Synopsis

Title of Study: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (ClinicalTrials.gov Identifier: NCT04283461)

Investigator: Lisa A. Jackson

Study Centers: A total of 3 study sites (one of which had a satellite site) in the United States enrolled at least 1 participant in the study.

Publications:

Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383(25):2427-38.

Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020;383(20):1920-31.

Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. 2021;384(1):80-82.

Study Period: 16 March 2020 (first participant first visit) to 07 October 2020 (data freeze date for this Day 119 clinical study report)

Drug Development Phase: 1

Background and Rationale: In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus (CoV) RNA was quickly identified in some of these first patients. This novel CoV was originally referred to as 2019-nCoV but was subsequently named SARS-CoV-2 (because of its similarity to the severe acute respiratory syndrome [SARS] CoV [SARS-CoV]). On March 11, 2020 the World Health Organization (WHO) declared CoV disease 2019 (COVID-19) a pandemic.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat SARS-CoV-2 severe infections have intensified, but no proven therapeutic currently exists. Therefore, there is an urgent public health need for rapid development of novel interventions. Furthermore, since older adults are at higher risk for severe illness from COVID-19, it is important to rapidly assess clinical safety of novel vaccines in this vulnerable population as early as possible.

ModernaTX, Inc. has developed a rapid-response proprietary messenger RNA (mRNA)-based vaccine platform. The platform is based on the principle and observations that cells can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. ModernaTX, Inc. has used its mRNA-based platform to develop mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 encodes the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein into a prefusion conformation (S-2P).

The aim of this Phase I clinical study was to evaluate the safety, reactogenicity, and immunogenicity of ModernaTX's mRNA-1273, administered as 2 doses 28 days apart, in healthy adults across the age spectrum (≥ 18 years of age). The study included older adults (56 to 70 years or ≥ 71 years), because this population is at increased risk of severe illness from COVID-19.

This clinical study report (CSR) provides the interim analysis of safety and immunogenicity data through the data cutoff date of 07 October 2020 (data freeze date) and includes data through Day 119 for Cohorts 1 through 5, 7, and 8 and through Day 57 for Cohorts 10, 11, and 12.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 5 dosages in healthy adults	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination • Frequency of SAEs, NOCMCs, and MAAEs from Day 1 to Day 394
Secondary	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57	• GMT of antibody at Day 57 • Percentage of participants who seroconverted, defined as a 4-fold change in antibody titer from baseline • The GMFR in IgG titer from baseline

Objectives	Endpoints
Exploratory	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S protein following a 2-dose vaccination schedule of mRNA-1273 at all time points, other than Day 57	• GMT of antibody at each time point • Percentage of participants who seroconverted at each time point • The GMFR in IgG titer from baseline for each post-vaccination time point
• To evaluate the immunogenicity as measured by IgM and IgA ELISA to the SARS-CoV-2 S protein following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart	• GMT at each time point • Percentage of participants who seroconverted at each time point • The GMFR in IgM and IgA titer from baseline at each post-vaccination time point
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart	• GMT of nAb at each time point • Percentage of participants who seroconverted, defined as a 4-fold change in nAb titer from baseline at each time point • The GMFR nAb titer from baseline at each post-vaccination time point
• To evaluate the immunogenicity as measured by live wild-type SARS-CoV-2 neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart	• GMT of nAb at each time point • Percentage of participants who seroconverted, defined as a 4-fold change in nAb titer from baseline at each time point • The GMFR in nAb titer from baseline at each post-vaccination time point
• To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points post vaccination relative to baseline

Abbreviations: AE = adverse event; ELISA = enzyme-linked immunosorbent assay; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MAAE = medically attended adverse event; nAb = neutralizing antibody; NOCMC = new onset of chronic medical condition; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Methodology:

This was a Phase 1, open-label, dose-ranging study in males and nonpregnant females, at least 18 years of age, who were in good health and met all eligibility criteria. This clinical study was designed to assess the safety, reactogenicity, and immunogenicity of mRNA-1273 manufactured by ModernaTX. mRNA-1273 is a novel LNP-encapsulated mRNA-based vaccine that encodes a full-length, prefusion stabilized S protein of SARS-CoV-2.

Up to 155 participants were planned to be enrolled in up to 13 cohorts. Participants received an intramuscular (IM) injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid

muscle of the same arm. Participants were observed at the study site for at least 60 minutes after each dose of study vaccine. The injection site was examined immediately prior to each study vaccine administration. Participants are being followed through 12 months after the second vaccination (Day 394). This CSR provides the interim analysis of safety and immunogenicity data through Day 119 for Cohorts 1 through 5, 7, and 8 and through Day 57 for Cohorts 10, 11, and 12; no participants were enrolled in Cohorts 6, 9, and 13.

Planned Study Cohorts

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

[a] Based on review of available interim safety and immunogenicity data, dosing at the 250 µg-dose level was deferred after Cohort 3 (18 to 55 years, n = 15) and prior to enrollment in Cohorts 6 (56 to 70 years, n = 10) and 9 (≥ 71 years, n = 10) to explore lower dosages. Subsequently, a decision was made not to enroll these groups.

[b] Based on review of available interim immunogenicity data, Cohort 13 (10 µg, 18 to 55 years, n=15) will not be enrolled.

Follow-up visits occurred at 1, 2, and 4 weeks post each vaccination (Days 8, 15, 29, 36, 43, and 57) and at 3 months post second vaccination (Day 119). Additional follow-up visits will occur at 6 and 12 months after the second injection (Days 209 and 394). To determine safety signals, enrollment proceeded in a staged fashion for Cohorts 1 through 8 (excluding Cohort 6), with enrollment of 4 sentinel participants each in Cohorts 1, 2, and 3.

Based on review of available interim safety and immunogenicity data, Cohorts 6 and 9 (250 µg; 56 to 70 years of age and ≥ 71 years of age, respectively) and Cohort 13 (10 µg; 18 to 55 years of age) will not be enrolled.

Safety Assessment:

The primary endpoint in this study was evaluation of the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart. The safety assessments included monitoring and recording the frequency and grade of solicited local and systemic adverse events (AEs) and unsolicited AEs, the frequency of serious adverse events (SAEs) and AEs of special interest (AESIs; medically attended AEs [MAAEs] and new onset of chronic medical conditions [NOCMCs]), as well as clinical laboratory evaluations, vital sign measurements, and physical examinations.

Reactogenicity was measured by the occurrence of solicited local (injection site) and systemic AEs from the time of each vaccination through 7 days post each vaccination using a memory aid. Additional safety and reactogenicity data were solicited via telephone calls to participants at 1 and 2 days post each vaccination (Days 2, 3, 30, and 31). For consistency across the mRNA-1273 program, solicited AEs were referred to as solicited adverse reactions (ARs) when summarized in the results.

Unsolicited nonserious AEs were collected from the time of each vaccination through 28 days post each vaccination. Serious AEs, NOCMCs, and MAAEs are being collected through 12 months after the last vaccination (Day 394).

Immunogenicity

The secondary and exploratory immunogenicity assessments included the following:

- Immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) to the SARS-CoV-2 S protein
- Immunoglobulin M and immunoglobulin A ELISA to the SARS-CoV-2 S protein
- Neutralization assay using a SARS-CoV-2 pseudovirus
- Neutralization assay using a live wild-type SARS-CoV-2

Number of Participants (Planned and Analyzed):

Planned: up to 155 participants

Analyzed: 120 participants

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion criteria:

A participant must have met all of the following criteria to be eligible to participate in this study:

1. Provided written informed consent prior to initiation of any study procedures.
2. Able to understand and agreed to comply with planned study procedures and was available for all study visits.
3. Agreed to the collection of venous blood per protocol.
4. Male or nonpregnant female, ≥18 years of age at time of enrollment.
5. Body mass index (BMI) 18.0 to 35.0 kg/m^2, inclusive (< 56 years of age), at Screening; BMI 18.0 to 30.0 kg/m^2, inclusive (≥ 56 years of age), at Screening.
6. Women of childbearing potential agreed to use or practiced true abstinence or used at least 1 acceptable primary form of contraception.
7. Women of childbearing potential must have had a negative urine or serum pregnancy test within 24 hours prior to each vaccination.
8. Male participants of childbearing potential: use of condoms to ensure effective contraception with a female partner of childbearing potential from first vaccination until 60 days after the last vaccination.
9. Male participants agreed to refrain from sperm donation from the time of first vaccination until 60 days after the last vaccination
10. In good health.
11. Oral temperature was less than 100.0°F (37.8°C).
12. Pulse no greater than 100 beats per minute.
13. Systolic blood pressure was 85 to 150 mm Hg, inclusive.
14. Clinical screening laboratory evaluations (white blood cells, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, creatinine, alkaline phosphatase, total bilirubin, lipase, prothrombin time, partial thromboplastin time) were within acceptable normal reference ranges at the clinical laboratory being used.
15. Agreed to have samples stored for secondary research.
16. Agreed to adhere to Lifestyle Considerations throughout study duration.

17. Agreed to refrain from donating blood or plasma during the study (outside of this study).

Exclusion criteria:

A participant who met any of the following criteria was excluded from participation in this study.

1. Positive pregnancy test either at Screening or just prior to each vaccine administration.
2. Female participant who was breastfeeding or planned to breastfeed from the time of the first vaccination through 60 days after the last vaccination.
3. Had any medical disease or condition that, in the opinion of the participating site investigator or appropriate subinvestigator, precluded study participation.
4. Presence of self-reported or medically documented significant medical or psychiatric condition(s).
5. Had an acute illness, as determined by the participating site investigator or appropriate subinvestigator, with or without fever [oral temperature ≥ 38.0°C (100.4°F)] within 72 hours prior to each vaccination.
6. Had a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at Screening.
7. Participated in another investigational study involving any investigational product within 60 days, or 5 half-lives, whichever was longer, before the first vaccine administration.
8. Currently enrolled in or planned to participate in another clinical trial with an investigational agent that was to be received during the study reporting period.
9. Previously participated in an investigational study involving LNPs (a component of the investigational vaccine assessed in this trial).
10. Had a history of hypersensitivity or severe allergic reaction (eg, anaphylaxis, generalized urticaria, angioedema, other significant reaction) to any previous licensed or unlicensed vaccines.
11. Chronic use (more than 14 continuous days) of any medications that may have been associated with impaired immune responsiveness.
12. Anticipated the need for immunosuppressive treatment within the next 6 months.

13. Received immunoglobulins and/or any blood or blood products within the 4 months before the first vaccine administration or at any time during the study.
14. Had any blood dyscrasias or significant disorder of coagulation.
15. Had any chronic liver disease, including fatty liver.
16. Had a history of alcohol abuse or other recreational drug (excluding cannabis) use within 6 months before the first vaccine administration.
17. Had a positive test result for drugs of abuse at screening or before the first vaccine administration. If cannabis was the only detected drug, inclusion was permitted.
18. Had any abnormality or permanent body art (eg, tattoo) that would interfere with the ability to observe local reactions at the injection site (deltoid region).
19. Received or planned to receive a licensed, live vaccine within 4 weeks before or after each vaccination.
20. Received or planned to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
21. Received any other SARS-CoV-2 or other experimental coronavirus vaccine at any time prior to or during the study.
22. Had close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.
23. History of COVID-19 diagnosis.
24. On current treatment with investigational agents for prophylaxis of COVID-19.
25. Current use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the investigator or necessary to manage a chronic condition.
26. Planned to travel outside the United States (continental United States, Hawaii, and Alaska) from enrollment through 28 days after the second vaccination.
27. Resided in a nursing home or other skilled nursing facility or had a requirement for skilled nursing care.
28. Nonambulatory.
29. For participants ≥ 56 years of age, history of chronic smoking within the prior year.
30. For participants ≥ 56 years of age, current smoking or vaping.

31. For participants ≥ 56 years of age, individuals currently working with high risk of exposure to SARS-CoV-2 (eg, active health care workers with direct patient contact, emergency response personnel).

Test Product, Dose and Mode of Administration, Batch Number: 25 µg, 50 µg, 100 µg, and 250 µg of mRNA-1273 administered as an IM injection (0.5 mL) into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with a 28-day interval between doses. The second dose of study vaccine was administered preferably in the same arm as the first dose. Lot 8520100101.

Control Product, Dose and Mode of Administration, Batch Number: Not applicable.

Duration of Treatment: Participants received their assigned dose of mRNA-1273 as a 2 vaccination schedule separated by approximately 28 days.

Estimands and Intercurrent Events: Not applicable

Statistical Methods:

Safety:

Solicited AEs: Solicited AEs were graded on a scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe). Solicited systemic AEs included fatigue (captured in the memory aid as tiredness), headache, myalgia (captured in the memory aid as body aches/muscle pain), arthralgia (captured in the memory aid as joint pain), nausea, feverishness (captured in the memory aid as chills), and fever. Solicited local AEs included pain at injection site, erythema (captured in the memory aid as redness), and induration (captured in the memory aid as swelling/hardness).

For consistency across the mRNA-1273 program, these solicited AEs were referred to as solicited ARs when summarized in the results.

The proportion of participants reporting at least 1 solicited AR was summarized for each solicited AR, any systemic symptom, any local symptom, and any symptoms. The mean, SD, median, minimum, and maximum duration of solicited ARs were summarized. Day of solicited symptom onset and maximum severity on the day of onset were also summarized.

Unsolicited AEs: The proportion of participants reporting at least 1 unsolicited AE was summarized by Medical Dictionary for Regulatory Activities system organ class and preferred term for each dose of study vaccine and over all doses.

Immunogenicity:

Summaries and analysis of immunogenicity data were presented for the per-protocol population.

Seroconversion was defined as a 4-fold increase in antibody titer over baseline. For the secondary immunogenicity endpoint, seroconversion rates, geometric mean fold rise (GMFR), geometric mean titer (GMT), and Williams mean of the area under the curve (AUC) for SARS-CoV-2 (S-2P and receptor binding domain [RBD]) as measured by IgG ELISA were calculated on Days 1 (GMT only) and 57 by cohort and were summarized graphically. Seroconversion rates, GMFR, GMT, and Williams mean of the AUC were presented with their corresponding 95% confidence interval (CI) estimates (using Student's t-distribution) at each time point.

For SARS-CoV-2–specific binding antibodies, seroconversion rates, GMFR, GMT, and Williams mean of AUC for SARS-CoV-2 (S-2P and RBD) as measured by IgG ELISA were calculated for specified time points by cohort.

The SARS-CoV-2 pseudovirus neutralization assay (PsVNA) and a wild-type SARS-CoV-2 plaque reduction neutralization test (PRNT) were performed using serial dilutions of sera. The serum dilution required to achieve 50% and 80% neutralization (ID_{50} and ID_{80}, respectively) were calculated for PsVNA data using a 5-parameter logistic regression model and were summarized by group using the geometric mean (GM) and 95% CI (using Student's t-distribution). Similarly, for PRNT data, 80% plaque reduction neutralization titer ($PRNT_{80}$) was calculated using a 5-parameter logistic model and was summarized using a GM and 95% CI. The minimum, median, and maximum were also reported.

Similar methods were used to summarize all additional neutralization assays performed (eg, a live-virus focus-reduction neutralization test [FRNT]; and FRNT using mNeonGreen [FRNT-mNG]). Spearman correlation between various neutralization assays were assessed.

The magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells were summarized at each time point by vaccination group.

Summary of Results:

The results reported in this CSR include interim analysis of safety and immunogenicity data through Day 119 for Cohorts 1 through 5, 7, and 8 and through Day 57 for Cohorts 10, 11, and 12.

Participant Disposition: A total of 256 potential participants were screened across all age groups, and 120 participants were enrolled. All participants received the first injection, and 116 participants received the second injection; 4 participants discontinued the vaccine after the first injection (1 participant due to potential COVID-19 exposure and 3 participants due to AEs). No participant discontinued from the study at the time of data cutoff. All participants in Cohorts 10, 11, and 12 completed the planned follow-up visits through Day 57, and all participants in Cohorts 1 through 5, 7, and 8 completed the planned follow-up through Day 119.

Safety Results:

Note: For consistency across the mRNA-1273 program, solicited AEs were referred to as solicited ARs when summarized in the results.

- Overall, mRNA-1273 demonstrated an acceptable safety profile.
- No serious AEs or AEs leading to study discontinuation were noted.
- Most of the solicited ARs were mild or moderate. In the 18 to 55 years of age group, severe solicited ARs predominantly occurred at the highest dose (250 µg): 4 participants in the 250 µg versus 1 participant each in the 50 µg and 100 µg vaccination groups. Additionally, severe solicited ARs were reported in 1 participant each in the 25 µg and 50 µg vaccination groups (age group: 56 to 70 years) and 1 participant in the 100 µg vaccination group (age group: ≥ 71 years).
- The most commonly reported solicited systemic ARs after any dose across all age groups were fatigue (captured in the memory aid as tiredness), headache, myalgia (captured in the memory aid as body aches/muscle pain), and feverishness (captured in the memory aid as chills). The incidence of solicited systemic ARs was higher after the second injection than after the first injection. Overall, fatigue and headache were the most commonly reported solicited systemic ARs after the first injection; fatigue, headache, myalgia, and feverishness were the most commonly reported solicited

systemic ARs after the second injection. Notably, in the 18 to 55 years of age group, the incidence of arthralgia, feverishness, headache, myalgia, and nausea increased by more than 2-fold after the second injection compared with the incidence after the first injection, and no participant reported fever after the first injection, but 15 (26%) participants reported fever after the second injection. In all age groups, severe solicited systemic ARs occurred only after the second injection.

- Overall, injection site pain was the most commonly reported solicited local AR. The incidence of the solicited local ARs was similar after the first injection and after the second injection.

- Most of solicited ARs had an onset within 2 days after vaccination, and the median durations of solicited ARs were 1 to 2 days. Notably, all severe solicited ARs resolved within 1 to 2 days.

- The incidence of unsolicited AEs was similar among vaccination groups across all age groups. Most unsolicited AEs were mild or moderate in severity.

- All unsolicited AEs related to mRNA-1273 were mild or moderate in severity, except for 2 severe AEs (dizziness and syncope, both occurring on Day 1 after the second injection) in 1 participant in the 18 to 55 years of age group (250 µg vaccination group). All AEs related to mRNA-1273 resolved.

- Adverse events leading to treatment discontinuation were reported in 3 participants. Of these, 1 mild AE of urticaria (25 µg vaccination group, age group: 18 to 55 years) was related to mRNA-1273.

- A total of 33 MAAEs were reported in 24 participants. All MAAEs were considered not related to mRNA-1273, except 1 MAAE (moderate abdominal discomfort) in 1 participant in the 18 to 55 years of age group (250 µg vaccination group). One AE (moderate bone density decreased) in one participant in the 56 to 70 years of age group (25 µg vaccination group) was captured as both an MAAE and NOCMC and was not related to mRNA-1273.

- Overall, no notable trends were observed in the hematology and chemistry laboratory test results for any vaccination group, and no trends were observed among dose level and the severity of events.

- One severe abnormal laboratory result (serum lipase; 18 to 55 years of age group, 250 µg vaccination group) was considered related to mRNA-1273.

- No notable trends were observed in vital sign results and physical examination findings for any age group or vaccination group, and no trend was observed among dose levels and the severity of events.

- Based on the safety findings that a higher incidence of severe solicited ARs was noted in the 250 µg group, the only participant reporting severe unsolicited AEs related to mRNA-1273 received 250 µg of mRNA-1273, and the only severe clinically meaningful laboratory abnormality (increased serum lipase) related to mRNA-1273 was noted in the 250 µg group; the 100 µg, 50 µg, and 25 µg dose levels can be considered to have a more acceptable safety profile than the 250 µg dose level. This was the rationale for not continuing to evaluate the 250 µg dose in the older age cohorts.

Immunogenicity:

mRNA-1273 administered as 2 doses separated by 28 days induced robust humoral and cellular immune responses. In general, dose-dependent increases in binding and neutralizing antibody responses were detected across age groups. Binding and neutralizing antibody responses among all age groups for the 100 µg vaccination dose persisted through Day 119 at levels that declined modestly relative to Day 57 but remained similar to or higher than responses in a convalescent sera panel. mRNA-1273 elicited a strong Th1-biased CD4 T cell response.

- S-2P IgG ELISA Endpoint

    - The S-2P ELISA results demonstrated a robust antibody response after each dose. The S-2P ELISA GMT values were generally numerically higher in the 100 µg vaccination group than in the 25 µg and 50 µg vaccination groups across all age groups. The S-2P ELISA GMT values in the 250 µg vaccination group were numerically higher than those in the 100 µg vaccination group in the 18 to 55 years of age group.

    - The S-2P ELISA GMT values for Day 43 and Day 57 were numerically higher than those for the convalescent sera control group across all age groups and dosage levels.

- Seroconversion (4-fold rise in endpoint titer from baseline) to S-2P was observed by Day 15 in all participants in the 18-55 years of age groups, by Day 29 in all participants in the 56-70 years of age groups, and by Day 36 in all participants in the ≥71 years of age group.

- For the 100 µg and 250 µg mRNA-1273 doses, the S-2P ELISA GMT values at Day 119 were numerically higher than that for the convalescent sera control group.

- RBD IgG ELISA Endpoint

  - The RBD ELISA results demonstrated a robust antibody response after each dose.

  - The RBD ELISA GMT values were numerically higher in the 100 µg vaccination group than in the 25 µg and 50 µg vaccination groups in the 56 to 70 and ≥ 71 years of age groups.

  - For all age groups and mRNA-1273 dose levels, the RBD ELISA GMT values for Day 36 and beyond exceeded the median GMT values for the convalescent sera control group.

  - The RBD ELISA GMFR results consistently showed robust responses across all age groups, and the seroconversion criteria were met at the majority of postbaseline visits.

- Pseudovirus Neutralization ID_{50} and ID_{80}

  - The PsVNA GM titers (ID_{50} and ID_{80}) for the 614D variant were undetectable prior to the first injection, marginally increased after the first injection, and substantially increased after the second injection.

  - The PsVNA GM titers (ID_{50} and ID_{80}) after 2 injections were similar at Day 57 among the 50 µg, 100 µg, and 250 µg vaccination groups in the 18 to 55 years of age group. In both the 56 to 70 and ≥ 71 years of age groups, the PsVNA GM titers (ID_{50} and ID_{80}) after 2 injections numerically were higher in the 100 µg vaccination group than in the 25 µg and 50 µg vaccination groups.

- The GM titers for the 100 µg mRNA-1273 vaccination group from Day 36 through Day 119 were similar to (≥ 71 years of age group) or exceeded (18 to 55 and 56 to 70 years of age groups) the GM titers from the convalescent sera control group.

- Robust neutralizing antibody responses to the 614G variant were also observed at Day 43 for the 100 µg vaccination group regardless of age.

- $PRNT_{80}$ GMT

  - The $PRNT_{80}$ GM values were undetectable prior to the first injection but were readily detectable and increased substantially after the second injection.

- FRNT-mNG

  - The FRNT-mNG GM neutralizing titers (ID_{50} and ID_{80}) were undetectable prior to the first injection, marginally increased after the first injection, and substantially increased after the second injection on Day 43 for all age groups and mRNA-1273 dose groups.

- Correlations were found within and between the values from binding antibody assays and neutralizing activity. The correlation between live-virus and pseudovirus neutralization with S-2P and RBD ELISA provides orthogonal support for each assay in characterizing the humoral response induced by mRNA-1273.

The T-cell response data supported the cellular immunity profile for mRNA-1273 with the following observations:

- The 25 and 100 µg doses elicited CD4 T-cell responses that, upon stimulation by S-specific peptide pools, were strongly biased toward the expression of Th1 cytokines (tumor necrosis factor α > interleukin 2 > interferon γ) with minimal Th2 cytokine expression (interleukin 4 and interleukin 13). The responses to the 100 µg dose were numerically higher than those for the 25 µg dose across all age groups.

- The CD8 T-cell responses were low to absent across the age stratum in the 25 µg and 100 µg vaccination groups.

Conclusions:

mRNA-1273, administered as 2 doses 28 days apart, was safe and immunogenic in healthy adult participants aged ≥ 18 years. After mRNA-1273 administration, fatigue, headache, myalgia, feverishness, and injection site pain were the most commonly reported solicited systemic and local ARs, with higher incidence noted after the second injection than after the first injection for the solicited systemic ARs. Most of the solicited ARs were mild or moderate; severe solicited ARs predominantly occurred at the highest dose (250 µg). The ARs lasted a median of 2 days or less. In general, ARs were less severe and less commonly reported in older than in younger adults. All unsolicited AEs related to mRNA-1273 were mild or moderate in severity, except for 2 severe AEs reported in 1 participant in the 250 µg vaccination group (18 to 55 years of age group).

mRNA-1273 induced robust binding antibody responses (S-2P and RBD specific) after 2 injections. Notably, 100 µg of mRNA-1273 resulted in numerically higher S-2P specific binding titers than 25 µg and 50 µg of mRNA-1273 in all age groups and higher RBD–specific binding titers in participants aged > 55 years. Two injections of mRNA-1273 induced robust neutralizing antibody responses. The neutralizing antibody response increased marginally after the first injection but increased substantially after the second injection. The neutralizing antibody response (assessed by a pseudovirus neutralization assay) at the 100 µg mRNA-1273 dose level was similar to that at the 250 µg mRNA-1273 dose level in the 18 to 55 years of age group and numerically higher than that observed at the 25 µg and 50 µg mRNA-1273 dose levels in the older age groups. The neutralizing antibody response at the 100 µg dose was similar across all age groups. mRNA-1273 also elicited CD4 T-cell responses that, upon stimulation by S-specific peptide pools, were strongly biased toward the expression of Th1 cytokines.

Based on the results of safety and immunogenicity at data cutoff, the 100 µg dose provides promising immunogenicity results in adults of all ages with an acceptable safety profile and was the dose selected for further evaluation in the Phase 3 clinical study.

Date and Version of This Report: 31 March 2021