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. DOI: 10.1016/j.vaccine.2021.02.007.

Study Period: 22 May 2020 (first participant, first visit) to 05 Nov 2020 (database lock).

Drug Development Phase: 2a

Objectives and Endpoints:

Objectives	Endpoints
Primary safety	
• To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs throughout the entire study period • Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only) • Vital sign measurements and physical examination findings
Primary immunogenicity	
• To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific bAb	• Level of SARS-CoV-2-specific bAb measured by ELISA on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13)

Objectives	Endpoints
Secondary	
• To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of nAb	• Titer of SARS-CoV-2-specific nAb on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) • Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the LLOQ to equal to or above LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers
Exploratory	
• To profile S protein-specific serum Ig class and subclass and nAb in serum • To describe the ratio or profile of specific bAb relative to nAb in serum • To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29) • To characterize the clinical profile and immune response of participants infected by SARS-CoV-2 • To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection	• Serum titers of S protein-specific binding Ig assessed by class and subclass and nAb in serum • Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum • Clinical severity and immune response of participants infected by SARS-CoV-2 • Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect nonvaccine antigens of SARS-CoV-2

Abbreviations: AE=adverse event; AR=adverse reaction; bAb=binding antibody; ELISA=enzyme-linked immunoabsorbent assay; Ig=immunoglobulin; LLOQ=lower limit of quantification; M=month; MAAE=medically attended adverse event; nAb=neutralizing antibody; S=spike; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus that causes COVID-19.

Methodology: The mRNA-1273-P201 was a randomized, observer-blind, and placebo-controlled study, with adult participants at least 18 years of age.

This primary analysis clinical study report (CSR) provides the primary analysis of safety and immunogenicity data through Day 57 (data cutoff date of 05 Nov 2020). The end-of-study (EOS) CSR will include final analysis of all endpoints and will be completed after all participants have completed the Month 13 study procedures and the database is cleaned and locked.

Two dose levels of mRNA-1273, 50 µg and 100 µg, were evaluated in this study, based in part on initial safety data from the Phase 1 Division of Microbiology and Infectious Diseases study of mRNA-1273. The 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.

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 study treatment. Before initiating study treatment of 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.

The full study 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 Day 394 (Month 13). Scheduled participant contact continued approximately every 2 weeks after Day 57 to collect medically attended adverse events (MAAEs), adverse events (AEs) leading to withdrawal, serious AEs (SAEs), concomitant medications associated with these events, receipt of nonstudy vaccinations, exposure to someone with known coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus that causes COVID-19 (SARS-CoV-2) infection, and participant experience of COVID-19 symptoms as indicated in the Schedule of Events. Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363, each participant completed a questionnaire in an electronic diary (eDiary) that was reviewed by study site personnel. Safety telephone calls occurred every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377. At study completion, the study duration for each participant will be approximately 14 months: a screening period of up to 1 month and a study period of 13 months, which includes the first dose of investigational product (IP) on Day 1 and the second dose on Day 29. A participant's final visit will be Day 394 (Month 13), 12 months after the second dose of the IP on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples were collected at Day 1, Day 29, and 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.

Each participant received 2 injections of mRNA-1273 or placebo by 0.5 mL intramuscular (IM) injection on Day 1 and Day 29. Investigational product accountability, dose preparation, and administration were performed by unblinded pharmacy personnel who did not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) remained blinded to dosing assignment.

All participants were followed for safety and reactogenicity and provided pre- and postinjection blood specimens for immunogenicity through 12 months after the last dose of IP. An SMC met

on a regular basis to assess safety throughout the study conduct and could have convened on an ad hoc basis if study pause rules were met.

The EOS was defined as the release of the last testing result of samples collected at Visit 9 or the completion of the last participant's last visit, whichever occurred later. Participants will be considered to have completed the study if they completed the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants were instructed (Day 1) or reminded (Day 29) how to document and report solicited adverse reactions (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 safety and immunogenicity at scheduled study visits. Blood samples were drawn from participants in case of any medical concerns according to the investigator's judgment. In addition, participants provided blood samples at unscheduled visits for acute respiratory symptoms.

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.

All 600 participants in the Randomized Set received IP and were included in the Safety Set and the Solicited Safety Set. The majority of participants who received mRNA-1273 or placebo were included in the Per-Protocol (PP) Set for SARS-CoV-2-specific binding antibody (bAb) (374/400 [93.5%] and 186/200 [93.0%], respectively), with no notable differences observed for the Day 29 and Day 57 analyses. Similarly, the majority of participants who received mRNA-1273 or placebo were included in the PP Set for SARS-CoV-2-specific neutralizing antibody (nAb) from the First Lot (365/400 [91.3%] and 181/200 [90.5%], respectively), with no notable differences observed for the Day 29 and Day 57 analyses.

Diagnosis and Main Criteria for Inclusion and Exclusion: Participants eligible for enrollment in this study included males or females (those of nonchildbearing and childbearing potential) 18 years of age or older at the time of consent who were in good general health with a body mass index of 18 kg/m^2 to 30 kg/m^2 (inclusive); male participants and female participants of

childbearing potential agreed to comply with protocol-defined contraception requirements. Participants were excluded if they had a known history of SARS-CoV-2 infection or known exposure to someone with SARS-CoV-2 infection or COVID-19, had traveled outside of the United States in the 28 days prior to the Screening Visit, were a healthcare worker or member of emergency response team, resided in a nursing home, or had any exclusionary pre-existing condition or test result.

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 IP 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 IP of mRNA-1273 or placebo as 2 injections administered 28 days apart (Day 1 and Day 29).

Statistical Methods:

Safety

All safety analyses were conducted on the Safety Set, except summaries of solicited ARs, which were based on the Solicited Safety Set. Unsolicited AEs and medical history were coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

All solicited ARs (local and systemic) were considered causally related to injection.

All solicited ARs analyses were summarized by overall treatment group and by age cohort for the first injection, second injection, and any injection, unless otherwise specified. The following summary tables were provided:

- The number and percentage of participants who reported each individual solicited local AR (severity $\geq$ grade 1) and solicited systemic AR (severity $\geq$ grade 1) during the 7-day follow-up period after each injection were summarized by severity grade.

- The number and percentage of participants who reported each individual solicited AR were summarized by severity grade and day of reporting, within this summary the number and percentage of participants experiencing fever (≥ 38.9°C/102.1°F; oral, axillary, or tympanic route) were summarized by severity grade.
- 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), where onset of individual solicited AR was defined as the time point after each injection at which the respective solicited AR first occurred.
- The number of days reporting each solicited AR was summarized descriptively and summarized by the following time windows: 1 to 2 days, 3 to 4 days, 5 to 6 days, and ≥ 7 days.
- The number and percentage of participants who reported solicited rash and lymphadenopathy, as assessed by healthcare provider (HCP), were summarized by severity grade.

In the summary by severity grade and summary by severity grade and day of reporting, a 2-sided 95% exact confidence interval (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. Within each summary of systemic ARs, the number and percentage of participants experiencing fever (≥ 38.9°C/102.1°F; oral, axillary, or tympanic route) were summarized by severity grade.

All summary tables for unsolicited treatment-emergent AEs (TEAEs; except for the overall summary of TEAEs) were presented by SOC and PT for TEAEs with counts of participants included. All safety analyses were summarized by overall treatment group and by age cohort, unless otherwise specified. Unsolicited TEAEs were summarized separately by stage (28 days after any vaccination stage and overall stage [Day 1 to Day 57 for this primary analysis; the EOS CSR will provide overall stage Day 1 to Day 394]). Participants with multiple occurrences of the same AE or a continuing AE were counted once in summaries within each SOC and PT. Participants who reported multiple events under the same SOC and/or PT were presented in summaries according to the highest severity (the strongest relationship).

The following summaries of unsolicited TEAEs (number and percentage) for each stage were included: overview summary of TEAEs, all unsolicited TEAEs, all unsolicited treatment-related TEAEs, all serious TEAEs, all treatment-related serious TEAEs, all unsolicited TEAEs leading to discontinuation from participation in the study, all unsolicited severe TEAEs, all unsolicited treatment-related TEAEs, all unsolicited TEAEs that were MAAEs. A summary of TEAEs by

SOC, PT, and severity (mild, moderate, and severe) using frequency counts and percentages was provided for all unsolicited TEAEs and all unsolicited treatment-related TEAEs.

For continuous hematology, serum chemistry, and coagulation measurements, the observed values and changes from baseline were summarized at each visit by treatment group for Cohort 2. The number and percentage who had any abnormal result based on toxicity grades in hematology, serum chemistry, or coagulation measurements also were summarized by visit and treatment group for Cohort 2. Shift from baseline in the toxicity grades to the worst postbaseline result in the vaccination stage was summarized by treatment group for Cohort 2.

Observed values and changes from baseline for all vital sign measurements were summarized at each visit by overall treatment group and by age cohort. Shift from baseline in the toxicity grades at each visit and shift from baseline in the toxicity grades to the worst postbaseline result also were summarized by overall treatment group and by age cohort.

Immunogenicity

The analyses of immunogenicity were based on the PP Set and were performed by treatment group for each age cohort separately. For each analysis listed below, the 95% CIs were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation and descriptive statistics at each time point were the number of participants, median, minimum, and maximum (unless otherwise specified). For each group, the following evaluations were performed at each time point at which blood samples were collected for immunogenicity (unless otherwise specified):

- The geometric mean (GM) level of SARS-CoV-2-specific bAb levels with corresponding 95% CI were provided at each time point. The GM level and corresponding 95% CI were plotted at each time point.
- The GM fold-rise (GMFR) of SARS-CoV-2-specific bAb levels with corresponding 95% CI were provided at each postbaseline time point over pre-injection baseline at Day 1. The GMFR and corresponding 95% CI were plotted at each time point.
- The GM titer of SARS-CoV-2-specific nAb titers with corresponding 95% CI were provided at each time point.
- The GMFR of SARS-CoV-2-specific nAb titers with corresponding 95% CI were provided at each postbaseline time point over pre-injection baseline at Day 1. The proportion of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers from Day 1 (baseline) at each postinjection time points were tabulated with 2-sided 95% Clopper-Pearson CIs.

- The proportion of participants with seroconversion were tabulated with 2-sided 95% Clopper-Pearson CIs at each postbaseline time point. Seroconversion at a participant level was defined as a change of nAb titer from below the lower limit of quantification (LLOQ) to equal to or above LLOQ (respectively) or a 4-times higher titer ratio in participants with pre-existing nAb titers.
- The GM level, GM titer, and GMFR with corresponding 95% CI were also evaluated using an analysis of covariance model with baseline level/titer as a covariate and age cohort as a factor in the analysis in the overall group. The model was conducted based on the log-transformed values then back transformed to the original scale for presentation.
- Additional sensitivity analysis of immunogenicity data was conducted for the above endpoints using the "adjusted" PP Set based on the more rigid visit window, -3/+7 for the Day 29 visit, as appropriate.

Summary of Results:

Participant Disposition: In each treatment group, all participants received the first injection of IP and the majority of participants in both age cohorts (> 95%) received the second injection. Seven of 400 (1.8%) participants who received mRNA-1273 (5/200 [2.5%] and 2/200 [1.0%] in the mRNA-1273 50 and 100 µg groups, respectively) and 6 of 200 (3.0%) participants who received placebo discontinued the IP. Six and 4 participants in the mRNA-1273 overall group and placebo group, respectively, discontinued from the study.

The reasons for mRNA-1273 discontinuation were AEs (other), lost follow-up, and "other" reasons (each 2/400 [0.5%]) and withdrawal of consent (1/400 [0.3%]). The reasons for discontinuation of placebo were AE (COVID-19 infection; 1/200 [0.5%]), lost to follow-up (3/200 [1.5%]), and "other" reasons (2/200 [1.0%]; related to false-positive COVID-19 results).

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: The participants in the Safety Set were approximately two-thirds female (390/600 [65.0%] overall) and mostly White (569/600 [94.8%] overall) and not of Hispanic or Latino descent (552/600 [92.0%]), with a mean (standard deviation) age of 50.8 (15.85) years and an age range of 18 to 87 years. No apparent differences were observed in baseline demographics across treatment groups. Participant demographics for the Randomized Set and the primary analysis PP Sets for SARS-CoV-2–specific bAb and nAb were comparable to those observed for the Safety Set.

Safety: In this primary 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) as well as Cohort 2 (≥ 55 years old).

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

Solicited Adverse Reactions

- More participants reported any solicited ARs within 7 days of any injection in the mRNA-1273 overall group (93.5%) than in the placebo group (51.5%).
- The incidence of solicited local ARs and systemic ARs within 7 days of any injection were both higher for participants who received mRNA-1273 (overall; 89.0% and 78.8%, respectively) than for those who received placebo (19.0% and 45.5%, respectively).
- The incidence of solicited local ARs within 7 days after injection was comparable after the first and second injections for the mRNA-1273 overall group (74.8% versus 83.0%). In the mRNA-1273 overall group, the incidence of solicited systemic ARs was numerically higher after the second injection than after the first injection (73.3% and 43.1%, respectively).
- Across all treatment groups, the majority of solicited ARs were grade 1 or grade 2; no grade 4 solicited ARs were reported. More grade 3 solicited ARs were reported in the mRNA-1273 overall group (14.3%) than in the placebo group (3.0%). In the mRNA-1273 overall group, most grade 3 solicited ARs occurred after the second injection and the most common solicited ARs were fatigue, myalgia, and headache.
- In the mRNA-1273 overall group, the most common solicited local AR was pain: 74.4% after the first injection and 82.4% after the second injection.
- The most common solicited systemic ARs in the mRNA-1273 overall group were headache (25.3%) and fatigue (24.6%) after the first injection and fatigue (59.0%), headache (50.9%), myalgia (47.1%), arthralgia (36.9%), and chills (32.3%) after the second injection.
- There was a dose-dependent increase in pain between the mRNA-1273 50 µg and 100 µg groups after the first injection (65.5% and 83.4%, respectively).
- Fever, fatigue, myalgia, arthralgia, nausea/vomiting, and chills showed a dose-dependent increase between the mRNA-1273 50 µg and 100 µg groups after the second injection but not after the first injection.

- After the first injection, the incidence of any solicited ARs and solicited local ARs was (88.0% and 84.0%, respectively) in the mRNA-1273 100 µg group and (71.0% and 65.5%, respectively) in mRNA-1273 50 µg group.
- In the mRNA-1273 overall group, the incidence of any solicited ARs, solicited local ARs, and solicited systemic ARs after the first injection were 85.0%, 80.0%, and 49.0%, respectively, in Cohort 1 (≥ 18 to < 55 years) and 74.0%, 69.5%, and 37.2%, respectively, in Cohort 2 (≥ 55 years).
- In the mRNA-1273 overall group, the incidence of any solicited ARs, solicited local ARs, and solicited systemic ARs after the second injection was 90.8%, 85.2%, and 75.0%, respectively, in Cohort 1 (≥ 18 to < 55 years) and 86.8%, 80.7%, and 71.6%, respectively, in Cohort 2 (≥ 55 years).
- In the mRNA-1273 overall and placebo groups, participants most often reported solicited local ARs and systemic ARs within the first 3 days after any injection, with an onset of each on Day 1 or Day 2 after any injection in both groups. The mean number of days solicited local ARs and systemic ARs were reported within the 7 days after any injection was 2.9 and 3.1 days, respectively, in the mRNA-1273 overall group and 2.0 and 2.4 days, respectively, in the placebo group.
- The incidence of solicited ARs that were ongoing 7 days after any injection and reported as TEAEs in the mRNA-1273 overall group was 28/400 (7.0%) and that in the placebo group was 8/200 (4.0%); no solicited AR met the SAE criteria. In the mRNA-1273 overall group or placebo group, the highest incidence (> 1.0%) of solicited ARs ongoing 7 day after any injection and reported as TEAEs (by decreasing incidence in the mRNA-1273 overall group) were fatigue (3.5% and 2.5%, respectively), headache (2.8% and 0.5%, respectively), and arthralgia and myalgia (both 1.8% and 1.0%, respectively).
- One participant in the mRNA-1273 100 µg group discontinued vaccination due to three grade 3 solicited ARs (fatigue, myalgia, and arthralgia).
- Ad hoc analysis of medication use for pain or fever, which was based on patient-reported use in Diary entries (after any, first, or second injection), demonstrated that more participants reported medication use in the mRNA-1273 groups (50 µg, 100 µg) than the placebo group (39.5%, 51.5%, and 14.5%, respectively) after any injection.

Unsolicited TEAEs

- The incidence of unsolicited TEAEs up to 28 days after any IP administration was comparable between the mRNA-1273 overall group (28.3%) and the placebo group (25.5%), with no dose-dependent increase with mRNA-1273 dose (50 and 100 µg both approximately 28%).
- The incidence of the most common unsolicited TEAEs was comparable between the mRNA-1273 overall group and placebo group. The common TEAEs with the highest incidence (≥ 2%) in the mRNA-1273 overall group or placebo group (by decreasing incidence in the mRNA-1273 overall group) were headache (3.8% and 2.5%, respectively), fatigue (3.5% and 3.0%, respectively), arthralgia (2.3% and 2.0%, respectively), and myalgia (2.0% and 1.5%, respectively).
- Most unsolicited TEAEs reported up to 28 days after any injection in both the mRNA-1273 overall and placebo groups were mild or moderate in severity. Few participants reported severe unsolicited TEAEs: 3.0% in the mRNA-1273 overall group and 2.0% in the placebo group, and approximately half of the reported severe unsolicited TEAEs in the each treatment group were considered related to IP.
- More participants reported treatment-related unsolicited TEAEs in the mRNA-1273 overall group (10.8%) than in the placebo group (6.5%). The treatment-related TEAEs with the highest incidence (> 1%) in mRNA-1273 overall group or the placebo group (by decreasing incidence in the mRNA-1273 overall group) were fatigue (3.3% and 3.0%, respectively), headache (2.8% and 0.5%, respectively), arthralgia (1.8% and 2.0%, respectively), myalgia (1.8% and 1.0%, respectively), and injection site pain (1.3% and 0.5%, respectively). No treatment-related SAEs were reported though Day 57.
- Of the 7 participants with confirmed SARS CoV 2 infection, 3 participants were symptomatic (2 participants in the placebo group and 1 participant in the mRNA-1273 50 µg group) and 4 participants remained asymptomatic (3 participants in the placebo group and 1 participant in the mRNA-1273 50 µg group). No cases of asymptomatic SARS-CoV-2 infection or symptomatic COVID-19 were reported in the 100-µg group. All participants with SARS-CoV-2 infection or COVID-19 reported TEAEs of COVID-19; none were severe, all resolved, and none were considered related to the IP.
- No deaths occurred up to the data cutoff for this primarily analysis and one participant (mRNA-1273 50 µg) had a serious TEAE (pneumonia), which occurred > 28 days after any IP administration and was considered not related to IP.
- Due to positive COVID-19 on Day 6, one participant in the mRNA-1273 50 µg group discontinued IP administration. One participant each in the mRNA-1273 50 µg and

placebo groups had a TEAE that led to IP discontinuation that occurred > 28 days after any IP administration; both TEAE were considered not related to IP.

- No unsolicited TEAE led to study discontinuation from Day 1 through Day 57.
- The incidence of MAAEs up to 28 days after any injection was comparable in the mRNA-1273 overall group (9.8%) and placebo group (8.5%). Few participants in any treatment group had MAAEs considered related to IP.
- As identified from ad hoc analysis based on a Standardized MedDRA Query (SMQ) search of the database, the incidence of hypersensitivity was comparable between the mRNA-1273 overall group (2.8%) and placebo group (3.0%). No participants had AEs of special interest in the SMQs of vasculitis, peripheral neuropathy, demyelination, or convulsions. One participant in the mRNA-1273 100 µg group had an AE of special interest in the arthritis SMQ (gout).
- No treatment-related, dose-related, or clinically relevant trends in changes from baseline from Day 1 through Day 57 were observed for the hematology, coagulation, and chemistry laboratory test results of participants in Cohort 2.
- Mean vital sign measurements (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and temperature) observed from Day 1 and through Day 57 were similar to those observed at baseline, with no notable trends or differences between any of the treatment groups.
- The only notable difference by age cohorts was for treatment-related TEAEs in the mRNA-1273 100 µg group, with a higher incidence in Cohort 1 (18.0%) than in Cohort 2 (9.0%). In addition, in Cohort 1, more participants in the mRNA-1273 100 µg group reported treatment-related unsolicited TEAEs than participants in the mRNA-1273 50 µg and placebo groups (18.0%, 7.0%, and 6.0%, respectively).

Immunogenicity: In this primary analysis, mRNA-1273 50 µg and 100 µg both induced anti-SARS-CoV-2 spike bAbs and nAbs at Day 29 (28 days after the first injection) that peaked at Day 43 and persisted though Day 57 (14 and 28 days, respectively, after the second injection), with generally comparable immunogenicity demonstrated in each age cohort.

The following are the key findings supporting the immunogenicity conclusions:

- The GMFRs (95% CI) of VAC58 spike immunoglobulin G (IgG) antibodies at Day 29 were 4.29 (3.87, 4.76) in the mRNA-1273 100 µg group and 3.36 (3.05, 3.69) in the mRNA-1273 50 µg group, and were 33.51 (30.37, 36.96) in the mRNA-1273 100 µg group compared with 27.46 (24.86, 30.33) in the mRNA-1273 50 µg group at Day 43.

- In both mRNA-1273 50 and 100 µg groups, the GMFR in VAC58 spike IgG antibody levels were > 27 at Day 43 and > 20 at Day 57.
- The GMFRs (95% CI) of VAC58 spike IgG antibodies trended higher in the mRNA-1273 100 µg group than in the mRNA-1273 50 µg group at Day 29 (4.29 [3.87, 4.76] and 3.36 [3.05, 3.69], respectively), Day 43 (33.51 [30.37, 36.96] and 27.46 [24.86, 30.33, respectively) and Day 57 (25.04 [22.51, 27.86] and 20.39 [18.31, 22.70], respectively). In Cohort 1, the GMFRs (95% CI) were generally higher in the mRNA-1273 100 µg group than in the mRNA-1273 50 µg group at Day 29 (5.26 [4.57, 6.06] and 3.65 [3.20, 4.16], respectively), Day 43 (38.47 [34.54, 42.85] and 26.82 [23.46, 30.67], respectively), and Day 57 (29.13 [25.68, 33.03] and 20.70 [17.92, 23.90], respectively). No apparent trend was observed between the two mRNA-1273 doses in Cohort 2.
- Both mRNA-1273 doses induced nAb responses, assessed by microneutralization (MN) endpoint titers and MN_{50} at each postbaseline visit. While no formal statistical testing was done, nAb responses were generally comparable in participants who received the mRNA-1273 100 µg and the 50 µg dose at all time points.
- At Day 29 (28 days after the first injection), the MN endpoint GMFRs (95% CI) were 5.59 (4.65, 6.71) in the mRNA-1273 50 µg group and 7.46 (6.32, 8.81) in the mRNA-1273 100 µg group. At both Day 43 and Day 57, the GMFR was > 53 in each mRNA-1273 dose group.
- At Day 29 (28 days after the first injection), the MN_{50} GMFRs (95% CI) were 3.75 (3.16, 4.45) in the mRNA-1273 50 µg group and 4.97 (4.23, 5.85) in the mRNA-1273 100 µg group. At both Day 43 and Day 57, the GMFR was > 35 in each mRNA-1273 dose group.
- At Day 29, the seroconversion rates based on the MN endpoint titers and MN_{50} titers were 78.0% and 65.5%, respectively, in the mRNA-1273 50 µg group and 88.9% and 76.7%, respectively, in the mRNA-1273 100 µg group.
- At Day 43 and Day 57, 100% of participants met seroconversion criteria based on MN endpoint titers and MN_{50} titers in both mRNA-1273 dose groups.
- Generally, no apparent difference in MN endpoint titers and MN_{50} titers was observed between Cohort 1 and Cohort 2.

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 two age cohorts: Cohort 1 (≥ 18 to < 55 years old) as well as Cohort 2 (≥ 55 years old).

- Vaccination with mRNA-1273 resulted in significant immune responses to SARS-CoV-2 in participants 18 years and older at both dose levels, confirming the selection of the 100-µg dose that was brought forward in the pivotal Phase 3 (COVE) study.

This report is based on the primary analysis through Day 57. The full study analyses will be presented in the end-of-study CSR. The 13-month end-of-study assessment of this study and the ongoing Phase 3 (COVE) study may provide additional longer-term data on the safety and effectiveness of mRNA-1273 vaccine.

Date of This Report: 23 February 2021