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

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 (References):

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.

Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med. 2021;Apr 6. doi: 10.1056/NEJMc2103916.

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 (Years):

Original Report (Day 119): 16 Mar 2020 (first participant first visit) to 07 Oct 2020 (data cutoff date).

Report Addendum 1 (Day 209): 16 Mar 2020 (first participant first visit) to 17 Mar 2021 (data cutoff date).

Drug Development Phase: 1

Objectives:

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
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 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 lipid nanoparticle (LNP)-encapsulated messenger (mRNA)-based vaccine that encodes a full-length, prefusion stabilized spike (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 their last vaccination. The original (Day 119) clinical study report (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 through 12; no participants were enrolled in Cohorts 6, 9, and 13. This Day 209 Immunogenicity and Safety CSR Addendum 1 (CSR Addendum 1) provides safety and immunogenicity data through Day 209 (±7 days) for Cohorts 1 through 5, 7, 8, and 10 through 12.

Number of Participants (Planned and Analyzed):

Planned: up to 155 participants

Analyzed: 120 participants

Diagnosis and Main Criteria for Inclusion and Exclusion: Refer to the Day 119 CSR for the inclusion and exclusion criteria for the study.

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

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

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

Estimands and Intercurrent Events: Not applicable**.**

Statistical Methods: Refer to the Day 119 CSR for the statistical methods for safety and immunogenicity data.

Summary of Results:

The results reported in this CSR Addendum 1 include interim analysis of safety and immunogenicity data through Day 209 (±7 days) for Cohorts 1 through 5, 7, 8, and 10 through 12.

Participant Disposition: Disposition of the participants are provided in the Day 119 CSR. No participant discontinued the study after the data cutoff date of the Day 119 CSR (07 October 2020) up to the data cutoff date of this CSR Addendum 1 (17 March 2021).

Safety Results: No safety concerns were found in the healthy adult participants aged ≥ 18 years 6 months after the second dose of mRNA-1273. A total of 32 new unsolicited AEs in 26 participants were reported in this CSR Addendum 1. This included a severe AE of parotid duct obstruction on Day 185 after the second injection in 1 participant in the 250 µg vaccination group (18 to 55 years of age group) and an SAE of renal mass 170 days after the second injection in 1 participant in the 100 µg vaccination group (≥71 years of age group). Of the 32 new unsolicited AEs, there were a total of 29 MAAEs reported in 25 participants; 5 of these MAAEs were also reported as NOCMCs. One MAAE previously reported as related to mRNA-1273 (abdominal discomfort in the 250 µg vaccination group [age group: 18 to 55 years]) in the Day 119 CSR (data cutoff of 07 October 2020) was updated to the event term of pancreatitis and the relationship was changed to not related to mRNA-1273. In addition, all new unsolicited AEs were not related to mRNA-1273. No notable trends were observed in vital sign results or physical exam findings for any age group or vaccination group, and no trend was observed among dose levels and the severity of events.

Immunogenicity Results

S-2P IgG ELISA Endpoint

- After reaching a peak level between Day 36 and Day 57, the S-2P ELISA GMT values decreased by Day 209; however the values remained numerically higher than on Day 15 (except in the 250 µg vaccination group) Notably, endpoint titers at Day 209 remained at least 4-fold higher than baseline.

- In the 18 to 55 years of age group, the S-2P ELISA GMT values on Day 209 were numerically higher in the 50 µg vaccination group compared with the other vaccination groups and were similar to the median GMT values for the convalescent sera control group. In both the 56 to 70 years and ≥71 years of age groups, the S-2P ELISA GMT values on Day 209 were numerically higher in the 100 µg vaccination groups compared with the other vaccination groups and were similar to the median GMT values for the convalescent sera control group.

S-2P RBD ELISA Endpoint

- After reaching a peak level between Day 36 and Day 43, the RBD ELISA GMT values decreased by Day 209; however, the values generally remained similar to or numerically higher than on Day 29 (except in the 50 µg and 250 µg vaccination groups in the 18 to 55 years of age group). Notably, endpoint titers at Day 209 remained at least 4-fold higher than baseline.

- In the 18 to 55 years of age group, the RBD ELISA GMT values on Day 209 were higher in the 100 µg vaccination group compared with the other vaccination groups. In both the 56 to 70 years and ≥71 years of age groups, the RBD ELISA GMT values on Day 209 were higher in the 50 µg vaccination group compared with the other vaccination groups. Compared to the convalescent sera, the RBD ELISA GMT values on Day 209 were numerically higher in all participants except in the 25 µg (all age groups) and 50 µg (18 to 55 years of age group) vaccination groups.

Pseudovirus Neutralization ID_{50} and ID_{80}

- After reaching a peak level between Day 36 and Day 57, the PsVNA GM neutralizing ID_{50} and ID_{80} values decreased by Day 209; however, in general the values remained similar to or numerically higher than on Day 29. The values were lower than the median GM values for the convalescent sera control group.

- Across all age groups, the PsVNA GM neutralizing ID_{50} and ID_{80} values on Day 209 were higher in the 100 µg vaccination group compared with the 25 µg and 50 µg vaccination groups.

FRNT-mNG

- After reaching a peak level on Day 43, the FRNT-mNG GM neutralizing ID_{50} and ID_{80} values decreased by Day 209; however, the values remained similar to or numerically higher than on Day 29 (prior to the second injection) across all age groups and dose levels.

- Across all age groups, the FRNT-mNG GM neutralizing ID_{50} and ID_{80} values on Day 209 were higher in the 100 µg vaccination group compared with the 25 µg and 50 µg vaccination groups, and were similar to or numerically higher than values for convalescent sera controls.

Conclusions: Overall, mRNA-1273, administered as 2 doses 28 days apart, was safe 6 months after the second dose in healthy adult participants aged ≥ 18 years. The immune response elicited by mRNA-1273 persisted through 6 months after the second dose with the 100 µg dose regimen eliciting higher neutralizing antibody responses compared with the 25 or 50 µg dose across all age groups and higher binding antibody responses in the 56 to 70 years and ≥71 years of age groups.

Original Report Date: 31 Mar 2021

Report Addendum Date: 14 Jul 2021