Synopsis

Title of Study: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, 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 8 study sites in the United States.

Publication (Reference): Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, Leav B on behalf of the mRNA-1273 Study Group. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021;39(20):2791-2799.

Study Period:

Original Report (Primary Analysis [Day 57] CSR):	22 May 2020 (first participant, first visit) to 05 Nov 2020 (database lock date)
Report Addendum 1 (CSR Addendum 1 [End of Part A]):	22 May 2020 (first participant, first visit) Database lock date (10 Jun 2021)

Drug Development Phase: 2a

Objectives and Endpoints: The study objectives and endpoints for Part A are presented in the primary analysis (Day 57) Clinical Study Report (CSR). This End of Part A CSR addendum provides safety (adverse events [AEs] leading to discontinuation from study participation, medically attended AEs [MAAEs], serious AEs [SAEs], vital sign measurements, and assessments for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection) and immunogenicity (binding antibody [bAb] and neutralizing antibody [nAb] titer) results presented through the Participant Decision Clinic Visit (database lock date of 10 Jun 2021).

Methodology: Study mRNA-1273-P201 is an ongoing 3-part, Phase 2a study: Part A, Part B, and Part C. Part A, the Blinded Phase of the study, was a randomized, observer-blind, and placebo-controlled study, with adult participants at least 18 years of age. Two dose levels, 50 µg and 100 µg, were evaluated, and were chosen based in part on initial safety data from the Phase 1 National Institute of Allergy and Infectious Disease (NIAID) Division of Microbiology and Infection Disease (DMID) study of mRNA-1273 (Study 20-0003; NCT04283461). The Phase 2a study included 2 age cohorts: Cohort 1 ≥ 18 to < 55 years old (300 participants planned) and

Cohort 2 ≥ 55 years old (300 participants planned). Eligible participants (approximately 600 planned) received either mRNA-1273 or saline placebo control according to a 1:1:1 randomization ratio, ie, within each age cohort, 100 participants received mRNA-1273 50 µg, 100 participants received mRNA-1273 100 µg, and 100 participants received saline placebo. Each participant was to receive 2 injections of mRNA-1273 or placebo by 0.5 mL intramuscular (IM) injection on Day 1 and Day 29. Part A, Blinded Phase comprised 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and a Participant Decision Clinic Visit (initiation of Part B) or Day 394 (Month 13), whichever was earlier. The End of Part A was defined as the earlier of Visit 9 (Day 394 [Month 13]), the completion of the last participant's last visit under Part A, or initiation of Part B (Participant Decision Clinic Visit). Participants were considered to have completed Part A of the study if they completed the final visit on Day 394 (Month 13) or initiated Part B (from Participant Decision Clinic Visit) of the study.

Given that the primary efficacy endpoint for mRNA-1273 against coronavirus disease 2019 (COVID-19) was met in a separate Phase 3 efficacy study (mRNA-1273-P301 COVE study; NCT04470427) conducted by the Sponsor and mRNA-1273 was authorized under Emergency Use Authorization (EUA) on 18 Dec 2020, this Phase 2a study moved to the Part B, Open-Label Interventional Phase. Transitioning the study to Part B permitted all ongoing study participants to be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study participants an opportunity to schedule a Participant Decision Clinic Visit to know their original treatment assignment (placebo vs. mRNA-1273 [50 µg or 100 µg] vaccine). Part B was designed to offer participants who received placebo in Part A of this study the option to receive 2 injections of open-label mRNA-1273 (100 µg). Participants who received 1 or 2 doses of 50 µg or 100 µg mRNA-1273 in Part A were offered a single booster dose of mRNA-1273 (50 µg) in Part B. All study participants received a Notification Letter summarizing the basis for a COVID-19 vaccine to receive an EUA and were asked to schedule a Participant Decision Clinic Visit. After the Participant Decision Clinic Visit, all participants were to proceed to the open-label Part B of the study and follow the Part B Schedule of Events.

Part C is a proof-of-concept rollover study of approximately 60 participants who were enrolled in Moderna's Phase 3 mRNA-1273-P301 COVE study, have already been unblinded, and have previously received 2 doses of mRNA-1273 at least 6 months earlier. Upon enrollment into Part C of this study, participants were to receive a single IM injection of mRNA-1273.351 (20 µg or 50 µg) or mRNA-1273/mRNA-1273.351 mixture (50 µg total) at least 6 months after receiving the second vaccination in the mRNA-1273-P301 COVE study.

Safety assessments in this CSR addendum included monitoring and recording of the following for each participant:

- AEs leading to discontinuation from study participation
- MAAEs, SAEs, and vital sign measurements
- AEs of interest
- Assessments for SARS-CoV-2 infection

Immunogenicity assessments included the following:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 spike protein (VAC65)
- Serum nAb titer against SARS-CoV-2 as measured by live virus microneutralization (MN) assays

For the detection of immunoglobulin G (IgG) specific to SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) in human serum, an ELISA method has been developed, qualified, and validated by PPD Laboratories (VAC65).

Assessment of nAb was based on a qualified assay (MN assay). For the SARS-CoV-2 MN assay, the vast majority of samples at Baseline, Day 29, Day 43 and Day 57 were tested using the first viral lot. Due to a limited volume of the first viral lot, a new viral lot was bridged into the qualified assay. All samples at Day 209 were tested using the new viral lot.

Number of Participants (Planned and Analyzed): Approximately 600 participants were planned and were enrolled in this study: 400 participants were planned and received mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level; and 200 participants were planned and received placebo, with 100 participants in each age cohort.

Diagnosis and Main Criteria for Inclusion and Exclusion: Refer to the primary analysis (Day 57) CSR for the inclusion and exclusion criteria for the study.

Test Product, Dose and Mode of Administration, Batch Number(s): mRNA-1273 was administered as an 0.5 mL IM injection containing 50 or 100 µg of mRNA-1273 (Lot Numbers: 8520100102 and 8520100103) into the deltoid muscle (preferably the nondominant arm) on a 2-dose injection schedule on Day 1 and Day 29. The second dose of the study vaccine should have been administered in the same arm as the first dose.

Control Product, Dose and Mode of Administration, Batch Number(s): Placebo (0.9% sodium chloride) 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 mRNA-1273 or placebo as 2 injections administered 28 days apart (Day 1 and Day 29).

Statistical Methods: An analysis of safety and immunogenicity data was performed after all participants completed Part A of the study.

For the End of Part A analysis, additional bAb data based on a validated ELISA assay, VAC65 spike IgG antibody, became available. Seroresponse, as measured by VAC65 spike IgG antibody at a participant level, was defined as a change of VAC65 spike IgG antibody titer from below the lower limit of quantification (LLOQ) to equal to or above LLOQ, or a 4.6-times or higher titer ratio in participants with baseline titers ≥ LLOQ. Seroresponse (≥ 4-fold rise) specific to SARS-CoV-2 spike protein measured by ELISA at a participant level was defined as a ≥ 4 × LLOQ for participants with baseline antibody level below the LLOQ, or a 4-times or higher ratio in participants with pre-existing bAb levels.

For VAC65 spike IgG antibody, proportions of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific bAb levels from baseline at each post-injection time points were tabulated with 2-sided 95% Clopper-Pearson confidence intervals (CIs), and proportions of participants with seroresponse were presented with 2-sided 95% Clopper-Pearson CIs at each postbaseline timepoint.

To thoroughly characterize all potential AEs of interest, summaries were produced by searching the database using individual Standardized MedDRA Queries (SMQs) for vasculitis, hypersensitivity, arthritis, angioedema, peripheral neuropathy, demyelinating disease of central nervous system, and convulsions.

More than 1 viral lot was used for detection of nAb, and each viral lot led to one set of LLOQ and upper limit of quantification (ULOQ). As a result, the proportions of participants achieving seroresponse and/or ≥ 2-fold, ≥ 3-fold, and ≥ 4-fold increase from baseline and the corresponding CI were not reported.

Summary of Results:

Participant Disposition: In each treatment group, all participants received the first injection of study vaccine and the majority of participants in both age cohorts (> 95%) received the second

injection. The details about participants who discontinued the study vaccine and reasons for discontinuations are summarized in the primary analysis (Day 57) CSR.

Twenty-seven and 18 participants in the mRNA-1273 overall group and placebo group, respectively, discontinued from the study. The most common reasons for study discontinuation were protocol deviation (6/400 [1.5%] participants in the mRNA-1273 overall group and 8/200 [4.0%] participants in the placebo group) and lost to follow-up (12/400 [3.0%] participants in the mRNA-1273 overall group and 7/200 [3.5%] participants in the placebo group). Other reasons for study discontinuation included physician decision (3/400 [0.8%] participants in the mRNA-1273 overall group and no participant in the placebo group), withdrawal of consent (COVID-19 noninfection related; 1/400 [0.3%] participant in the mRNA-1273 overall group and no participant in the placebo group), withdrawal of consent (5/400 [1.3%] participants in the mRNA-1273 overall group and no participant in the placebo group), and other (no participant in the mRNA-1273 overall group and 3/200 [1.5%] participants in the placebo group).

Drug Exposure: A total of 600 participants (100%) received the first injection and 587 participants (97.8%) received the second injection.

Demography and Baseline Characteristics: Demographic data and baseline characteristics are summarized in the primary analysis (Day 57) CSR (Section 5.4).

Safety: Solicited adverse reactions reported after each injection are presented in the primary analysis (Day 57) CSR (Section 7.1).

In this End of Part A analysis, the mRNA-1273 vaccine, administered as 2 doses (50 µg or 100 µg) 28 days apart, demonstrated an acceptable safety profile in the participant population enrolled in this study in both age cohorts: Cohort 1 (≥ 18 to < 55 years old) and Cohort 2 (≥ 55 years old). No new safety findings since the primary analysis (Day 57) CSR were identified in this End of Part A analysis.

The following are the key safety findings supporting the safety conclusion:

- The incidence of unsolicited treatment-emergent AEs (TEAEs) during Part A was similar between the mRNA-1273 overall group (45.3%) and the placebo group (47.0%). The number of participants who experienced unsolicited TEAEs regardless of causality was 105/200 (52.5%) participants in the mRNA-1273 50 µg group and 76/200 (38.0%) participants in the mRNA-1273 100 µg group. The number of participants who experienced unsolicited TEAEs related to the study vaccine was 19/200 (9.5%)

participants in the mRNA-1273 50 µg and 28/200 (14%) participants in the mRNA-1273 100 µg group.

- The incidence of the most common unsolicited TEAEs was similar between the mRNA-1273 overall and placebo groups except for the AE of COVID-19, where the incidence was notably higher in the placebo group.
- The most common unsolicited TEAEs (incidence ≥ 2%) in the mRNA-1273 overall or placebo groups were COVID-19 (5/400 [1.3%] and 26/200 [13.0%], respectively), headache (25/400 [6.3%] and 8/200 [4.0%], respectively), fatigue (21/400 [5.3%] and 7/200 [3.5%], respectively), arthralgia (11/400 [2.8%] and 4/200 [2.0%], respectively), oropharyngeal pain (8/400 [2.0%] and 4/200 [2.0%], respectively), myalgia (8/400 [2.0%] and 3/200 [1.5%], respectively), upper respiratory tract infection (6/400 [1.5%] and 4/200 [2.0%], respectively), and dermatitis contact (8/400 [2.0%] and 3/200 [1.5%], respectively).
- Of the 6 participants in the overall mRNA-1273 group with confirmed SARS-CoV-2 infection (4 participants in the 50 µg group and 2 participants in the mRNA-1273 100 µg group), only 1 TEAE was reported outside of the Infections and Infestations system organ class (SOC; migraine in 1 participant that was not temporally associated with COVID-19 infection). In the placebo group, the TEAEs reported outside of the Infections and Infestations SOC included hyperestrogenism, depression, oral disorder, rash papular, fatigue, and vitamin D decreased (1 participant each). No meaningful conclusion can be drawn for these participants due to the limited number of cases.
- No deaths occurred during Part A of the study. A total of 7 participants (1.8%) reported SAEs (5 participants [2.5%] in the 50 µg mRNA-1273 group and 2 participants [1.0%] in the 100 µg mRNA-1273 group). No individual preferred term (PT) was reported in more than 1 participant. No SAEs were reported in the placebo group.
- No participants reported unsolicited TEAEs leading to discontinuation from the study during Part A.
- The incidence of MAAEs from Day 1 to End of Part A was similar in the mRNA-1273 overall group (28.0%) and the placebo group (32.0%). The incidence of MAAEs regardless of causality increased during the overall Part A period compared with that observed in the up to 28-day follow-up after any vaccination (from 39 to 112 participants in the mRNA-1273 overall group and from 17 to 64 participants in the placebo group) which was likely due to the longer duration of follow-up. The incidence of treatment-related MAAEs was similar in the overall Part A period compared with that observed in the up to 28-day follow-up after any vaccination (8 and 6 participants in the mRNA-1273 group, respectively, and 2 and 1 participants in the placebo group, respectively).

- As identified from analyses of AEs of interest based on an SMQ search of the database, the incidence of hypersensitivity was similar between the mRNA-1273 overall group (3.5%) and placebo group (3.0%). No participants had AEs of interest in the SMQs of vasculitis, demyelination, or convulsions. Two participants in the mRNA-1273 overall group had AEs of interest in the arthritis SMQ (gout in 1 participant and periarthritis in 1 participant). One participant in the placebo group had a TEAE in the peripheral neuropathy SMQ (PT of neuralgia).
- Mean vital sign measurements (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and temperature) observed through Day 209 were comparable to those observed at baseline, with no notable trends or differences across groups.

Immunogenicity: Data in this End of Part A analysis provided evidence of the robust immunogenicity of both 100 µg and 50 µg dose levels of mRNA-1273 when administered as 2 doses separated by 28 days.

- The time course of bAb response to vaccination was similar in both dose groups: mRNA-1273 induced increases in geometric mean (GM) levels from baseline by Day 29 (28 days after the first injection), and declined from the peak at Day 43 (14 days after the second injection) to Day 209. At Day 209, GM levels remained higher than the levels observed at Day 29 (before the second injection) for both mRNA-1273 100 µg and mRNA-1273 50 µg dose groups.
- The geometric mean fold-rise (GMFR) of bAb response trended higher in the mRNA-1273 100 µg group than in the mRNA-1273 50 µg group at all postbaseline visits. GMFR results showed a robust response in both dose groups, with seroresponse criteria being met in 100% of participants at Day 43 and Day 57.
- Similar trends in bAb response were observed in Cohort 1 (age ≥ 18 and < 55 years) and Cohort 2 (age ≥ 55 years), and GM levels and GMFRs were generally higher in Cohort 1 than Cohort 2 at each postbaseline visit. In both cohorts, seroresponse criteria were met in 100% of participants at Day 43 and Day 57.
- The time course of nAb response to vaccination was similar in both dose groups: mRNA-1273 induced increases in MN_{50} and MN endpoint titer values from baseline by Day 29 (28 days after the first injection) and declined from the peak at Day 43 (14 days after the second injection) to Day 209. The titers at Day 209 remained higher than the values observed at Day 29 (before the second injection) for both 100 µg and 50 µg dose groups.
- Within the mRNA-1273 100 µg group, nAb responses were numerically higher in Cohort 1 than in Cohort 2 at each postbaseline visit.

Overall, the magnitude and kinetics of immune response for both bAb and nAb was consistent across dose groups and age cohorts. Study 201 provided evidence of persistence of immune response through Day 209 (6 months after the second injection of mRNA-1273), which was lower than the peak observed at Day 43 but was higher than that at Day 29 (before the second injection).

Conclusions: This study was designed to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 vaccine, administered in 2 doses (50 µg or 100 µg) 28 days apart.

- mRNA-1273 demonstrated an acceptable safety profile in the participant population enrolled in this study at both dose levels in 2 age cohorts: Cohort 1 (≥ 18 to < 55 years old) as well as Cohort 2 (≥ 55 years old).

- Vaccination with mRNA-1273 resulted in robust immune responses to SARS-CoV-2 in participants 18 years and older at both dose levels, and persistence of immune response was observed up to 6 months after the second injection. The titers are numerically higher in participants who received 100 µg compared with 50 µg of mRNA-1273 at Day 209. These results confirm the selection of the 100 µg dose that was brought forward in the pivotal Phase 3 (COVE) study.

Date of This Report: 13 Aug 2021