 209, with overlapping 95% CIs (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 13).

In the 56 to 70 year age group, the 100 µg dose group had ID_{50} GMT values approximately 2 to 3 times higher than the 50 µg dose group at Days 36, 43, 57, and 119. At Day 209, the ID_{50} GMT value of the 100 µg dose group was approximately 3 times higher than both the 50 µg dose group and the 25 µg dose group (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 14). The results in the ≥ 71 year age group were similar to those in the 56 to 70 year age group, with an approximate 2-fold difference between 100 µg and 50 µg dose groups at Day 209 (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 15). In the 2 older age groups at Day 119, the ID_{50} GMT values at the 100 µg dose level were higher than the value for the convalescent serum panel. Apparent differences across age groups should be interpreted with caution due to the small sample sizes.

The ID_{80} analysis gave similar results to the ID_{50} analysis for the comparison between the 100 µg and 50 µg dose groups (Study 101 CSR Addendum 1 (Day 209) Section 14.2 Table 16, Table 17, and Table 18).

2.7.3.2.3.3 Intracellular Cytokine Stimulation Assay

An intracellular cytokine stimulation assay was used to evaluate T-cell responses elicited by the mRNA-1273 vaccine in peripheral blood mononuclear cell samples following stimulation with S1 and S2 subunit specific peptide pools. The T-cell response data supported the cellular immunity profile for mRNA-1273 with the following observations, from blood samples at Day 1 (before vaccination 1), Day 29 (before vaccination 2), and Day 43 (14 days after vaccination 2):

- The 25 µg and 100 µg doses elicited CD4+ T-cell responses after stimulation with S-specific peptide pools that were strongly biased toward the expression of Th1 cytokines (tumor necrosis factor α > interleukin 2 > interferon γ) versus minimal Th2 cytokine expression (interleukin 4 and interleukin 13). The response in the 100 µg mRNA-1273 group was numerically higher than that in the 25 µg mRNA-1273 group across all age groups, with minimal (if any) expression at Day 29 and response detected at Day 43.

- CD8+ T-cell responses were below the LLOQ of the assay at Day 29 and below the LLOQ or detected at low levels at Day 43 in the 100 µg mRNA-1273 group.

Days 29 and 43 may not have been the optimal timepoints for studying either CD4+ or CD8+ responses after vaccination, limiting interpretation of these results. Nonetheless, the minimal Th2 cytokine expression is consistent with the lack of vaccine-associated enhanced respiratory disease (VAERD) observed in Study 301 (Study 301 Part A CSR Section 7.3.3.4).

2.7.3.3 COMPARISON OF RESULTS ACROSS STUDIES

This Application presents VE analyses exclusively from the pivotal Phase 3 Study 301. Efficacy to protect against SARS-COVID-19 was only assessed in Study 301. Given the differences in study population size, baseline demographics and characteristics (including medical history), immunogenicity assays, and study objectives among the Phase 3 (Study 301), Phase 2a (Study 201), and Phase 1 (Study 101) studies, comparisons of results across studies are of limited utility.

2.7.3.3.1 Study Populations

All efficacy data were derived from Study 301, which enrolled more than 30,000 participants (of whom more than 15,000 received 100 µg of mRNA-1273) (Section 2.7.3.2.1). The other 2 studies were much smaller and contributed immunogenicity data to this SCE: Study 201 included 600 participants, 400 of whom received mRNA-1273 (Section 2.7.3.2.2) and Study 101 included 120 participants, all of whom received mRNA-1273 (Section 2.7.3.2.3).

An overview of differences in baseline characteristics of study populations among studies is presented in Section 2.7.3.3.1.3.

2.7.3.3.1.1 Characteristics of Disease

In all 3 studies with results presented in this SCE, the participants were included if they had no known history of COVID-19 prior to study randomization. Participants shown to have been infected before the second dose of IP were excluded from the per-protocol (PP) analysis across studies. In Study 301, 2.3% of participants overall had evidence of prior SARS-CoV-2 infection at baseline (Study 301 Part A CSR). There was no evidence of prior SARS-CoV-2 infection at baseline in either Study 201 (Study 201 Primary Analysis CSR) or Study 101 (Study 101 Day 119 CSR).

2.7.3.3.1.2 Study Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were similar across studies. All studies excluded participants with a known history of COVID-19 or recent exposure to COVID-19 prior to randomization. Study 301 sought inclusion of participants with a broad range of medical comorbidities, while Study 201 and Study 101 excluded participants with many (Study 201) or all (Study 101) medical comorbidities.

2.7.3.3.1.3 Differences in Baseline Characteristics of Study Populations

All 3 studies included adults across a broad age range (18 to 95 years of age), reasonably balanced between sexes, with a greater proportion of women in the older age groups. The studies differed in racial and ethnic diversity, medical comorbidities, and risk of exposure to COVID-19.

As a pivotal efficacy trial during the COVID-19 pandemic, Study 301 included participants who were at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. In addition to healthy adults, the study enrolled adults with pre-existing medical conditions who were in stable condition. This included the 16.7% of participants less than 65 years of age who had at least 1 of the prespecified comorbidities that put them at increased risk of severe COVID-19. In addition, 24.8% of participants were at least 65 years of age and may have had 1 or more medical comorbidities adding to their increased risk of severe COVID-19 based on their age. Study 301 included 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 was 10.2%, and 20.5% of participants self-reported as Hispanic or Latino. Communities of color (participants not White and non-Hispanic, including all others whose race or ethnicity is not unknown, unreported, or missing) represented 37.2% of the study population.

Participants in Study 101 and Study 201 were overwhelmingly White and non-Hispanic and were in good general health, without a medical condition that may have interfered with the evaluation of responses to vaccination or the participant's successful completion of the study. Study 101 and Study 201 were intended to show the immunogenicity and safety of the vaccine in populations that were unlikely to acquire SARS-CoV-2 infection during the study, to avoid complicating interpretation of results.

A comparison of baseline characteristics of study populations across studies is provided in Section 2.7.4.1.3.

2.7.3.3.1.4 Differences Between Populations Included in Efficacy Analyses

Efficacy analyses (VE) were performed only for Study 301.

2.7.3.3.1.5 Comparison to Overall Patient Population Expected in the Marketplace

For Study 301, 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 in the US, where the study was conducted (US Census Bureau 2019: Black [13.4%], Hispanic or Latino [18.5%]). Communities of color represented 37.2% of the study population. 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 (25.2%) of participants with a specified occupational risk for acquisition of SARS-CoV-2 were health care workers.

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 comorbid medical conditions such as diabetes (Type 1, Type 2, or gestational), significant cardiac disease, chronic pulmonary disease, severe obesity, liver disease, and human immunodeficiency virus infection. The study enrolled a total of 41.5% of participants who were considered at risk for severe COVID-19 (16.7% participants who were < 65 years and at risk, and 24.8% participants ≥ 65 years), indicating that enrollment goals were met

The proportion of participants in each demographic category were generally similar between the mRNA-1273 and placebo groups. The full demographics of the study population in Study mRNA-1273-P301 is presented in Table 14.1.3.1.3 of the Study 301 Part A CSR.

2.7.3.3.1.6 Assessment of Participants Discontinuing Treatment or Withdrawing From the Study Early

In the pivotal Study 301, 3.3% of participants who received a first injection did not receive a second injection (Study 301 Part A CSR Table 5-1). A total of 531 participants (3.5%) who were randomly assigned to receive placebo and 453 participants (3.0%) who were randomly assigned to receive mRNA-1273 discontinued the study vaccine. The most common reasons for discontinuation of study vaccine were confirmed SARS-CoV-2 infection (ie, diagnosed

COVID-19 by detection of SARS-CoV-2 in Day 1 NP swab or COVID-19 diagnosed prior to Day 29), other, and withdrawal of consent by participant.

A total of 2,099 participants (13.8%) in the placebo group and 730 participants (4.8%) in the mRNA-1273 group withdrew from the study before the 26 Mar 2021 data cutoff date. The most common reasons for discontinuation from the study were protocol deviation, other, and withdrawal of consent by participant. The bulk of discontinuations resulting in an imbalance between the placebo and mRNA-1273 groups coincided with the EUA of the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine. There was no evidence that the percentage discontinuing treatment or withdrawing was related to administration of mRNA-1273.

In Study 201, 1.8% (7/400) of participants who received a first injection mRNA-1273 did not receive a second injection (Study 201 Primary Analysis CSR Table 7). A similar percentage of participants (1.5%) withdrew from the study before the Study 201 Primary Analysis CSR data cutoff date. There was no evidence that the percentage discontinuing treatment or withdrawing was related to the administered dose of mRNA-1273.

In Study 101, 3.3% (4/120) participants who received a first injection mRNA-1273 did not receive a second injection and no participants withdrew from the study before the data cutoff date for the Study 101 Day 119 CSR.

2.7.3.3.2 Comparison of Efficacy Results Across Studies

mRNA-1273-P301 is the only study providing VE results in this Application (Section 2.7.3.2.1).

2.7.3.3.3 Comparison of Immunogenicity Results Across Studies

The kinetics of immunogenicity of the 100 µg dose level in Study 301 for Days 1 through 57 (Section 2.7.3.2.1.2) confirm and add needed precision to the immunogenicity kinetics first identified in Study 101, which were the basis for the selection of the 100 µg dose for Study 301. The immunogenicity of the 100 µg dose was qualitatively consistent across all studies for each age group for all common time points for both nAb and bAb (Section 2.7.3.2.1.2, Section 2.7.3.2.2, and Section 2.7.3.2.3). Study 301 tested drug product prepared with the final manufacturing process and provided immunogenicity data produced with fully validated assays for bAb and nAb.

Study 101 provided initial evidence that the 100 ug dose was more immunogenic than the 25 µg dose, supporting the selection of the 100 ug dose for Study 301. After the initiation of Study 301, Study 101 provided additional evidence of the high immunogenicity of 100 µg dose, with possibly higher efficacy than the 50 µg dose in older age groups at Days 119 and 209.

Study 201 provided confirmation of the robust immunogenicity of the 100 µg and 50 µg doses. For the 100 µg and 50 µg dose levels, immunogenicity was qualitatively consistent between Study 201 and Study 101 for each age group for all common time points for both nAb and bAb.

2.7.3.3.3.1 Immunogenicity Correlates of Protection

While vaccination with mRNA-1273 was highly immunogenic and protective against COVID-19, there was no apparent bAb level or nAb titer through Day 57 in Study 301 that was predictive of the presence or absence of COVID-19 cases (Study 301 Part A CSR Section 6.5.2).

Data on viral genotypic correlates of risk, as reflected in VE, are presented in Section 2.7.3.2.1.1.

2.7.3.3.4 Comparison of Results in Subpopulations

In Study 301, the efficacy of mRNA-1273 for the primary efficacy endpoint was consistently high across major demographic and baseline characteristic subgroups (Figure 2). Comparisons of VE results across and between subpopulations are only available from Study 301 in this Application (Section 2.7.3.2.1.1).

Comparing immunogenicity across studies, participants who received 2 doses of mRNA-1273 100 µg developed consistently robust immune responses measured by SARS-CoV-2-specific bAb and nAb, regardless of age cohort (Section 2.7.3.2.1.2, Section 2.7.3.2.2, and Section 2.7.3.2.3). Differences in age cohort ranges across studies complicate direct comparisons.

For Study 201 and Study 101 immunogenicity analyses, small subpopulation sizes and restricted participant diversity in Study 201 and Study 101 relative to Study 301, reduce the utility of comparing results in subpopulations across studies. Small subpopulations are particularly problematic in Study 101, while in Study 201, immunogenicity assay values were capped at high titers.

2.7.3.4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Study 301, conducted in more than 30,000 participants randomized in a 1:1 ratio between mRNA-1273 and placebo groups, demonstrated that mRNA-1273 prevents COVID-19 when administered as two 100 µg doses 28 days apart (Section 2.7.3.2.1.1). Study 301 also demonstrated that the 100 µg dose level was highly immunogenic (Section 2.7.3.2.1.2) and well-tolerated (Section 2.7.4).

No other dose level was evaluated in this pivotal Phase 3 study. Evidence for VE after the first injection was limited to the 14-day interval between Day 15 and Day 29, and 96.6% of all participants who received a first injection also received a second injection at the Day 29 visit.

Study 101 provided initial evidence that the 100 ug dose was more immunogenic than the 25 µg dose and supported the selection of the 100 ug dose for Study 301. In addition, the 100 µg dose was less reactogenic than the 250 µg dose. Study 201 provided confirmation of the high immunogenicity of the 100 µg and 50 µg doses, with a larger sample size. For the 50 µg and 100 µg dose levels, immunogenicity was consistent between Study 201 and Study 101 for each age group for all common time points for both nAb and bAb, as were safety and reactogenicity profiles (Section 2.7.4.2.2). The immunogenicity analyses for the 100 µg dose provided by Studies 101 and 201 were consistent with the larger dataset analyzed in the final Part A immunogenicity analysis of Study 301 for the available immunogenicity time points in Study 301 (Days 1, 29, and 57).

With the immunogenicity of the 100 ug dose confirmed, the VE results of Study 301 (Section 2.7.3.2.1) and the Study 301 safety data (Section 2.7.4.2.1) support the dosing recommendation of an mRNA-1273 vaccine regimen comprising 2 doses of 100 µg mRNA-1273, administered 28 days apart.

2.7.3.5 PERSISTENCE OF IMMUNE RESPONSE

Study 201 (Section 2.7.3.2.2) and Study 101 (Section 2.7.3.2.3) provided evidence of persistence of immune response through Day 209, 6 months after the second injection of mRNA-1273, although levels at Day 209 were lower than the peak values observed at Day 43.

In the mRNA-1273 100 µg dose group in Study 201 (189 participants), the GM level of bAb declined from the peak at Day 43 to Day 209. The Day 209 GM level remained higher than the GM level at Day 29 prior to the second injection (Section 2.7.3.2.2.1).

In the mRNA-1273 100 µg dose group in Study 101 (35 participants), the GMT of bAb declined from the peak at Day 43 to Day 119 and then to Day 209. The GMT at Day 209 was similar to or numerically higher than GMT observed on Day 29 prior to the second injection and similar to the median GMT for the convalescent serum control (Study 101 CSR Addendum 1 (Day 209) Section 8.1.1).

The data on persistence of immune response are consistent with findings of the persistence of vaccine-induced protection for a median of 7.6 months from randomization through the data cutoff date for this analysis (Section 2.7.3.2.1.1).

2.7.3.6 APPENDIX

2.7.3.6.1 References

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