Synopsis

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

Investigators: This was a multicenter study.

Study Centers: This study was conducted at 99 study sites in the United States.

Publication (Reference): Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Eng J Med. 2021;384(5):403-16.

Study Period (Part A): 27 Jul 2020 (First participant first visit) to early unblinding, study discontinuation, the Part B participant decision visit (PDV) or data cutoff date (26 Mar 2021), whichever was earlier

Drug Development Phase: 3

Background and Rationale: An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and the disease has since spread globally. On 11 Mar 2020, the World Health Organization declared COVID-19 a pandemic. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for rapid development of novel vaccines to prevent the spread of this disease. ModernaTX, Inc. (Sponsor) has used rapid response, proprietary, mRNA-based vaccine platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273).

Study mRNA-1273-P301 was designed as a Phase 3, randomized, 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 have no known history of SARS-CoV-2 infection but whose occupation or location and living circumstances put them at increased risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The primary goals of this Phase 3 study are to evaluate the vaccine efficacy (VE) of mRNA-1273 to prevent COVID-19, compared to placebo and to further evaluate the safety and reactogenicity profile of mRNA-1273.

This Part A clinical study report (CSR) presents the data from the randomized, placebo controlled, blinded phase (Part A) of the study based on the database lock on 04 May 2021, and includes available participant level data up to early unblinding, study discontinuation, the Part B PDV or data cutoff date (26 Mar 2021), whichever was earlier.

Objectives and Endpoints:

Objectives	Endpoints
Primary efficacy	

• To demonstrate the efficacy of mRNA-1273 to prevent COVID-19.	• The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 was defined as symptomatic disease based on the following criteria:
	  • The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38ºC), 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 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Primary safety	
• To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.	• Solicited local and systemic ARs through 7 days after each dose of IP. • Unsolicited AEs through 28 days after each dose of IP. • MAAEs or AEs leading to withdrawal through the entire study period. • SAEs throughout the entire study period. • Pregnancies and perinatal outcomes.

Objectives	Endpoints
Secondary efficacy	
• To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.	• 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, $SpO_2 \leq 93\%$ on room air at sea level, or PaO_2/FIO_2 < 300 mm Hg, OR • Respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic BP < 90 mm Hg, diastolic BP < 60 mm Hg, or requiring vasopressors), OR • Significant acute renal, hepatic, or neurologic dysfunction, OR • Admission to an intensive care unit or death.
• To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.	• The VE of mRNA-1273 to prevent the first occurrence of either COVID-19 or SARS-CoV-2 infection starting 14 days after the second injection of IP. This endpoint includes COVID-19, as defined for the primary endpoint, and asymptomatic SARS-CoV-2 infection, determined by seroconversion assessed by bAb levels against SARS-CoV-2 as measured by a ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein or a positive RT-PCR test post baseline. This endpoint was evaluated in participants who were SARS-CoV-2 negative at baseline.
• To evaluate VE against a secondary definition of COVID-19.	• The VE of mRNA-1273 to prevent the secondary case definition of COVID-19 starting 14 days after the second injection of IP. The secondary case definition of COVID-19 was defined as the presence of at least 1 of the following systemic symptoms: fever (temperature ≥ 38ºC), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
• To evaluate VE to prevent death caused by COVID-19.	• 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.

Objectives	Endpoints
• To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP.	• The VE of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the first injection of IP.
• To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.	• 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 (FAS analysis population).
• To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.	• The VE 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. SARS-CoV-2 infection was determined by seroconversion assessed by bAb levels against SARS-CoV-2 as measured by a ligand-binding assay specific to the SARS-CoV-2 Nucleocapsid protein or a positive RT-PCR test at a scheduled visit (eg, predose on Day 29). This endpoint was evaluated in participants who were SARS-CoV-2 negative at baseline.
Secondary immunogenicity	
• To evaluate the immunogenicity of 2 doses of mRNA-1273 given 28 days apart.	• GMT of SARS-CoV-2 -specific nAb on Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759[a]. • GMFR of SARS-CoV-2-specific nAb relative to Day 1 on Day 29, Day 57, Day 209, Day 394, and Day 759[a]. • Quantified levels or GMT of S protein-specific bAb on Day 1, Day 29, Day 57, Day 209, Day 394, and Day 759[a]. • GMFR of S protein-specific bAb relative to Day 1 on Day 29, Day 57, Day 209, Day 394, and Day 759[a].
Exploratory - The following exploratory objectives and endpoints are addressed in this CSR:	
• To evaluate the effect of mRNA-1273 on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by RT-PCR and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR.	• The VE of mRNA-1273 on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by RT-PCR and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR.
• To assess VE to reduce the duration of symptoms of COVID-19.	• The VE of mRNA-1273 to reduce duration of COVID-19 symptoms.
• To evaluate VE against all-cause mortality.	• The VE of mRNA-1273 against all-cause mortality.
• To assess VE against BOD due to COVID-19	• The VE of mRNA-1273 against BOD based on the post SARS-CoV-2 infection follow-up.
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.	• The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
• To conduct additional analyses related to furthering the understanding of SARS-CoV-2 infection and COVID-19, including analyses	• Additional analyses related to furthering the understanding of SARS-CoV-2 infection and

Objectives	Endpoints
related to the immunology of this or other vaccines, detection of viral infection, and clinical conduct.	COVID-19, including analyses related to the immunology of this or other vaccines, detection of viral infection, and clinical conduct.

Abbreviations: AE = adverse event; AR = adverse reaction; ARDS = acute respiratory distress syndrome; bAb = binding antibody; BOD = burden of disease; BP = blood pressure; CSR = clinical study report; ECMO = extracorporeal membrane oxygenation; FAS = Full Analysis Set; FIO_2 = fraction of inspired oxygen; GMFR = geometric mean fold rise; GMT = geometric mean titer; IP = investigational product; MAAE = medically-attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PaO_2 = partial pressure of oxygen; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SpO_2 = oxygen saturation by pulse oximeter; VE = vaccine efficacy.

[a] This Part A CSR presents the immunogenicity endpoints through Day 57 for the Per-Protocol Random Subcohort for Immunogenicity.

Methodology:

This is an ongoing 2-part Phase 3 study: Part A and Part B. Participants in Part A, the randomized, placebo-controlled, blinded phase of this study, were blinded to their treatment assignment. Given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met per the protocol-defined interim analysis (IA), Part B, the Open-Label Observational Phase of this study, was designed to offer participants who received placebo in Part A of this study and who met Emergency Use Authorization (EUA) eligibility, an option to request open-label mRNA-1273 during a PDV.

This Part A CSR presents the data from the randomized, placebo-controlled, blinded phase (Part A) of the study based on the database lock on 04 May 2021, and includes available participant level data up to early unblinding, study discontinuation, the Part B PDV or data cutoff date (26 Mar 2021), whichever was earlier. Data from Part B, in which eligible participants were offered open-label mRNA-1273, will be included in a CSR addendum.

Part A, the Randomized, Placebo-Controlled, Blinded Phase

Part A of this study was a Phase 3, randomized, 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 occupation or locations and living circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection.

Participants were randomly assigned to receive doses of either 100 µg of mRNA-1273 vaccine or placebo in a 1:1 randomization ratio. Assignment was stratified by age and health risk.

All participants were assessed for efficacy and safety endpoints. A nasopharyngeal (NP) swab sample and blood sample were obtained from each participant before the first and second dose of investigational product (IP). In addition, a series of postdose blood samples for immunogenicity

are being collected through 24 months after the second dose of IP. Efficacy assessments included surveillance for COVID-19 with reverse transcriptase polymerase chain reaction (RT-PCR) confirmation of SARS-CoV-2 infection after the first and second dose of IP.

Each participant received 2 doses of IP by 0.5 mL intramuscular (IM) injection, the first on Day 1 and the second on Day 29. An NP swab sample was collected prior to the first and second dose of IP for evaluation by RT-PCR. To preserve observer blinding, only delegated unblinded study site personnel responsible for IP preparation, administration, and/or accountability had knowledge of study IP assignment.

Participants were given an electronic diary (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 the first 7 days after each dose of IP (or until resolution for solicited ARs that continued beyond 7 days) and were then followed by weekly eDiary prompts (every 7 days) to elicit an unscheduled Illness Visit if the participant experienced COVID-19 symptoms. All participants received safety calls on Day 8, Day 15, Day 22, Day 36, and Day 43 that served both to monitor for unsolicited adverse events (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 SoEs and were intended to capture serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, concomitant medications associated with these events, receipt of non-study vaccinations, and pregnancy. If an eDiary prompt resulted in identification of a relevant safety event, a follow-up safety call was triggered.

Surveillance for signs and symptoms of COVID-19 is being performed through weekly contacts with the participant via a combination of telephone calls and completion of specific eDiary prompts starting at Day 1 through the end of the study. Participants with symptoms of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) returned to the 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 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, their highest body temperature and lowest oxygen saturation for that day, and the investigator determined if medical attention was required due to worsening of COVID-19 symptoms. Study participants collected their own saliva (or nasal swab) sample at 3, 5, 7, 9, 14, and 21 days after the initial Illness Visit meeting criteria 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 IP 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 injection (or until resolution for solicited ARs that continued beyond 7 days), and unsolicited AEs were assessed for 28 days after each injection; SAEs, MAAEs, and AEs leading to withdrawal were assessed throughout the study.

Participants may have experienced AEs that necessitated an unscheduled visit. There may have also been situations in which the investigator asked a participant to report for an unscheduled visit following the report of an AE. Additional examinations may have been conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should have been completed for each unscheduled visit.

Number of Participants (Planned and Analyzed): Approximately 30,000 participants were planned to receive doses of either 100 μg of mRNA-1273 vaccine or placebo in a 1:1 randomization ratio.

In Part A, a total of 30,415 participants were randomized (Randomized Set): 15,206 in the placebo group and 15,209 in the mRNA-1273 group. Of these, 22,882 participants were ≥ 18 and < 65 years and 7,533 participants were ≥ 65 years. The number of participants included in the analysis sets used for the primary analyses of efficacy, immunogenicity, and safety are summarized as follows:

- Per-Protocol Set: 28,451 (93.5%) total (14,164 [93.1%] in the placebo group and 14,287 [93.9%] in the mRNA-1273 group)
- Per-Protocol Random Subcohort for Immunogenicity: 1,457 (4.8%) total (272 [1.8%] in the placebo group and 1,185 [7.8%] in the mRNA-1273 group)
- Safety Set: 30,346 total (15,162 in the placebo group and 15,184 in the mRNA-1273 group)

Main Criteria for Inclusion and Exclusion: Participants (males and females 18 years of age or older at time of consent), 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 the virus, who were heathy and had no known history of SARS-CoV-2 infection, or adults with pre-existing medical conditions who were in stable condition at screening comprised the planned target population. Additionally, potential study participants at high risk of severe COVID-19 were included based on age (65 years of age and older) and underlying medical conditions.

Test Product, Dose and Mode of Administration: mRNA-1273 was administered as an 0.5 mL IM injection containing 100 µg of mRNA-1273 into the deltoid muscle (preferably the nondominant arm) on a 2-dose injection schedule on Day 1 and Day 29 in Part A. The second dose of IP should have been administered in the same arm as the first dose.

Control Product, Dose and Mode of Administration: Placebo (0.9% sodium chloride) was administered as an 0.5 mL IM injection into the deltoid muscle on an identical schedule as mRNA-1273.

Duration of Treatment: Participants received the randomly assigned IP of mRNA-1273 or placebo as 2 injections administered 28 days apart (Day 1 and Day 29) in Part A.

Estimands and Intercurrent Events: The estimand of the primary analysis was VE measured using 1 – HR (mRNA-1273 vs. placebo) for prevention of first occurrence of COVID-19 from 14 days after second dose of IP in adults.

Statistical Methods:

Analysis Sets: The following analysis sets were defined:

- **Randomized Set:** All participants who were randomized, regardless of the participant's treatment status in the study. Participants were analyzed according to the treatment group to which they were randomized.
- **Full Analysis Set (FAS):** All randomized participants who received at least 1 dose of IP. Participants were analyzed according to the treatment group to which they were randomized.
- **Modified Intent-to-Treat (mITT) Set:** All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (negative SARS-CoV-2 status, ie, negative NP swab test and negative bAb against SARS-CoV-2 N-protein as measured by Roche Elecsys®) at Day 1 before the first dose of IP; ie, all FAS participants excluding those with RT-PCR and/or serology positive at baseline (Day 1 before the first dose of IP). Participants were analyzed according to the treatment group to which they were randomized.

- **PP Set:** All participants in the mITT Set who received planned doses of IP per schedule and had no major protocol deviations, as determined and documented by the Sponsor prior to database lock and unblinding, which impacted critical or key study data. Participants were analyzed according to the treatment group to which they were randomized. Participants who did not receive the second injection of IP within [21, 42] days after the first injection date were excluded from the PP Set.
- **Immunogenicity Subset and Analysis Populations for Immunogenicity:** For characterizing immunogenicity of the vaccine and for assessing correlates of risk and protection, a case-cohort sampling design was used for measuring bAb and nAb data from a randomly sampled subset of study participants (the case-cohort Immunogenicity Analysis Set [ccIAS]) or immunogenicity subset. The ccIAS cohort consisted of a stratified, random sample of study participants (random subcohort) augmented with a subset or all primary endpoint cases and SARS-CoV-2 infection endpoint cases. The immunogenicity samples of the ccIAS cohort were processed and the immunogenicity data were available for the ccIAS cohort. The immunogenicity subset consisted of all participants in the ccIAS who had a valid baseline immunogenicity test result (prior to the first dose of IP) and at least 1 valid post-baseline result.
- The **Per-Protocol Random Subcohort for Immunogenicity** (PPRSI) was used as the analysis population to characterize immunogenicity of mRNA-1273. The PPRSI for immunogenicity consisted of participants in the FAS who were sampled into the random subcohort and

    a) Received both planned doses (ie, received the treatment as the participant was randomized to) with Dose 2 received within [21, 42] days after Dose 1, and

    b) No major protocol deviation that impacted critical or key data.

- **Solicited Safety Set:** All randomized participants who received at least 1 dose of IP and contributed any solicited AR data; ie, had at least 1 post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set was used for the analyses of solicited ARs, and participants were included in the treatment group corresponding to the study vaccination they actually received.

  In addition, the following Solicited Safety Set was defined for each injection separately. **The First (Second) Injection Solicited Safety Set** consisted of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days.

Participants were analyzed according to the treatment group a participant received, rather than the treatment group to which the participant was randomized. If a participant was randomized to placebo but received any dose of mRNA-1273 vaccine at any injection, the participants were included in the mRNA-1273 group in the Solicited Safety Set.

- **Safety Set:** All randomized participants who received at least 1 dose of IP. The Safety Set was used for all analysis of safety except for the solicited ARs. Participants were included in the treatment group corresponding to the IP they actually received. For a participant who was randomized to placebo but received any dose of mRNA-1273 at any injection, the participant will be included in the mRNA-1273 group in the Safety Set.

Efficacy: The PP Set was the primary analysis population for efficacy analyses, unless otherwise specified.

Primary Efficacy Endpoint:

The number and percentage of participants who had an event (ie, the first occurrence of COVID-19 starting 14 days after the second injection) and the participants who were censored were summarized.

The non-parametric Kaplan-Meier method was used to estimate the time to first occurrence of COVID-19 curve in each treatment group.

Vaccine efficacy was defined as the percent reduction in the hazard of the primary endpoint (mRNA-1273 vs. placebo), ie, 1 – HR. The null hypothesis was:

$$H_0^{efficacy}: VE \leq 0.3$$

Equivalently, the null hypothesis was:

$$H_0^{efficacy}: HR \geq 0.7$$

A stratified Cox proportional hazard model with Efron's method of tie handling and with treatment group as covariate was used to assess the magnitude of the treatment group difference (ie, HR) between mRNA-1273 and placebo. The same stratification factors used for randomization were applied to the stratified Cox model. The VE with corresponding alpha adjusted confidence interval (CI), 95% CI, and 1-sided *p* value for testing the null hypothesis from the stratified Cox model was reported at a planned IA up to the analysis at which VE was demonstrated. After VE was demonstrated, VE and 95% CI were to be provided for subsequent analysis/updates of efficacy.

In this study, VE was demonstrated based on prespecified statistical criterion at the IA, at which, 1-sided *p* value for testing the null hypothesis of VE ≤ 0.3, 95% CI, and alpha-adjusted CI were provided from the stratified Cox model. At the primary analysis where the total number of

COVID-19 cases > 151, total target number of cases, VE, 1-sided *p* value for testing the null hypothesis of VE ≤ 0.3, and 95% CI were provided. In subsequent analysis/updates of efficacy, VE and 95% CI were provided.

The number and percentage of participants who had an event (ie, the first occurrence of COVID-19 at least 14 days after the second injection) were reported.

Sensitivity analyses were performed, with COVID-19 cases counted starting at various time points using the PP Set as follows:

- After the second injection of IP
- Fourteen days after the first injection of IP (also as primary analysis approach for the secondary efficacy objective: to evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP).
- After randomization

Analysis of the primary efficacy endpoint based on the mITT Set was also performed using the same statistical methods used for the primary analysis. The sensitivity analyses, with COVID-19 cases counted starting at various time points were also performed using the mITT Set.

To assess consistency of VE across various subgroups, subgroup analyses of the primary efficacy endpoint were performed based on the PP Set. The primary efficacy endpoint was analyzed by each of the subgroups using the same methods described for the primary analysis (ie, stratified Cox proportional hazard model with Efron's method of tie handling with a single treatment covariate), and the estimate of VE and its 95% CI were provided within each category of the following subgroups:

- Age groups: ≥ 18 and < 65 years, ≥ 65 years
- Age groups: ≥ 18 and < 65 years, ≥ 65 years and < 75 years, ≥ 75 years
- Stratification factor at randomization: ≥ 18 and < 65 years and not at risk, ≥ 18 and < 65 years at risk, ≥ 65 years
- Sex (female, male)
- Race
- Ethnicity
- Race and ethnicity: non-Hispanic White, communities of color
- Each risk factor for severe COVID-19 illness

Secondary Efficacy Endpoints:

Similar analysis methods, as detailed for the primary efficacy endpoint, were applied to the following secondary efficacy endpoints based on the PP Set, unless otherwise specified:

- VE to prevent severe COVID-19.
- VE to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.

  The analysis population for this endpoint, serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity [COV-INF], was the PP Set (primary analysis population) and the mITT Set that included participants with negative SARS-CoV-2 status at baseline. Infection [COV-INF] was defined by any post-baseline positive RT-PCR results, and/or, seroconversion due to infection defined as positive bAb specific to SARS-CoV-2 NP as measured by Roche Elecsys at post-baseline scheduled visits for participants with negative SARS-CoV-2 status at baseline (PP and mITT Sets). Both RT-PCR tests from the scheduled NP swab tests at Day 29 as well as those prompted by symptom(s) were considered. A COVID-19 case or secondary definition of COVID-19 case was always a COV-INF case.
- VE to prevent COVID-19 using a secondary definition of symptoms.
- VE to prevent death caused by COVID-19

For each of the above secondary endpoints, the following analyses were performed:

- VE was estimated with 1 – HR (mRNA-1273 vs. placebo) using a Cox proportional hazard model based on the PP Set as described for the primary efficacy endpoint. Kaplan-Meier curves of time to event were presented for each treatment group. Cases were counted starting 14 days after the second injection of IP.
- Analysis was performed using the same model based on the mITT Set as described for the primary efficacy endpoint. Kaplan-Meier curves of time to event were presented for each treatment group.
- Sensitivity analyses were performed, with cases counted starting immediately after the second injection of IP (onset date ≥ date of second injection, considering positive RT-PCR at Day 29), starting 14 days (≥ 14 days) after the first injection of IP, and immediately after randomization, respectively.
- VE and 95% CI based on the incidence were estimated with 1 – ratio of incidence rates using the exact method conditional upon the total number of cases.

For the secondary efficacy objective: VE to prevent asymptomatic SARS-CoV-2 infection

- The analysis populations for asymptomatic infection were the PP Set (primary analysis population) and mITT Set. Asymptomatic infection was COV-INF (detected by positive RT-PCR or seroconversion [bAb specific to SARS-CoV-2 NP as measured by Roche Elecsys at scheduled visits]) with absence of symptoms.

  As diseased cases (COVID-19 or secondary definition of COVID-19) were competing events for asymptomatic SARS-CoV-2 infections, competing risk method (Fine and Gray's [FG] subdistribution hazard model) was used to estimate the VE of mRNA-1273. Competing risk method was also used to estimate the cumulative incidence function, and the cumulative incidence of asymptomatic SARS-CoV-2 infections were plotted.

  In the primary approach with cases of asymptomatic SARS-CoV-2 infection counted starting 14 days after the second injection, only seroconversion at Day 57 or later was to be considered.

  As serum samples were taken at scheduled visits (eg, Day 29 [Month 1], Day 57 [Month 2]), sensitivity analyses with cases counted starting after second injection, 14 days after the first injection, after the first injection, and after randomization were the same. Only 1 set of sensitivity analysis with cases counted starting from randomization was provided. In this sensitivity analysis, asymptomatic cases detected by positive RT-PCR result at scheduled Day 29 (before the second injection), or seroconversion at time points with scheduled visits were considered. Sensitivity analysis using the mITT Set with cases counted starting from 14 days after the second injection, and from randomization were also performed.

For the secondary efficacy objective: VE to prevent COVID-19 after the first injection of IP

- This endpoint was analyzed as a sensitivity analysis of the primary efficacy endpoint with cases counted starting 14 days (≥ 14 days) after the first injection of IP.

For the secondary efficacy objective: VE to prevent COVID-19 disease regardless of prior SARS-CoV-2 infection

- VE to prevent COVID-19 disease regardless of prior SARS-CoV-2 infection was analyzed using the FAS. The same methods described for the primary efficacy endpoint were applied with cases counted starting 14 days after the second injection of IP.

Sensitivity analyses with cases counted starting immediately after the second injection, 14 days after the first injection, and after randomization were also performed. In sensitivity analysis with cases counted starting after the second injection, participants who received only the first injection and were cases, were censored at the time of COVID-19.

The VE was also estimated with 1 – the ratio of incidence rates with the 95% CI using the exact method conditional upon the total number of cases adjusting for person-time.

In addition, an exploratory analysis with the same Cox model was performed in the subgroup of the FAS whose baseline SARS-CoV-2 status was positive with cases counted starting 14 days after the second dose to assess the VE in those with positive baseline SARS-CoV-2 status, at baseline, if sample size permitted. Such analysis in the subgroup of the FAS whose baseline SARS-CoV-2 status was negative with cases counted starting 14 days after the second dose was the same as the sensitivity analysis of COVID-19 starting 14 days after the second dose in the mITT Set.

Immunogenicity: The PPRSI was used as the analysis population to characterize immunogenicity of mRNA-1273.

Data from quantitative immunogenicity assays were summarized for each treatment group using positive response rates and geometric means (GMs) with 95% CI at each time point when an assessment was performed. Data from qualitative (ie, yielding a positive or negative result) assays were summarized by tabulating the frequency of positive responses for each assay by treatment group and by baseline SARS-CoV-2 status, if applicable, at each time point that an assessment was performed.

At the time the final blinded efficacy analysis, immunogenicity analyses to characterize immunogenicity of mRNA-1273 were performed. At the time of the immunogenicity analyses, data for bAb to S (MSD, PPD-VAC65) and psVNA ID_{50} and ID_{80} titers were available. The assay by MSD to measure bAb against RBD and N-protein had not yet been validated at the time of the immunogenicity analysis; therefore, these data were not summarized/analyzed. Immunogenicity data at the prespecified time points (Baseline [Day 1], Day 29 [Month 1], and Day 57 [Month 2]) were included.

- The GMT or value with corresponding 95% CI was provided at each time point. The 95% CIs were calculated based on the *t*-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics were also provided at each time point: the number of participants (n), median, minimum, and maximum.

- The geometric mean fold rise (GMFR) with corresponding 95% CI was provided at each post-baseline time point over pre-injection baseline at Day 1. The 95% CIs were calculated based on the *t*-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics were also provided at each time point: the number of participants (n), median, minimum, and maximum.
- Reverse cumulative distribution function curve (RCDF) at each time point. The number and percentage of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 from baseline at each post-injection time point were tabulated with 2-sided 95% Clopper-Pearson CIs.
- The Ab assay of interest [bAb to spike (MSD, PPD-VAC65) and PsVNA ID_{50} and ID_{80}] are listed in the table below. For each of them, seroresponse rate was defined as the proportion of participants achieving seroresponse, defined below for each assay/test of interest. Please note that these assay-specific definition of seroresponse was an update of 'seroconversion due to vaccination' used in the protocol and relevant SAP incorporating assay-specific fold-rise criteria based on assay-specific performance characteristics. These assay-specific definitions of seroresponse were documented in a memo that became available prior to DBL.

Assay Name	Category	Test Name/ Description	Definition of Seroresponse
Pseudovirus (PsVNA)	nAb	PsVNT50 (ID_{50})	baseline <LLOQ: ≥LLOQ baseline ≥LLOQ: 3.3-fold rise
		PsVNT80 (ID_{80})	baseline <LLOQ: ≥LLOQ baseline ≥LLOQ: 2.3-fold rise
Anti-Spike ELISA	bAb	anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: ≥LLOQ baseline ≥LLOQ: 4.6-fold rise
MSD multiplex	bAb	anti-Spike	baseline <LLOQ: ≥LLOQ baseline ≥LLOQ: 1.9-fold rise

Abbreviations: bAb = binding antibody; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; MSD = MesoScale Discovery; nAb = neutralizing antibodies; PsVNA = pseudotyped virus neutralization assay; PsVNT50 = 50% pseudotyped lentivirus reporter test; PsVNT80 = 80% pseudotyped lentivirus reporter test.

- Number and proportion of participants achieving seroresponse were provided with 2-sided 95% Clopper-Pearson CIs at each post-baseline time point.

To assess the magnitudes of the differences between the 2 treatment groups (mRNA-1273 vs. placebo) in SARS-CoV-2-specific nAb and S protein-specific bAb, a mixed-effect model repeated measures (MMRM) using SAS PROC MIXED was used. The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the antibody titers for each treatment

group were provided by visit. The GLSM and corresponding 95% CI results in log-transformed scale estimated from the model were back-transformed to obtain these estimates in the original scale. Geometric mean ratio (GMR), estimated by the ratio of GLSM and the corresponding 2-sided 95% CI, was provided to assess the treatment difference between the mRNA-1273 versus placebo groups at each visit. With each treatment group, within-group comparison of time points may also have been estimated using the same model.

In addition, an analysis of covariance (ANCOVA) model with the treatment group as explanatory variables, adjusting for the stratification factor at randomization, baseline value if applicable, was used to assess the treatment effect at specific time points (scheduled visits) such as Day 57. The GLSM with 95% CI for each treatment group, GMR with 95% CI for treatment difference was estimated from the ANCOVA model. The model also adjusted for minority group used to sample for the random subcohort.

It was of interest to examine the immune response in participants on mRNA-1273 with baseline SARS-CoV-2 negative status who were COVID-19 or SARS-CoV-2 infection cases. Immunogenicity data was provided in a subset of baseline SARS-CoV-2 negative participants on mRNA-1273 who were adjudicated COVID-19 cases.

Safety: Safety and reactogenicity were assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AEs leading to withdrawal from study vaccine and/or study participation, vital signs, and physical examination findings.

All safety analyses were based on the Safety Set, except summaries of solicited ARs which were based on the Solicited Safety Set. All safety analyses were provided by treatment group, unless otherwise specified.

Solicited ARs:

The number and percentage of participants who reported each individual solicited local AR and solicited systemic AR during the 7-day follow-up period (or until resolution for solicited ARs that continued beyond 7 days) after each injection were provided by severity grade. The number and percentage of participants who reported each individual solicited AR were also summarized by severity grade, days of reporting, and injection.

The number and percentage of participants experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by severity grade and the number and percentage of participants experiencing a fever of Grade 3 or higher temperature (a temperature greater than or equal to 39.0°C/102.1°F by the oral, axillary, or tympanic route) were summarized.

A 2-sided 95% exact CI using the Clopper-Pearson method was provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The number and percentage of participants with onset of individual solicited AR were summarized by study day relative to the corresponding injection (Day 1 through Day 7). All solicited ARs that continued beyond 7 days post injection were summarized.

The above analyses of solicited ARs were summarized separately for the following subgroups:

- Age group (< 65 and ≥ 65 years)
- Sex (male, female)
- Baseline SARS-CoV-2 status
- Race and ethnicity

Unsolicited AEs:

Unsolicited TEAE summaries were provided for TEAEs up to 28 days after any injection and during Part A.

The overall summaries of unsolicited TEAEs (number and percentage) by treatment group included the following: any unsolicited TEAEs, any serious TEAEs, any unsolicited TEAEs that were MAAEs, any unsolicited TEAEs leading to discontinuation from participation in the study or study vaccine, any unsolicited severe TEAEs (severity of AEs was assessed as mild, moderate, or severe), and any unsolicited fatal TEAEs. The overviews also included a summary of participants with treatment-related TEAEs in each category.

The following summary tables of TEAEs were provided by SOC and preferred term (PT) using frequency counts and percentages (ie, number and percentage of participants with an event):

- All unsolicited TEAEs
- All treatment-related unsolicited TEAEs
- All SAEs
- All treatment-related SAEs
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited severe TEAEs
- All treatment-related unsolicited severe TEAEs

- All unsolicited TEAEs that were MAAEs

A summary of TEAEs by maximum toxicity grade (mild, moderate, and severe) using frequency counts and percentages was provided for all unsolicited TEAEs and all treatment-related unsolicited TEAEs.

The overview of TEAEs and the TEAE summaries presented by SOC and PT were also summarized for the following subgroups: age (< 65 and ≥ 65 years), sex (male, female), and baseline SARS-CoV-2 status.

Separate listings of individual participant AE data were provided for the following: unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, SAEs, treatment-related SAEs, and unsolicited treatment-related MAAEs. A listing of deaths including cause of death and a listing of TEAEs in participants who died were provided.

Other Safety:

Observed values and changes from baseline for all vital sign measurements were summarized at each visit by baseline SARS-CoV-2 serostatus and treatment group. Shift from baseline in the toxicity grades at each visit were summarized by treatment group.

Pregnancies and outcome (if available) were summarized by treatment group and a listing of pregnancies including outcome were provided.

Summary of Results:

Participant Disposition: A total of 30,415 participants were randomly assigned to study treatment: 15,206 participants in the placebo group and 15,209 in the mRNA-1273 group. Of these, 99.8% of participants overall received the first injection and 96.5% received the second injection.

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 2099 participants (13.8%) who were randomly assigned to receive placebo and 730 participants (4.8%) who were randomly assigned to receive mRNA-1273 discontinued the study, Part A and Part B inclusive. The imbalance of discontinuations between the placebo and mRNA-1273 groups coincided with the EUA of the Pfizer BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine.

IP Exposure in Part A: A total of 30,346 participants received the first injection: 15,162 received placebo and 15,184 received mRNA-1273. Of these, 29,362 participants (96.8%) received the second injection: 14,631 (96.5%) received placebo and 14,731 (97.0%) received mRNA-1273.

A total of 13 participants (7 participants in the placebo group; 6 participants in the mRNA-1273 group) received incorrect study vaccination per the randomization schedule.

Duration of Follow-up: Overall, the median duration of follow-up after randomization for the entire period up to the data cutoff for DBL (26 Mar 2021; inclusive of Part A and Part B) was 212 days (range, 1 to 243 days): 211 days in participants ≥ 18 to < 65 years and 214 days in participants ≥ 65 years.

The median duration of follow-up from randomization to PDV (ie, Part A) for participants who had a PDV on or before the data cutoff date was 148 days (range, 30 to 241 days): 148 days (range, 31 to 241 days) in participants ≥ 18 to < 65 years and 147 days (range, 30 to 234 days) in participants ≥ 65 years.

Demography and Baseline Characteristics: Overall, in the FAS, participant demographics and baseline characteristics were similar between the groups. A slightly higher proportion of males versus females (52.6% versus 47.4%. respectively) were enrolled. The mean age at screening was 51.4 years (range: 18 to 95 years); 75.2% of participants were ≥ 18 to < 65 years of age and 24.8% were ≥ 65 years. The majority of participants were White (79.2%) and not Hispanic or Latino (78.6%). Communities of color comprised 37.2% of the study population; the racial and ethnicity proportions observed in this study were generally representative of US demographics.

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 who were ≥ 65 years).

Overall, the majority of participants (82.5%) had a specified occupational risk for acquisition of SARS-CoV-2 infection; the most common occupational risks included other (31.9%) and health care workers (25.2%). A total of 83.8% of participants had a location or living circumstances risk for acquisition of SARS-CoV-2.

Efficacy Results: The results of the primary and secondary efficacy endpoint analysis are summarized for the PP Set in Table S-1 and presented graphically in Figure S-1.

Table S-1: Summary of Primary and Secondary Efficacy Endpoint Analysis Results (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)
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)

	Placebo (N=14164)	mRNA-1273 (N=14287)
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.

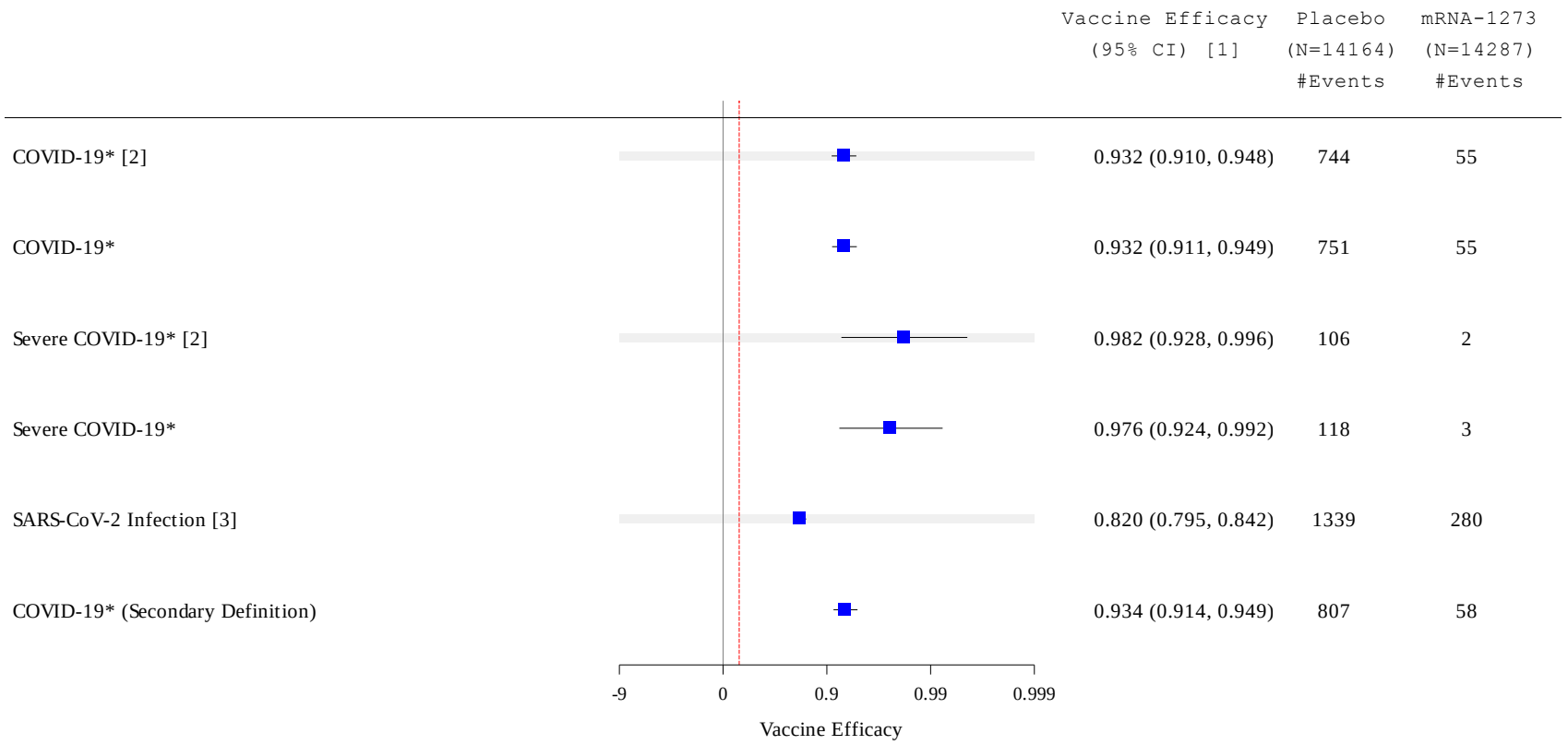
[b] 1-sided p-value from stratified Cox proportional hazard model to test the null hypothesis VE <= 0.3.

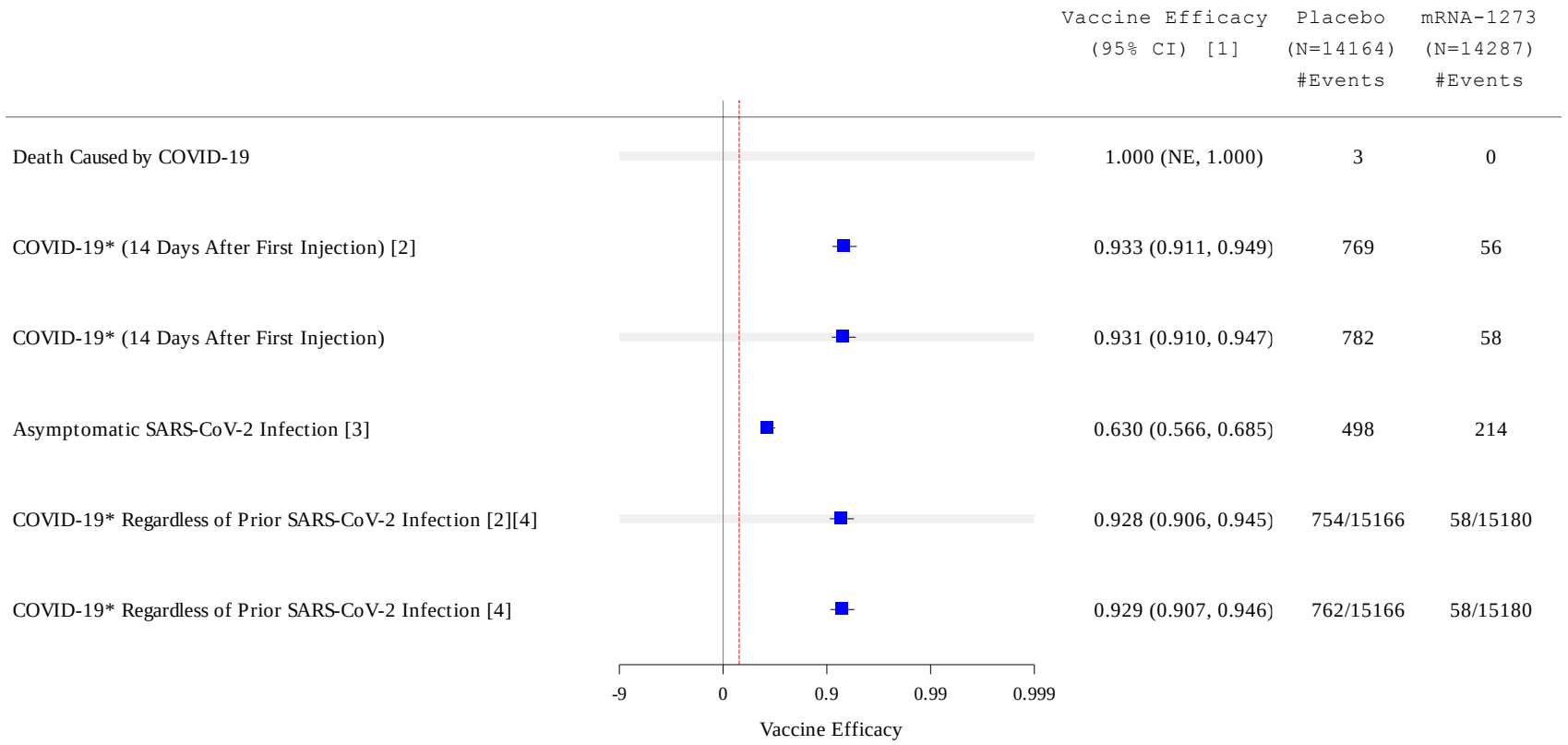
[c] Including participant decision visit.

[d] n and N are based on the number of subjects in the Full Analysis Set.

Source: Table 14.2.1.1.1.1.1.2.

Figure S-1: Forest Plot of Primary and Secondary Efficacy Endpoint Results of Cases Starting 14 Days After Second Injection (Per-Protocol Set)





Reference line indicates vaccine efficacy of 0.3.

* 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.

[1] 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.

[2] Based on Adjudication Committee assessments.

[3] Including participant decision visit.

[4] Based on the number of subjects in the Full Analysis Set.

Source: Figure 14.2.1.1.1.2.

The primary efficacy endpoint was VE of mRNA-1273 to prevent the first occurrence of adjudicated COVID-19 starting 14 days after the second dose of IP in the PP Set.

The final efficacy analysis of the primary endpoint for Part A (04 May 2021) was performed on 799 cases. The results of this analysis were consistent with the results of the interim and primary efficacy analyses, confirming persistent, high efficacy over a substantially larger case database over a longer median observation period of over 5.3 months. For the final efficacy analysis, the VE point estimate was 93.2% ($p < 0.0001$) and within the 95% CIs of the VE point estimates for the interim and primary efficacy analyses.

- Divergence of case incidence began early between mRNA-1273 and placebo groups, starting in the period from randomization up to 14 days after the first injection. Thereafter, cumulative incidence rate for the placebo group increased steadily while it remained stable and low in the mRNA-1273 group for the remainder of the observation period.
- Vaccine efficacy was consistent across subgroups for the primary efficacy endpoint.

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 and was numerically higher than the VE for the primary endpoint.

- For the final analysis of efficacy for Part A, 108 participants had adjudicated severe COVID-19 starting 14 days after second injection in the PP Set (106 cases in the placebo group and 2 cases in the mRNA-1273 group); the VE point estimate based on the hazard ratio was 98.2%, confirming and extending the primary analysis of 25 Nov 2020 based on more than 3 times as many cases accrued over an approximately 2 times longer period of observation.
- Divergence of case incidence of severe COVID-19 began early between mRNA-1273 and placebo groups, starting in the period from 7 to 14 days after the first injection.
- Subgroup analyses were consistent with the primary analysis of efficacy and the point estimates of efficacy remained very high. Consistent VE point estimates were observed in subgroup analyses of participants with 1 risk factor, at last 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and human immunodeficiency virus (HIV) infection.

The VE of mRNA-1273 to prevent SARS-CoV-2 infection, regardless of COVID-19 symptomatology and severity starting 14 days after second injection was consistent with the VE for the primary endpoint.

- Including the RT-PCR and Elecsys results from the PDV, a total of 1,619 participants had a SARS-CoV-2 infection starting 14 days after second injection in the PP Set (1,339 cases in the placebo group and 280 cases in the mRNA-1273 group); the VE point estimate based on the hazard ratio was 82.0%.
- Compared to the primary endpoint analyses, there were similar early onset of divergence in case incidence between treatment groups and similar stable and low rate of incidence rate for mRNA-1273 with increasing incidence rate in the placebo group.
- There were consistent, high VE point estimates across subgroups.

For the less restrictive secondary definition of COVID-19, the VE of mRNA-1273 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, including the RT-PCR and Elecsys results from the PDV, based on a total of 712 participants who had an asymptomatic SARS-CoV-2 infection starting 14 days after randomization (498 cases in the placebo group and 214 cases in the mRNA-1273 group). The VE point estimate based on the hazard ratio was 63.0%. This analysis confirms that vaccination with mRNA-1273 protects against asymptomatic infection (albeit at a lower VE than for symptomatic cases).

Immunogenicity Results: 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 mRNA-1273 treated 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, while seroresponse by nAb assay was 81.4% at Day 29 and 98.9% at Day 57.

Similar results were observed for subgroups stratified by age ($\geq$ 18 to < 65 years and $\geq$ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive mRNA-1273 treated 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 breakthrough COVID-19 cases.

Safety Results: In this final, randomized, blinded phase (Part A) analysis, the mRNA-1273 vaccine administered as 2 injections 28 days apart demonstrated an acceptable safety profile in the study population. This conclusion is supported by reactogenicity and key safety findings summarized here.

Solicited local and systemic adverse reactions were more frequent in mRNA-1273 than in placebo recipients, with most events considered grade 1 or 2 in severity, and most events in mRNA-1273 recipients occurring within 1 to 2 days and lasting a median of 1 to 3 days. The most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. Older adults (≥ 65 years) had lower rates of solicited ARs than younger adults (< 65 years). Participants SARS-CoV-2 positive at baseline had rates of solicited ARs comparable to those among baseline negative participants. More mRNA-1273 recipients reported use of medication for pain or fever than placebo recipients, consistent with vaccine reactogenicity.

Unsolicited TEAEs in the 28 days after any injection occurred at similar rates in the mRNA-1273 and placebo groups. The higher rate of unsolicited TEAEs considered treatment-related by the investigator among mRNA-1273 participants was largely driven by events that mapped to solicited ARs but occurred beyond the solicited AR collection period or were ARs similar to solicited ARs. In addition, TEAEs were assessed for: (i) imbalances between study groups, and (ii) AEs of interest following COVID-19 vaccination or vaccinations in general. Imbalances were investigated based on the degree of imbalance and the biological plausibility and temporal occurrence relative to study treatment. An imbalance in the overall number of herpes zoster cases was noted, with more cases in the mRNA-1273 than in the placebo group; however, most cases in the mRNA-1273 group occurred more than 28 days after any dose and at an incidence expected in the general population. In contrast, most cases in the placebo group occurred within 28 days and at rates lower than expected of the general population. These findings are not supportive of relatedness to mRNA-1273.

Certain AEs are of theoretical interest for COVID-19 vaccines and were carefully assessed in the blinded study phase. mRNA-1273 vaccine was highly efficacious in preventing COVID-19 and severe COVID-19, and this efficacy has been sustained, dispelling concerns of VAERD. No significant clinical findings were identified from the SMQ/CMQ searches performed for the analyses of AEs of clinical interest for COVID-19 vaccines. A search (SMQ) for CNS vascular disorders identified a categorical imbalance, with 21 participants in the mRNA-1273 and 11 participants in the placebo group experiencing events in this SMQ, but the apparent imbalance was largely due to inclusion of 5 participants with subarachnoid hemorrhage and subdural hematoma (3 and 2 participants, respectively in the mRNA-1273 group and none in placebo) in this category. These latter events were mostly related to trauma and not to study treatment. Other

events of potential interest for COVID-19 vaccines are thrombotic and embolic events, for which no imbalance between groups was identified. Finally, assessments for TEAEs of myocarditis or pericarditis, or the symptoms suggestive of these diagnoses (including chest pain, dyspnea, and tachycardia) was performed. No events of myocarditis were identified. Pericarditis without concurrent myocarditis was reported as an SAE for 2 participants in each treatment group; the 2 events in the mRNA-1273 group occurred more than 28 days after second dose and in participants older than 55 years. Symptoms consistent with myocarditis or pericarditis were assessed, seeking patterns in grouping of symptoms or clustering in time, and only a single participant met a diagnosis of pericarditis. Assessment of events often associated with vaccination was performed, with a focus on hypersensitivity and anaphylaxis. Hypersensitivity events were more common among mRNA-1273 than placebo recipients; most of the imbalance derived from injection site urticaria and rashes. No anaphylaxis events were reported within 30 minutes after any injection.

In total, mRNA-1273 has a reactogenicity profile consistent with parenteral vaccination and generally well tolerated. Similarly, the safety profile is acceptable. No unexpected findings were identified in this final assessment of the randomized, blinded phase of the study.

Conclusions: This study was designed 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 have no known history of SARS-CoV-2 infection but whose occupation or location and living circumstances put them at increased risk of acquiring COVID-19 and/or SARS-CoV-2 infection.

- The final efficacy analysis of the primary endpoint for Part A (04 May 2021) included 799 cases. The results of this analysis were consistent with the results of the interim and primary efficacy analyses, confirming persistent, high efficacy over a substantially larger case database and over a longer median observation period of over 5.3 months. For the final efficacy analysis, the VE point estimate was 93.2% ($p < 0.0001$) and within the 95% CIs of the VE point estimates for the interim and primary efficacy analyses.
    - Divergence of case incidence began early between mRNA-1273 and placebo groups, starting in the period from randomization up to14 days after the first injection. Thereafter, cumulative incidence rate for the placebo group increased steadily while it remained stable and low in the mRNA-1273 group for the remainder of the observation period.
    - Vaccine efficacy was consistent across subgroups for the primary efficacy endpoint.
    - Vaccine efficacy was also consistent across the secondary endpoints characterized by high VE point estimates and tight 95% CIs, with the lower bounds of the 95% CIs well above 30%.

- 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).
- mRNA-1273 demonstrated an acceptable safety profile in the participant population enrolled in this study. mRNA-1273 has a reactogenicity profile consistent with parenteral vaccination and generally well tolerated. No unexpected findings were identified in this final assessment of the randomized, blinded phase of the study.

This report is based on the data from the randomized, placebo controlled, blinded phase (Part A) of the study. Data from Part B, in which eligible participants were offered open-label mRNA-1273, will be included in a CSR addendum.

Date and Version of This Report: Final, 05 August 2021