

**Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV  
Vaccine (mRNA-1273) in Healthy Adults**

**DMID Protocol Number: 20-0003**

**IND Sponsor: Division of Microbiology and Infectious Diseases (DMID)**

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## STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federal wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and Division of Microbiology and Infectious Diseases (DMID)
- The National Institute of Allergy and Infectious Diseases (NIAID) Terms of Award
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed: \_\_\_\_\_ Date: \_\_\_\_\_  
Name, Credentials  
Title

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# 1. PROTOCOL SUMMARY

## 1.1 Synopsis

### Rationale for Proposed Clinical Study

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. On January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, rising to more than 110,000 confirmed cases and 3996 deaths as of March 9, 2020. On March 11, 2020 the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) a pandemic. SARS-CoV-2 has continued to spread globally with cases being reported in at least 216 countries, and as of May 14, 2020, 4,307,287 confirmed cases and 295,101 deaths had been reported to the WHO. There is currently no vaccine against the 2019-novel Coronavirus (2019-nCoV; SARS-CoV-2). Therefore, there is an urgent public health need for rapid development of novel interventions.

ModernaTX, Inc. has developed a rapid response, proprietary messenger RNA (mRNA)-based vaccine platform. This is based on the principle and observations that antigens can be produced in vivo by delivery and uptake of the corresponding mRNA by cells. ModernaTX, Inc. is using its mRNA-based technology to develop a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against SARS-CoV-2 (mRNA-1273). Prior preclinical studies have demonstrated that coronavirus spike (S) proteins are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

Based on currently available information and clinical experience suggesting that older adults may be 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. Thus, this phase I clinical trial proposes to evaluate the safety and immunogenicity of different dosages of Moderna's mRNA-1273 in healthy adults across the age spectrum ( $\geq 18$  years of age).

### Study Design

This is a phase I, open-label, dose-ranging clinical trial in males and non-pregnant females,  $\geq 18$  years of age, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of mRNA-1273 manufactured by ModernaTX, Inc. mRNA-1273 is a novel LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2. Enrollment will occur at up to three domestic clinical research sites.

**Table 1: Treatment Arms**

Cohort	Sample Size	Stratum (Years of Age)	First and Second Dose
1	15	18-55	25 mcg mRNA-1273



<b>Cohort</b>	<b>Sample Size</b>	<b>Stratum (Years of Age)</b>	<b>First and Second Dose</b>
2	15	18-55	100 mcg mRNA-1273
3	15	18-55	250 mcg mRNA-1273
4	10	56-70	25 mcg mRNA-1273
5	10	56-70	100 mcg mRNA-1273
6*	10	56-70	250 mcg mRNA-1273
7	10	≥71	25 mcg mRNA-1273
8	10	≥71	100 mcg mRNA-1273
9*	10	≥71	250 mcg mRNA-1273
10	15	18-55	50 mcg mRNA-1273
11	10	56-70	50 mcg mRNA-1273
12	10	≥71	50 mcg mRNA-1273
13*	15	18-55	10 mcg mRNA-1273

\*Cohorts 6, 9 and 13 were not enrolled.

Up to one hundred and fifty-five (155) subjects will be enrolled into one of thirteen cohorts (10 micrograms [mcg], 25 mcg, 50 mcg, 100 mcg, or 250 mcg). Subjects will receive an intramuscular (IM) injection (0.5 milliliters [mL]) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394). The second dose of vaccine (0.5 mL) will be administered preferably in the same arm used for the first dose.

Follow-up visits will occur 1, 2 and 4 weeks post each vaccination (Days 8, 15, 29, 36, 43, and 57), as well as 3, 6 and 12 months post second vaccination (Days 119, 209 and 394).

Reactogenicity will be assessed at these visits, as well as blood will be drawn for immunogenicity assays. Additional safety and reactogenicity data will be solicited via telephone calls to subjects 1 and 2 days post each vaccination (Days 2, 3, 30, and 31).

To determine early safety signals for this phase I clinical trial, vaccination will proceed in a staged fashion. Sentinel subject dosing will begin with 4 subjects in cohort 1 (25 mcg). The 4 sentinel subjects for cohort 2 (100 mcg) will be enrolled no earlier than one day after enrollment of the last of the 4 sentinel subjects in cohort 1. If no halting rules have been met after the 8 sentinel subjects have completed Day 5, then full enrollment will proceed first with the remaining subjects in cohort 1, followed by the remaining subjects in cohort 2 without

interruption. If no halting rules have been met after all subjects in cohort 2 have completed Day 8, then dosing of 4 sentinel subjects will begin in cohort 3. If no halting rules have been met after the 4 sentinel subjects in cohort 3 have completed Day 5, then full enrollment of cohort 3 will proceed.

If no halting rules have been met after all subjects in cohorts 1 and 2 have completed Day 8, dosing will begin for cohorts 4 (25 mcg; 56-70 years of age) and 5 (100 mcg; 56-70 years of age). If no halting rules have been met after all subjects in cohorts 4 and 5 have completed Day 8, dosing will begin for cohorts 7 (25 mcg;  $\geq 71$  years of age) and 8 (100 mcg;  $\geq 71$  years of age).

Based on the interim immunogenicity data available as of May 15, 2020, enrollment into cohorts 6 and 9 (250 mcg; 56-70 years of age and  $\geq 71$  years of age) will be deferred in order to explore lower dosages. Therefore, enrollment of cohorts 10-12 (50 mcg; 18-55 years of age, 56-70 years of age and  $\geq 71$  years of age) will be prioritized. Subjects will be enrolled simultaneously in cohorts 10-12; there will be no staging. To further explore dosage sparing, cohort 13 (10 mcg dose; 18-55 years of age) may be enrolled. A decision regarding the enrollment of cohorts 6, 9 and 13 will be made after review of interim immunogenicity data from cohorts 1-5, 7, 8, and 10-12.

If no halting rules have been met after all subjects in cohorts 5 and 8 have completed Day 8, dosing will begin concurrently for cohorts 10-12. If no halting rules have been met after all subjects in cohorts 3, 7 and 8 have completed Day 8, dosing may begin for cohort 6, if enrolled. If no halting rules have been met after all subjects in cohort 6 have completed Day 8, dosing may begin for cohort 9, if enrolled.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each vaccination through 7 days post each vaccination. Unsolicited non-serious adverse events (AEs) will be collected from the time of each vaccination through 28 days post each vaccination. Serious adverse events (SAEs), protocol specified adverse events of special interest (AESIs), new-onset chronic medical conditions (NOCMCs), and medically-attended adverse events (MAAEs) will be collected through 12 months after the second vaccination (Day 394).

Clinical safety laboratory evaluations will be performed at screening, as well as immediately prior to and 7 days post each vaccination (Days 1, 8, 29, and 36).

To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled in cohorts 2, 3, 5, 10, and 11 may undergo leukapheresis to collect additional samples for secondary research. If enrollment in cohort 6 proceeds, a subset of subjects in this cohort may also undergo leukapheresis.

Based on interim immunogenicity and reactogenicity data, Cohorts 6, 9 and 13 were not enrolled.

During the course of this clinical trial, interim efficacy data from a Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE), administered as 2 doses of 100 mcg given 28 days apart, demonstrated vaccine efficacy of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic, confirmed COVID-19. After review of the interim safety and efficacy data from that clinical trial, the FDA granted on December 18, 2020 an Emergency Use Authorization (EUA) for the mRNA-1273 vaccine in adults 18 years of age and older.

To potentially enhance and extend the duration of protection provided by the 2-dose vaccination schedule of mRNA-1273 administered in the main study, and to gain an understanding of the immune responses to a third dose of mRNA-1273, subjects in the main study may participate in an optional third mRNA-1273 vaccination substudy, detailed in [Section 12, Appendix A](#). Substudy subjects will receive a third mRNA-1273 vaccination, administered via an IM injection at a dosage of 100 mcg/0.5 mL, given six to twelve months after receipt of their second vaccination in the main study. Substudy subjects will be followed for safety, reactogenicity, and immunogenicity endpoints through 12 months post third vaccination (Substudy Day 366).

To be eligible to participate in the substudy, subjects must have received both the first and second mRNA-1273 vaccinations in the main study. Other eligibility criteria are specified in [Appendix A](#). Subjects who received only one mRNA-1273 vaccination in the main study will be advised to receive an FDA authorized or approved COVID-19 vaccine, according to the recommended schedule, when available to them outside of this trial, unless they have a contraindication to COVID-19 vaccines that are available.

Subjects who elect not to participate in the optional third mRNA-1273 vaccination substudy or are not eligible for the substudy will continue to be followed according to the Schedule of Activities for the main study (see [Table 4](#)) with the Final Study Visit 14 occurring at Day 394 ( $\pm 14$  days).

### **Objectives and Endpoints**

**Table 2: Objectives and Endpoints (Outcome Measures)**

<b>OBJECTIVES</b>	<b>ENDPOINTS (OUTCOME MEASURES)</b>
<b>Primary</b>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination.</li> <li>Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination.</li> <li>Frequency of any SAEs, Protocol Specified AESIs, NOCMCs, and MAAEs from Day 1 to Day 394.</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by Immunoglobulin G (IgG) enzyme-linked immunosorbent assay ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.</li> </ul>	<ul style="list-style-type: none"> <li>Geometric mean titer (GMT) of antibody at Day 57.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline.</li> </ul>

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	<ul style="list-style-type: none"> <li>The geometric mean fold rise (GMFR) in IgG titer from baseline.</li> </ul>
Exploratory	
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted at each timepoint.</li> <li>The GMFR in IgG titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by Immunoglobulin M (IgM) and Immunoglobulin A (IgA) ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.</li> </ul>	<ul style="list-style-type: none"> <li>GMT at each timepoint.</li> <li>Percentage of subjects who seroconverted at each timepoint.</li> <li>The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of neutralizing (Neut) antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.</li> <li>The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of Neut antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.</li> <li>The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.</li> </ul>

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<ul style="list-style-type: none"> <li>To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.</li> </ul>	<ul style="list-style-type: none"> <li>Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.</li> </ul>

**Inclusion Criteria (abbreviated)**

See full inclusion criteria in [Section 5.1](#).

A subject must meet all the following criteria to be eligible to participate in this study:

1. Provides written informed consent prior to initiation of any study procedures.
2. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
3. Agrees to the collection of venous blood per protocol.
4. Male or non-pregnant female,  $\geq 18$  years of age at time of enrollment.
5. Body mass index (BMI) 18.0-35.0 kg/m<sup>2</sup>, inclusive (<56 years of age), at screening; BMI 18.0-30.0 kg/m<sup>2</sup>, inclusive ( $\geq 56$  years of age), at screening.
6. Women of childbearing potential must agree to use or have practiced true abstinence or use at least one acceptable primary form of contraception.
7. In good health.
8. Oral temperature is less than 100.0°F (37.8°C).
9. Pulse no greater than 100 beats per minute.
10. Systolic blood pressure (BP) is 85 to 150 mm Hg, inclusive.
11. Clinical screening laboratory evaluations (White Blood Cells [WBCs], hemoglobin [Hgb], platelets [PLTs], Alanine Transaminase [ALT], Aspartate Transaminase [AST], Creatinine [Cr], Alkaline Phosphatase [ALP], Total Bilirubin [T. Bili], Lipase, Prothrombin Time [PT], Partial Thromboplastin Time [PTT]) are within acceptable normal reference ranges at the clinical laboratory being used.
12. Must agree to have samples stored for secondary research.

**Exclusion Criteria (abbreviated)**

See full exclusion criteria in [Section 5.2](#).

A subject who meets any of the following criteria will be excluded from participation in this study:

1. Positive pregnancy test either at screening or just prior to each vaccine administration.
2. Female subject who is breastfeeding or plans to breastfeed from the time of the first vaccination through 60 days after the last vaccination.

3. Has any medical disease or condition that, in the opinion of the participating site Principal Investigator (PI) or appropriate sub-investigator, precludes study participation.
4. Presence of self-reported or medically documented significant medical or psychiatric condition(s).
5. Has an acute illness, as determined by the participating site PI or appropriate sub-investigator, with or without fever [oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ )] within 72 hours prior to each vaccination.
6. Has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) types 1 or 2 antibodies at screening.
7. Has participated in another investigational study involving any investigational product within 60 days, or 5 half-lives, whichever is longer, before the first vaccine administration.
8. Has previously participated in an investigational study involving LNPs (a component of the investigational vaccine assessed in this trial).
9. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to any previous licensed or unlicensed vaccines.
10. History of COVID-19 diagnosis.
11. Reside in a nursing home or other skilled nursing facility or have a requirement for skilled nursing care.

### **Study Phase**

- 1

### **Study Population**

Up to one hundred and fifty-five (155) males and non-pregnant females,  $\geq 18$  years of age, who are in good health and meet all eligibility criteria will be enrolled.

### **Sites**

Up to three domestic clinical research sites

### **Study Intervention:**

- mRNA-1273 is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized spike protein SARS-CoV-2. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.
- mRNA-1273 (0.5 milligrams [mg]/mL) will be diluted in 0.9% Sodium Chloride (NaCl) for injection, United States Pharmacopeia (USP) to obtain 10, 25, 50, 100, and 250 mcg in 0.5 mL dosages. Each dose will be administered via IM injection (0.5 mL) into the deltoid muscle on Days 1 and 29. The second dose of vaccine (0.5 mL) will be administered preferably in the same arm used for the first dose. The pharmacist will prepare a single dose (0.5 mL) for each subject based on cohort assignment.

**Table 3: Dosing and Administration**

Cohort	Product Name	Dose	Route	Frequency of Administration
1	mRNA-1273	25 mcg	IM	D1, D29
2	mRNA-1273	100 mcg	IM	D1, D29
3	mRNA-1273	250 mcg	IM	D1, D29
4	mRNA-1273	25 mcg	IM	D1, D29
5	mRNA-1273	100 mcg	IM	D1, D29
6*	mRNA-1273	250 mcg	IM	D1, D29
7	mRNA-1273	25 mcg	IM	D1, D29
8	mRNA-1273	100 mcg	IM	D1, D29
9*	mRNA-1273	250 mcg	IM	D1, D29
10	mRNA-1273	50 mcg	IM	D1, D29
11	mRNA-1273	50 mcg	IM	D1, D29
12	mRNA-1273	50 mcg	IM	D1, D29
13*	mRNA-1273	10 mcg	IM	D1, D29

\*Cohorts 6, 9 and 13 were not enrolled.

### **Study Duration**

- The duration of the main study is anticipated to be 20 months (from start of screening to last subject last visit in the main study).
- The duration of the optional third mRNA-1273 vaccination substudy is anticipated to be 12 months from the last subject vaccinated with the third mRNA-1273 vaccination.

### **Subject Duration**

- The duration for each individual subject in the main study is approximately 14 months (from first contact to last visit in the main study).
- The duration for each individual subject in the optional third mRNA-1273 vaccination substudy is approximately 26 months (from first contact to last visit).

### **Safety**

- The study will use a series of halting rules – for sentinel subjects, for the halting of each cohort, and for not vaccinating individual subjects. See [Section 7.1](#) for details.
- This study will use a Safety Monitoring Committee (SMC) for objective oversight of the study. SMC reviews are required for study halting. The SMC does not need to meet for dose escalation or for initiation of the optional third mRNA-1273 vaccination substudy.

## 1.2 Schedule of Activities (SOA)

**Table 4: Schedule of Activities for the Main Study**

	Screening Visit 00, Day -42 to -1	Enrollment/Baseline Visit 01, Day 1	Visit 02, Day 2 1 day post Dose 1	Visit 03, Day 3 2 days post Dose 1	Visit 04 Day 8 +/- 1 day	Visit 05 Day 15 +/- 2 days	Visit 06 Day 29 +/- 2 days	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09 <sup>f</sup> Day 36 +/- 1 day	Visit 10 <sup>f</sup> Day 43 +/- 2 days	Visit 11 <sup>f</sup> Day 57 +/- 2 days	Visit 11A <sup>f</sup> Day 71 -7/+ 21 days	Visit 12 <sup>f</sup> Day 119 +/- 7 days	Visit 13 <sup>f</sup> Day 209 +/- 7 days	Final Study Visit 14 <sup>fg</sup> Day 394 +/- 14 days	Unscheduled Visit	Early Termination Visit
<b>Procedures</b>																		
Informed Consent	X																	
Review Eligibility Criteria	X	X					X											
Medical History	X																	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Vaccination		X					X											
Telephone Contact			X	X				X	X									
Interim History		X			X	X	X			X	X	X		X	X	X	X	X
Physical Examination <sup>a</sup>	X	X			X	X	X			X	X	X		X	X	X	X	X
Vital Signs	X	X			X	X	X			X	X	X		X	X	X	X	X
Height and Weight (for BMI)	X																	
Hematology <sup>b</sup>	X	X			X		X			X								
Chemistry <sup>b</sup>	X	X			X		X			X								
Serology <sup>b</sup>	X																	
Pregnancy Test <sup>c</sup>	X	X					X											
Urine Drug Screen	X																	
Memory Aid: Solicited AEs			Days 1-8					Days 29-36										
Unsolicited AEs			Days 1-57															
SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs			Days 1-394															
Serum for Serological Immunogenicity Assays		X				X	X			X	X	X		X	X	X		X
Peripheral Blood Mononuclear Cells (PBMCs) for Cellular Immunology Assays		X				X	X			X	X	X		X	X			X
Serum for Secondary Research <sup>d</sup>		X				X	X			X	X	X		X	X	X		X
Serum for Product Assay Development		X				X	X			X	X	X		X	X	X		X
Leukocytes for Secondary Research (subset of subjects)													X <sup>e</sup>					



- a) Full physical examination will be performed at screening and symptom-directed (targeted) physical examination at all other timepoints if indicated.
- b) Clinical screening laboratory evaluations will include WBCs, Hgb, PLTs, Cr, ALT, AST, ALP, T. Bili, Lipase, PT, PTT, hepatitis B surface antigen, hepatitis C virus antibody, and HIV types 1 and 2 antigen/antibody. Clinical safety laboratory evaluations obtained on Days 1, 8, 29, and 36 will include WBCs, Hgb, PLTs, Cr, ALT, AST, ALP, T. Bili, and Lipase.
- c) For women of childbearing potential serum pregnancy test at screening, and urine or serum pregnancy test on Days 1 and 29 with results confirmed as negative prior to enrollment on Day 1 and administration of each vaccination.
- d) Depending on the timepoint approximately 8 or 16 mL of each venous blood sample is designated for secondary research.
- e) For those subjects consented for leukapheresis, screening procedures, including screening laboratory evaluations, will be performed locally prior to the leukapheresis procedure. Refer to the protocol-specific MOP for details on the leukapheresis procedure.
- f) Visits 09-14 windows should be based off the actual Visit 06 date.
- g) Subjects who participate in the optional third mRNA-1273 vaccination substudy will exit the Schedule of Activities for the main study between Visit 13 and the close of the window for Visit 14 and will not have Visit 14, instead will have Visit 14A and subsequent substudy visits. See [Section 12](#), Appendix A for the Schedule of Activities for the optional third mRNA-1273 vaccination substudy.

## **2. INTRODUCTION**

### **2.1 Background and Study Rationale**

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel Coronavirus (nCoV) was originally referred to as 2019-nCoV but has now been named SARS-CoV-2 (due to its similarity to the Severe Acute Respiratory Syndrome [SARS] Coronavirus [CoV; SARS-CoV]). It has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (Chan JF et al., 2020). The disease caused by SARS-CoV-2 is called Coronavirus disease 2019 (COVID-19). On January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, rising to more than 110,000 confirmed cases and 3996 deaths as of March 9, 2020 according to various international health reporting agencies. Outbreak forecasting and modeling suggest that these numbers will continue to rise (Wu et al., Lancet, Jan. 31, 2020). On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. On March 11, 2020 the WHO declared COVID-19 a pandemic. SARS-CoV-2 has continued to spread globally with cases being reported in at least 216 countries, and as of May 14, 2020, 4,307,287 confirmed cases and 295,101 deaths had been reported to the WHO [WHO, 2020].

Global efforts to evaluate novel antivirals and therapeutic strategies to treat SARS-CoV-2 severe infections have intensified, but no proven therapeutic currently exists. There is currently no vaccine against the SARS-CoV-2 virus. Therefore, there is an urgent public health need for rapid development of novel interventions. Based on currently available information and clinical experience suggesting that older adults may be 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. This phase I clinical trial proposes to evaluate safety and immunogenicity of Moderna's mRNA-1273 in healthy adults across the age spectrum ( $\geq 18$  years of age). To further explore dose-ranging, additional cohorts will be enrolled.

ModernaTX, Inc. has developed a rapid response, proprietary messenger RNA (mRNA)-based vaccine platform. This is based on the principle and observations that antigens can be produced *in vivo* by delivery and uptake of the corresponding mRNA by cells. The mRNA then undergoes intracellular ribosomal translation to endogenously express the protein antigen(s) encoded by the vaccine mRNA. This mRNA-based vaccine does not enter the cellular nucleus or interact with the genome, is nonreplicating, and expression is transient. mRNA vaccines thereby offer a mechanism to stimulate endogenous production of structurally intact protein antigens in a way that mimics wild-type viral infection and are able to induce good immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043). ModernaTX, Inc. is using its mRNA-based technology to develop a novel LNP-encapsulated messenger RNA (mRNA)-based vaccine against SARS-CoV-2. mRNA-1273 is a novel LNP mRNA-based vaccine that encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce two proline residues to stabilize the S protein into a pre-fusogenic form.

The coronavirus spike (S) protein mediates attachment and entry of the virus into host cells, making it a primary target for neutralizing antibodies that prevent infection (Johnson et al. 2016; Wang et al. 2016; Wang et al. 2015; Wang et al. 2018; Chen et al. 2017; Corti et al. 2015; Yu et al. 2015; Kim et al. 2019; Widjaja et al. 2019). The Vaccine Research Center (VRC) and collaborators have identified 2 proline mutations at the apex of the S2 central helix that stabilize the S protein in its prefusion conformation (S-2P) (Pallesen et al. 2017). These mutations have been applied to 9 diverse coronaviruses from three coronavirus genera and found to stabilize the prefusion conformation and improve protein expression. Since this mutation has consistently stabilized other beta-CoV S proteins, this mutation was applied to the SARS-CoV-2 S protein. The VRC and collaborators found that the stabilized SARS-CoV-2 S-2P expressed well and is in the prefusion conformation based on negative-stain electron microscopy.

The S proteins of closely related beta-CoVs stabilized by the 2P mutation, including HKU1, Middle East Respiratory Syndrome (MERS), SARS, and WIV1, are potent immunogens in mice. In collaboration with ModernaTX, Inc, mRNA expressing the MERS S-2P protein sequence was produced and compared to mRNA expressing wild-type S protein. mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 mcg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in dipeptidyl peptidase 4 (hDPP4) mice and protected mice from MERS challenge. Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and ModernaTX, Inc. designed mRNA expressing a membrane-anchored

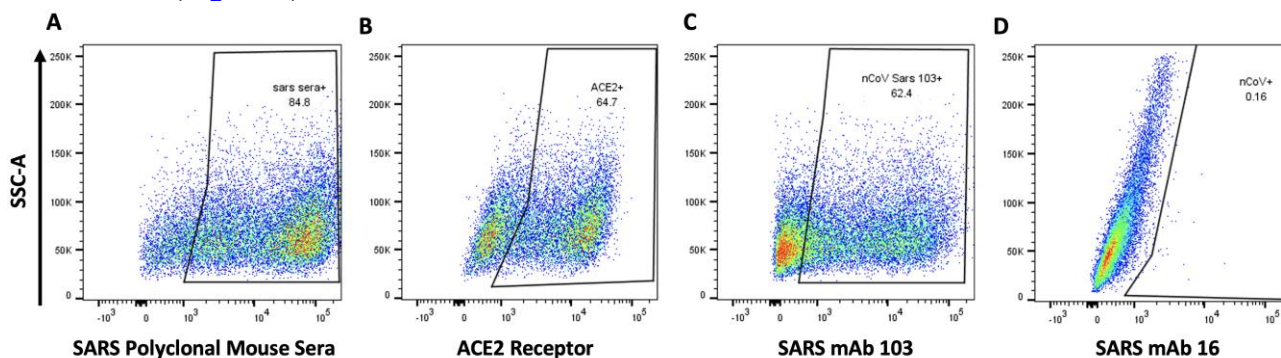
SARS-CoV-2 S protein stabilized with the 2P mutation. HEK293 cells transfected with mRNA expressing the SARS-CoV-2 S-2P protein successfully expressed the protein.

mRNA-1273 is immunogenic in BALB/c mice, demonstrating a dose-dependent antibody response as measured in both SARS-CoV-2 S protein binding and virus neutralizing antibody assays. A strong correlation was measured between S protein binding antibody and virus neutralization. In addition, a single dose of mRNA-1273 elicited robust S protein binding antibody titers, but with no virus neutralization titers observed. Mice from this study were challenged with mouse-adapted SARS-CoV-2 virus, and preliminary results indicate that mRNA-1273-induced immunity is protective after challenge. Mice immunized with a single dose of 10 or 1 mcg of mRNA-1273 were protected from viral replication in the lung following challenge 7 weeks after vaccination, despite the absence of measurable neutralization titers. Mice immunized with 2 doses of either 1 or 0.1 mcg of mRNA-1273 were also protected, dependent upon the dosing schedule.

There is some clinical experience with vaccines targeting coronavirus S proteins. The first candidate DNA vaccine expressing SARS S protein was evaluated in 10 healthy adults age 21 to 49 years in 2004 and 2005 following a rapid vaccine development response to the SARS outbreak (Martin et al. 2008). DNA vaccine at a dosage of 4 mg was administered IM by a Biojector needle free device at baseline, week 4 and week 8. The vaccine was safe and well tolerated. Local and systemic reactogenicity events were mild and transient. There were no SAEs and no grade 3 or 4 AEs. The SARS candidate vaccine was immunogenic as assessed by ELISA and pseudotyped lentiviral vector reporter neutralization assay following the first injection in most subjects with peak response after the 3rd vaccination. Vaccine induced T cell responses as assessed by ICS and ELISPOT were detected in all subjects (Martin et al. 2008).

Additionally, a candidate DNA vaccine expressing MERS S was evaluated in 75 healthy subjects ages 19 to 50 years in 2016 (Modjarrad et al. 2019). In a dose escalation trial, DNA vaccine at a dosage of 0.67 mg, 2 mg or 6 mg was administered IM followed by electroporation at baseline, week 4 and week 12. Overall, the vaccine was safe and well tolerated. Local and systemic reactogenicity events were generally mild and transient. There were no SAEs or grade 3 or 4 laboratory abnormalities attributed to vaccination. The MERS candidate vaccine was immunogenic as assessed by seroconversion and vaccine induced T cell responses in most vaccine recipients. (Modjarrad et al. 2019).

The expression of functional prefusion stabilized S-protein delivered by mRNA was evaluated in HEK293 cells (Figure 1).



**Figure 1.** The SARS-CoV-2 full-length stabilized spike protein (S-2P) delivered by mRNA is expressed on the cell surface. HEK293T cells were transfected with mRNA encoding for the SARS-CoV-2 S-2P protein. After 24hrs, cell flow cytometry was used to measure surface expression by staining with (A) mouse polyclonal antibody raised against SARS S-2P protein; (B) a flag-tagged ace2 receptor and anti-flag antibody; (C) a SARS S-protein monoclonal antibody (mAb-103) that cross-reacts with SARS-CoV-2 S-2P; (D) a SARS S protein-specific monoclonal antibody (mAb 16) that does not bind SARS-CoV-2 was used as a negative control.

The expressed prefusion, stabilized S protein binds to its proposed receptor, human ACE-2, and is recognized by cross-reactive antibodies to SARS S protein. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

### 2.1.1 Public Readiness and Emergency Preparedness Act

The study vaccine, mRNA-1273, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributors, program planners, and other qualified persons who prescribe, administer or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273. The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 10, 2020 and is retroactively effective from February 4, 2020.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) Countermeasures Injury Compensation Program (<http://www.hrsa.gov/cicp/>) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at <http://www.hrsa.gov/cicp/>. Compensation may then be available for reasonable and necessary

medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

## **2.2 Risk/Benefit Assessment**

### **2.2.1 Known Potential Risks**

The potential risks of participating in this trial are those associated with having blood drawn, IM injection, leukapheresis (only for those subjects consented for leukapheresis), possible reactions to mRNA-1273, and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IM injection may also cause transient discomfort and fainting. Drawing blood and IM injection may cause infection. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or where the vaccination will be given extremely unlikely.

#### **Risks of Leukapheresis (only for those subjects consented for leukapheresis)**

Leukapheresis may be associated with pain, bruising, and discomfort in the arms at the site of needle placement. Vasovagal episodes, characterized by transient hypotension, dizziness, nausea, and rarely syncope, are seen in less than 5% of procedures. Additional risks include increased pulse, seizures, and blood loss. Anticoagulants added to prevent the blood from clotting may lead to a sour taste in the mouth, mild muscle cramps and/or tingling sensation around the mouth, feet or hands. These reactions may be seen to a mild degree in 30-50% of leukapheresis procedures and can usually be relieved by slowing or temporarily interrupting the procedure or administering calcium carbonate tablets.

A temporary decrease (1-2 days) in red blood cell count is common. Rarely, machine malfunction or if the procedure needs to be stopped before completion may result in the loss of a half pint to a pint of blood. Leukapheresis does not affect the blood's ability to form clots in the event of subsequent cuts or injuries.

There may be additional risks that are unknown at this time.

Preclinical evaluations will occur in parallel with this phase I clinical trial. However, in support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, a Good Laboratory Practice (GLP)-compliant, repeat dose toxicology study, as well as biodistribution and genotoxicity studies have been completed with similar mRNA-based vaccines formulated in SM-102-containing LNPs.

### **Risks of mRNA-1273**

In preclinical models, the aggregate toxicity profile observed across multiple repeat-dose toxicology studies at IM doses ranging from 9 to 150 mcg/dose administered once every 2 weeks for up to 6 weeks is generally consistent and considered as being representative of mRNA vaccines formulated in the same SM-102 LNP formulation, differing only by the encapsulated mRNA sequence(s). All doses administered were tolerated and the lowest no-observed-adverse-effect-level (NOAEL) determined across the aggregate of the completed studies was 89 mcg/dose.

In a non-GLP biodistribution study with mRNA-1647, a similar mRNA-based vaccine formulated in SM-102-containing LNPs, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen in male Sprague Dawley rats.

In GLP-compliant studies, SM-102, the novel lipid component of the LNP formulation, was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in SM-102-containing LNPs (mRNA-1706, which encodes the ZIKV pre-membrane and envelope polypeptide [different from the sequence encoded in mRNA-1893]), induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

In a non-GLP study in Sprague Dawley rats to characterize the potential toxicity of mRNA-1273 at clinically relevant doses, mRNA-1273 exhibited clinical signs consisting of transient dose-dependent injection site edema with or without hindlimb impairment at approximately 24 hours post-dose that generally resolved within 7 days after dose administration. mRNA-1273-related clinical pathology changes associated with inflammation, including increased neutrophils, eosinophils, and/or globulin, were observed as well as other mild mRNA-1273-related changes including decreased red cell mass, reticulocytes, and lymphocytes and increased creatinine, triglyceride, cholesterol, and/or glucose. There were no mRNA-1273-related effects on body weight. In general, these changes are consistent with the results from previous GLP rat toxicity studies conducted with other mRNAs formulated in SM-102 LNP.

Information on possible risks and adverse reactions associated with IM administration of mRNA-1273 is derived from animal studies with mRNA-1273, interim safety information from this ongoing phase I clinical trial of mRNA-1273 (NCT04283461), interim findings from the Phase 3 placebo-controlled clinical trial of mRNA-1273 (NCT04470427, the COVE study), and the LNP components or animal and human studies of similar mRNA-based vaccines (mRNA-1647 and mRNA-1653).

As of March 2020, there had been 8 non-SARS-CoV-2 clinical studies initiated across Moderna's infectious disease vaccine platform with over 1,000 subjects receiving at least one dose of an mRNA vaccine. mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against human CMV (NCT03382405), hMPV/PIV3 (NCT03392389), and Zika virus (NCT04064905). In three Phase 1 studies as of January 6, 2020, approximately 365 subjects were dosed with either an SM-102-containing lipid vaccine or placebo (doses ranging from 10 mcg to 300 mcg). Of the 365 subjects dosed 264 subjects experienced at least 1 solicited AE. The most common solicited events were pain 28% of total events reported, headache 15%, fatigue 15%, myalgia 13%, arthralgia 9%, nausea 7%, chills 6%, fever, 4%, erythema, 2%, and swelling 2%. The majority of the events were grade 1-2 with approximately 9% being reported as grade 3; the most common grade 3 events were pain, myalgia, fatigue, headache, and chills. Grade 3 events were typically recorded on Day 1 or Day 2 following injection with most occurring on Day 2 and resolving by Day 6.

In an hMPV/PIV3 Phase 1 study, which is unblinded, unsolicited related AEs included mild to moderate chills, hot flushes, diarrhea, pyrexia, temperature intolerance, elevated WBC count, headache and erythematous rash, as well as severe injection site pain, prolonged PT and myalgia. All of the severe events occurred at the 300 mcg x 2 dose level. In the blinded Phase 1 CMV study, unsolicited related AEs in more than 2 subjects included chills (19 subjects, or 10.5%); fatigue (10 subjects, 5.5%); lymphadenopathy, injection site pain, and pyrexia, (9 subjects each, 5.0%); arthralgia (8 subjects, 4.4%); myalgia (7 subjects, 3.9%); headache (5 subjects, 2.8%); diarrhea (4 subjects, 2.2%); and injection site bruising (3 subjects, 1.7%). Of these AEs, severe events were reported in 3 of 19 subjects with chills, 5 of 10 subjects with fatigue, 4 of 9 subjects with pyrexia, 4 of 8 subjects with arthralgia, and 4 of 7 subjects with myalgia. There were no related SAEs reported in the Phase 1 CMV, hMPV/PIV3 or Zika virus vaccine studies.

In addition, other AEs that have been generally associated with approved IM administered vaccines have included mild hematological and clinical chemistry abnormalities, which are usually reversible.

To date, interim safety data from this phase I clinical trial of mRNA-1273 indicate that solicited adverse reactions within 7 days after the first or second vaccination were reported by over 90% of the 120 subjects (Jackson, LA, et al. 2020; Anderson, EJ, et al, 2020). Most were mild or moderate in severity. Moderate or severe solicited adverse reactions were reported more commonly after the second vaccination compared with the first and with higher dosages. Severe solicited systemic adverse reactions were reported in 6 (5%) of subjects. Evaluation of safety clinical laboratory values of grade 2 or higher and unsolicited adverse events revealed no patterns of concern. No deaths or SAEs related to mRNA-1273 have been reported in this trial and no prespecified halting rules for vaccination were met. Three study subjects discontinued due to an AE. One subject in the 25 mcg vaccination group (age stratum: 18 to 55 years) reported mild urticaria (hives on lower extremities) on Day 5 after Dose 1. The event was deemed related

to mRNA-1273 by the investigator. One subject in the 250 mcg vaccination group (age stratum: 18 to 55 years) reported mild oropharyngeal pain (sore throat) on Day 24 after Dose 1 and one subject in the 100 mcg vaccination group (age stratum: 56 to 70 years) reported moderate maculopapular rash on Day 9 after Dose 1. These two events were deemed not related to mRNA-1273 by the investigator.

Participants 18 years of age and older received a 2-dose regimen (0, 28 days) of mRNA-1273 in the Phase 3 placebo-controlled clinical trial (COVE) conducted in the United States, and were followed for the development of COVID-19 disease. Interim findings indicated that vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headache, fatigue, myalgia) than placebo recipients and that most reactions were mild to moderate and resolved over 1-3 days (Baden LR, et al. 2020). The severity of the solicited systemic events increased after the second dose of mRNA-1273, with an increase in events of moderate severity of from 16.5% after the first dose to 38.1% after the second dose, and with an increase in events graded as severe of from 2.9% after the first dose to 15.8% after the second dose. Both solicited injection-site and systemic adverse events were more common among younger subjects (18 to <65 years of age) than among older subjects ( $\geq 65$  years of age). The frequency of severe unsolicited events was similar in the placebo (1.3%) and vaccine (1.5%) groups, as were the frequencies of medically attended adverse events (9.7% vs. 9.0%) and serious adverse events (0.6% in both groups). Three deaths occurred in the placebo group (one from intraabdominal perforation, one from cardiopulmonary arrest, and 1 from severe systemic inflammatory syndrome in a subject with chronic lymphocytic leukemia and diffuse bullous rash) and 2 in the vaccine group (one from cardiopulmonary arrest and one by suicide). Bell's palsy occurred in the vaccine group (3 subjects [ $<0.1\%$ ]) and the placebo group (1 subject [ $<0.1\%$ ]) during the observation period of the trial (more than 28 days after injection). Hypersensitivity reactions occurred in 1.5% and 1.1% of subjects in the vaccine and placebo groups, respectively.

Following the issuance of the Emergency Use Authorization (EUA), rare anaphylactic-like reactions have occurred among recipients of both mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna). As of January 22, 2021, 10 cases of anaphylaxis, with no associated deaths, have been reported in patients who received mRNA-1273 under EUA (CDC COVID-19 Response Team; Food and Drug Administration, 2021). Based on the clinical experience to date with mRNA-based vaccines, mRNA-1273 should not be administered to individuals with a known hypersensitivity to any component of the study product, including polyethylene glycol (PEG).

Recently, myocarditis and pericarditis have been reported rarely following vaccination with the Moderna COVID-19 EUA Vaccine. Although causality has not been established, the majority of cases have been in young males ( $<30$  years old), occurring a few days to up to a week after the vaccination and seen more commonly after the second dose. However, cases have been reported in older males, females, as well as after the first dose of vaccine. Most cases are generally mild, and individuals tend to recover within a short time after treatment. However, long term outcomes are unknown. Additionally, it is not known whether the risks of myocarditis or pericarditis are increased following additional doses of vaccine.

Subjects will be informed of the potential risk of myocarditis or pericarditis and be advised to monitor for symptoms of myocarditis or pericarditis, including chest pain, shortness of breath,



tachycardia, or palpitations. Subjects will be encouraged to immediately contact research staff and their medical providers if these symptoms occur following a study vaccination.

Several animal studies with experimental whole-virus inactivated and subunit vaccines of other coronaviruses have shown enhanced immunopathology in a greater number of vaccinated animals compared to controls upon subsequent virus infection. These experimental vaccines often exhibited Th2-biased immune responses or elicited antibodies that had poor neutralizing activity against the virus. In mice vaccinated with two doses of mRNA-1273, a balanced antibody response resulting in high titers of both IgG1 and IgG2a was observed. A predominant Th2-focused immune response with only IgG1 responses was not observed. Data from mice and non-human primates have not identified risk with mRNA-1273 (Corbett KS et al, N Engl J Med 2020; Corbett KS et al, Nature 2020).

Most people during their lifetimes have likely been infected with one or more of the 4 endemic strains of human coronaviruses (hCoV 229E, NL63, OC43, and HKU1) that circulate globally and are responsible for 10-30% of mild to moderate upper respiratory tract infections. Despite the likelihood of cross-reactive antibody responses with poor functional activity, no evidence of enhanced CoV disease in humans has ever been reported.

Interim immunogenicity data from this phase I clinical trial of mRNA-1273 have indicated that vaccination induced type 1 helper T cell (Th1)-biased CD4<sup>+</sup> T cell responses and low or undetectable Th2 or CD8<sup>+</sup> T cell responses (Jackson LA et al, 2020; Anderson EJ et al, 2020). Additionally, no enhancement of respiratory disease has occurred in recipients of mRNA vaccines that had breakthrough SARS-CoV-2 infections (Baden LR et al, 2020; Polack FP et al, 2020). Importantly, of the 30 protocol-defined severe cases of COVID-19 that occurred in the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE), all 30 occurred in the placebo group (Baden LR et al, 2020). Thus, to date, enhanced SARS-CoV-2 respiratory disease has not been observed after mRNA-1273 administration.

### **Risks to Privacy**

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating site. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance (QA) and data analysis include groups such as the IRB, NIAID and the FDA.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by US Law. This web site will not include information that can identify subjects.

There may be other risks, discomforts or side effects that are unknown at this time.

### **Risks of Genetic Testing**

Any genetic data generated will be kept private. There may be a risk that information resulting from research genetic testing could be misused for discriminatory purposes. However, state and

federal laws provide protections against genetic discrimination. Researchers will need to maintain confidentiality in order to be granted access to genetic information.

### 2.2.2 Known Potential Benefits

There is no direct benefit to the subjects. There is potential benefit to society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. Vaccination using mRNA-1273 may or may not provide protection against infection by SARS-CoV-2. The duration of any such protection is currently unknown.

As outlined in [Section 12.2](#), data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE) suggests 94.1% efficacy of the vaccine when administered at 100 mcg versus placebo against SARS-CoV-2 infection when assessed on November 25, 2020 (Baden LR et al, 2020). The efficacy of other doses of mRNA-1273 (e.g., 25, 50, or 250 mcg) is not known. Although declines in binding and neutralizing antibodies are observed over time, 100 mcg of mRNA-1273 has the potential to provide durable humoral immunity (Widge AT et al, 2020).

## 3. OBJECTIVES AND ENDPOINTS

**Table 5: Objectives and Endpoints (Outcome Measures)**

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<b>Primary</b>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination.</li> <li>Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination.</li> <li>Frequency of any SAEs, Protocol Specified AESIs, NOCMCs, and MAAEs from Day 1 to Day 394.</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of antibody at Day 57.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline.</li> <li>The GMFR in IgG titer from baseline.</li> </ul>
<b>Exploratory</b>	

<b>OBJECTIVES</b>	<b>ENDPOINTS (OUTCOME MEASURES)</b>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted at each timepoint.</li> <li>The GMFR in IgG titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by IgM and IgA ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.</li> </ul>	<ul style="list-style-type: none"> <li>GMT at each timepoint.</li> <li>Percentage of subjects who seroconverted at each timepoint.</li> <li>The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of Neut antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.</li> <li>The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of Neut antibody at each timepoint.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.</li> <li>The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.</li> </ul>
<ul style="list-style-type: none"> <li>To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.</li> </ul>	<ul style="list-style-type: none"> <li>Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.</li> </ul>

## 4. STUDY DESIGN

### 4.1 Overall Design

This is a phase I, open-label, dose-ranging clinical trial in males and non-pregnant females,  $\geq 18$  years of age, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of mRNA-1273 manufactured by ModernaTX, Inc. mRNA-1273 is a novel LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2. Enrollment will occur at up to three domestic clinical research sites.

**Table 6: Treatment Arms**

Cohort	Sample Size	Stratum (Years of Age)	First and Second Dose
1	15	18-55	25 mcg mRNA-1273
2	15	18-55	100 mcg mRNA-1273
3	15	18-55	250 mcg mRNA-1273
4	10	56-70	25 mcg mRNA-1273
5	10	56-70	100 mcg mRNA-1273
6*	10	56-70	250 mcg mRNA-1273
7	10	$\geq 71$	25 mcg mRNA-1273
8	10	$\geq 71$	100 mcg mRNA-1273
9*	10	$\geq 71$	250 mcg mRNA-1273
10	15	18-55	50 mcg mRNA-1273
11	10	56-70	50 mcg mRNA-1273
12	10	$\geq 71$	50 mcg mRNA-1273
13*	15	18-55	10 mcg mRNA-1273

\*Cohorts 6, 9 and 13 were not enrolled.

Up to one hundred and fifty-five (155) subjects will be enrolled into one of thirteen cohorts (10 mcg, 25 mcg, 50 mcg, 100 mcg, or 250 mcg). Subjects will receive an IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394). The second dose of vaccine (0.5 mL) will be administered preferably in the same arm used for the first dose.

Follow-up visits will occur 1, 2 and 4 weeks post each vaccination (Days 8, 15, 29, 36, 43, and 57), as well as 3, 6 and 12 months post second vaccination (Days 119, 209 and 394).

Reactogenicity will be assessed at these visits, as well as blood will be drawn for immunogenicity assays. Additional safety and reactogenicity data will be solicited via telephone calls to subjects 1 and 2 days post each vaccination (Days 2, 3, 30, and 31).

To determine early safety signals for this phase I clinical trial, vaccination will proceed in a staged fashion. Sentinel subject dosing will begin with 4 subjects in cohort 1 (25 mcg). The 4 sentinel subjects for cohort 2 (100 mcg) will be enrolled no earlier than one day after enrollment of the last of the 4 sentinel subjects in cohort 1. If no halting rules have been met after the 8 sentinel subjects have completed Day 5, then full enrollment will proceed first with the remaining subjects in cohort 1, followed by the remaining subjects in cohort 2 without interruption. If no halting rules have been met after all subjects in cohort 2 have completed Day 8, then dosing of 4 sentinel subjects will begin in cohort 3. If no halting rules have been met after the 4 sentinel subjects in cohort 3 have completed Day 5, then full enrollment of cohort 3 will proceed.

If no halting rules have been met after all subjects in cohorts 1 and 2 have completed Day 8, dosing will begin for cohorts 4 (25 mcg; 56-70 years of age) and 5 (100 mcg; 56-70 years of age). If no halting rules have been met after all subjects in cohorts 4 and 5 have completed Day 8, dosing will begin for cohorts 7 (25 mcg;  $\geq 71$  years of age) and 8 (100 mcg;  $\geq 71$  years of age).

Based on the interim immunogenicity data available as of May 15, 2020, enrollment into cohorts 6 and 9 (250 mcg; 56-70 years of age and  $\geq 71$  years of age) will be deferred in order to explore lower dosages. Therefore, enrollment of cohorts 10-12 (50 mcg; 18-55 years of age, 56-70 years of age and  $\geq 71$  years of age) will be prioritized. Subjects will be enrolled simultaneously in cohorts 10-12; there will be no staging. To further explore dosage sparing, cohort 13 (10 mcg dose; 18-55 years of age) may be enrolled. A decision regarding the enrollment of cohorts 6, 9 and 13 will be made after review of interim immunogenicity data from cohorts 1-5, 7, 8, and 10-12.

If no halting rules have been met after all subjects in cohorts 5 and 8 have completed Day 8, dosing will begin concurrently for cohorts 10-12. If no halting rules have been met after all subjects in cohorts 3, 7 and 8 have completed Day 8, dosing may begin for cohort 6, if enrolled. If no halting rules have been met after all subjects in cohort 6 have completed Day 8, dosing may begin for cohort 9, if enrolled.

For public health reasons the following early data reviews by the study team are anticipated:

- Sentinel subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- Sentinel subjects in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohorts 4, 5, 7 and 8, ELISA IgG data through Day 29;
- All subjects in cohorts 10-12, ELISA IgG data through Day 29;
- All subjects in cohort 13, ELISA IgG data through Day 29 (if cohort is enrolled);

- All subjects in cohorts 6 and 9, ELISA IgG data through Day 29 (if cohorts are enrolled);
- Sentinel subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinel subjects in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohorts 4, 5, 7 and 8, ELISA IgG data through Day 57;
- All subjects in cohorts 10-12, ELISA IgG data through Day 57;
- All subjects in cohort 13, ELISA IgG data through Day 57 (if cohort is enrolled)
- All subjects in cohorts 6 and 9, ELISA IgG data through Day 57 (if cohorts are enrolled).
- Additional data review of immunogenicity may be performed to inform public health decisions.
- AEs and SAEs by cohort can be reviewed as necessary.
- After Day 57 of the last subject in cohort 3, all available data can be reviewed when applicable.
- After Day 57 of the last subject in cohort 8, all available data can be reviewed when applicable.
- After Day 57 of the last subject in cohort 12, all available data can be reviewed when applicable.
- After Day 57 of the last subject in cohorts 6 and 9 (if cohorts are enrolled), all available data can be reviewed when applicable.
- After Day 57 of the last subject in cohort 13 (if cohort is enrolled), all available data can be reviewed when applicable.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each vaccination through 7 days post each vaccination. Unsolicited non-serious AEs will be collected from the time of each vaccination through 28 days post each vaccination. SAEs, Protocol Specified AESIs, NOCMCs, and MAAEs, will be collected through 12 months after the second vaccination (Day 394).

Clinical safety laboratory evaluations will be performed at screening, as well as immediately prior to and 7 days post each vaccination (Days 1, 8, 29, and 36).

Evaluation of immunogenicity will include quantitation of antibodies to the SARS-CoV-2 S protein at multiple timepoints post vaccination as measured by ELISA, pseudovirus and live wild-type virus neutralization assays. In addition, exploratory studies to characterize T cell responses are planned. Venous blood will also be collected at multiple timepoints post vaccination for the secondary research use of serum, plasma and PBMCs.

To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled in cohorts 2, 3, 5, 10, and 11 may undergo leukapheresis to collect additional samples for secondary research. If enrollment in cohort 6 proceeds, a subset of subjects in this cohort may also undergo leukapheresis.

Based on interim immunogenicity and reactogenicity data, Cohorts 6, 9 and 13 were not enrolled.

After the IND is in effect, IRB review and approval, and site activation, the participating site will begin recruitment outreach efforts, which can include fliers, letters, telephone calls, etc. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the participating site. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use. Screening can occur up to 42 days prior to the first dose.

Schedule of assessments are found in [Section 1.2](#), Schedule of Activities for the Main Study.

Dose escalation or dose-ranging details are found in [Section 6.1.2](#), Dosing and Administration.

Full details of the interim analysis are found in [Section 9.4.6](#), Planned Interim and Early Analyses.

## 4.2 Scientific Rationale for Study Design

This phase I clinical trial is designed as an open-label study, without a placebo arm. Given the small sample size, the use of a placebo group is unlikely to improve understanding of AEs. Additionally, having the study unblinded will facilitate the need for rapid review and dissemination of study data for public health reasons.

## 4.3 Justification for Dose

No human trials of mRNA-1273 have been conducted to date. Preclinical evaluations will occur in parallel with this phase I clinical trial. In several ongoing Phase 1 dose-ranging studies (mRNA-1653, a combination vaccine against human metapneumovirus, hMPV and human parainfluenza type 3; mRNA-1647 and mRNA-1443, both CMV vaccines; mRNA-1893 against Zika virus) dosage levels of mRNA between 10 and 300 mcg were administered IM as one-, two- or three-dose vaccination schedules. Immunogenicity and reactogenicity increased in a dose-dependent manner. The dosage levels proposed for this trial (10 mcg, 25 mcg, 50 mcg, 100 mcg, and 250 mcg) are within the range of previous trials. However, in support of development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in SM-102-containing LNPs.

## 4.4 Optional Third mRNA-1273 Vaccination Substudy

All subjects in this clinical trial were scheduled to receive two mRNA-1273 vaccinations, 28 days apart, at dosages of 25, 50, 100, or 250 mcg (see [Table 1](#)), with the last scheduled follow-up visit occurring at 365 days after the second vaccination (see [Table 4](#)). During the course of the main study, interim efficacy data from a Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE), administered as 2 doses of 100 mcg given 28 days apart, demonstrated vaccine efficacy of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic, confirmed COVID-19

(Baden, LR, et al. 2020). After review of the interim safety and efficacy data from that clinical trial, the FDA granted on December 18, 2020 an Emergency Use Authorization (EUA) for the mRNA-1273 vaccine in adults 18 years of age and older.

To potentially enhance and extend the duration of protection provided by the 2-dose vaccination schedule of mRNA-1273 administered in the main study, and to gain an understanding of the immune responses to a third dose of mRNA-1273, subjects in the main study may participate in an optional third mRNA-1273 vaccination substudy, detailed in [Section 12, Appendix A](#). Substudy subjects will receive a third mRNA-1273 vaccination, administered via an IM injection at a dosage of 100 mcg/0.5 mL, given six to twelve months after receipt of their second vaccination in the main study. Substudy subjects will be followed for safety, reactogenicity, and immunogenicity endpoints through 12 months post third vaccination (Substudy Day 366).

To be eligible to participate in the substudy, subjects must have received both the first and second mRNA-1273 vaccinations in the main study. Other eligibility criteria are specified in [Appendix A](#). Subjects who received only one mRNA-1273 vaccination in the main study will be advised to receive an FDA authorized or approved COVID-19 vaccine, according to the recommended schedule, when available to them outside of this trial, unless they have a contraindication to COVID-19 vaccines that are available.

Subjects who elect not to participate in the optional third mRNA-1273 vaccination substudy or are not eligible for the substudy will continue to be followed according to the Schedule of Activities for the main study (see [Table 4](#)) with the Final Study Visit 14 occurring at Day 394 ( $\pm 14$  days).

Dosing for the optional third mRNA-1273 vaccination substudy is found in [Table 13](#).

Schedule of assessments for the optional third mRNA-1273 vaccination substudy is found in [Table 14](#).

Statistical Considerations for the optional third mRNA-1273 vaccination substudy are found in [Section 12.11](#).

## **5. STUDY POPULATION**

Up to one hundred and fifty-five (155) males and non-pregnant females,  $\geq 18$  years of age, who are in good health and meet all eligibility criteria will be enrolled. The target population should reflect the community at large. The estimated time from initiation of enrollment to complete enrollment in this clinical trial is approximately 16 weeks. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the participating site. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use. Screening can occur up to 42 days prior to the first dose.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator. No exemptions are granted on Subject Inclusion or Exclusion Criteria in DMID-sponsored studies.

### **5.1 Inclusion Criteria**



A subject must meet all of the following criteria to be eligible to participate in this study:

1. Provides written informed consent prior to initiation of any study procedures.
2. Be able to understand and agrees to comply with planned study procedures and be available for all study visits.
3. Agrees to the collection of venous blood per protocol.
4. Male or non-pregnant female,  $\geq 18$  years of age at time of enrollment.
5. BMI 18.0-35.0 kg/m<sup>2</sup>, inclusive (<56 years of age), at screening; BMI 18.0-30.0 kg/m<sup>2</sup>, inclusive ( $\geq 56$  years of age), at screening.
6. Women of childbearing potential<sup>1</sup> must agree to use or have practiced true abstinence<sup>2</sup> or use at least one acceptable primary form of contraception.<sup>3,4</sup>

*Note: These criteria are applicable to females in a heterosexual relationship and child-bearing potential (i.e., the criteria do not apply to subjects in a same sex relationship).*

<sup>1</sup>*Not of childbearing potential – post-menopausal females (defined as having a history of amenorrhea for at least one year) or a documented status as being surgically sterile (hysterectomy, bilateral oophorectomy, tubal ligation/salpingectomy, or Essure® placement).*

<sup>2</sup>*True abstinence is 100% of time no sexual intercourse (male's penis enters the female's vagina). (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).*

<sup>3</sup>*Acceptable forms of primary contraception include monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more prior to the subject's first vaccination, intrauterine devices, birth control pills, and injectable/implantable/insertable hormonal birth control products.*

<sup>4</sup>*Must use at least one acceptable primary form of contraception for at least 30 days prior to the first vaccination and at least one acceptable primary form of contraception for 60 days after the last vaccination.*

7. Women of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to each vaccination.
8. Male subjects of childbearing potential<sup>5</sup>: use of condoms to ensure effective contraception with a female partner of childbearing potential from first vaccination until 60 days after the last vaccination.

<sup>5</sup>*Biological males who are post-pubertal and considered fertile until permanently sterile by bilateral orchiectomy or vasectomy.*

9. Male subjects agree to refrain from sperm donation from the time of first vaccination until 60 days after the last vaccination.

10. In good health.<sup>6</sup>

<sup>6</sup>*As determined by medical history and physical examination to evaluate acute or ongoing chronic medical diagnoses/conditions that have been present for at least 90 days, which would affect the assessment of safety of subjects. Chronic medical diagnoses/conditions*

*should be stable for the last 60 days (no hospitalizations, ER, or urgent care for condition or need for supplemental oxygen). This includes no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis/condition in the 60 days before enrollment. Any prescription change that is due to change of health care provider, insurance company, etc., or done for financial reasons, and in the same class of medication, will not be considered a deviation of this inclusion criterion. Any change in prescription medication due to **improvement** of a disease outcome, as determined by the participating site PI or appropriate sub-investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the participating site PI or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity, and do not indicate a worsening of medical diagnosis/condition. Similarly, medication changes subsequent to enrollment and study vaccination are acceptable provided the change was not precipitated by deterioration in the chronic medical condition, and there is no anticipated additional risk to the subject or interference with the evaluation of responses to study vaccination.*

11. Oral temperature is less than 100.0°F (37.8°C).
12. Pulse no greater than 100 beats per minute.
13. Systolic BP is 85 to 150 mm Hg, inclusive.
14. Clinical screening laboratory evaluations (WBC, Hgb, PLTs, ALT, AST, Cr, ALP, T. Bili, Lipase, PT, and PTT) are within acceptable normal reference ranges at the clinical laboratory being used.
15. Must agree to have samples stored for secondary research.
16. Agrees to adhere to Lifestyle Considerations (defined in [Section 5.4](#)) throughout study duration.
17. Must agree to refrain from donating blood or plasma during the study (outside of this study).

### **5.1.1 Leukapheresis Inclusion Criteria**

A subject must meet all of the following criteria to be eligible for leukapheresis:

1. Written informed consent for leukapheresis is provided.
2. Weight  $\geq$  110 pounds.
3. Screening laboratory evaluations are within acceptable ranges at the site where the leukapheresis procedure will be performed.
4. Negative urine or serum pregnancy test within 48 hours of the leukapheresis procedure for women of childbearing potential.
5. Adequate bilateral antecubital venous access.
6. No use of blood thinners, aspirin or NSAIDs at least 5 days before the leukapheresis procedure.

7. Enrolled in cohorts 2, 3, 5, 10, or 11, and possibly cohort 6, if enrolled, and completed the two-dose vaccination series.

## 5.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from participation in this study:

1. Positive pregnancy test either at screening or just prior to each vaccine administration.
2. Female subject who is breastfeeding or plans to breastfeed from the time of the first vaccination through 60 days after the last vaccination.
3. Has any medical disease or condition that, in the opinion of the participating site PI or appropriate sub-investigator, precludes study participation.<sup>7</sup>

*<sup>7</sup>Including acute, subacute, intermittent or chronic medical disease or condition that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this trial.*

4. Presence of self-reported or medically documented significant medical or psychiatric condition(s).<sup>8</sup>

*<sup>8</sup>Significant medical or psychiatric conditions include but are not limited to:*

*Respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) requiring daily medications currently or any treatment of respiratory disease exacerbations (e.g., asthma exacerbation) in the last 5 years. Asthma medications: inhaled, oral, or intravenous (IV) corticosteroids, leukotriene modifiers, long and short acting beta agonists, theophylline, ipratropium, biologics.*

*Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease), history of myocarditis or pericarditis as an adult, myocardial infarction (MI) within past 6 months, coronary artery bypass surgery or stent placement, or uncontrolled cardiac arrhythmia.*

*Neurological or neurodevelopmental conditions (e.g., history of migraines in the past 5 years, epilepsy, stroke, seizures in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis, transverse myelitis, stroke or transient ischemic attack, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, or Alzheimer's disease).*

*Ongoing malignancy or recent diagnosis of malignancy in the last five years excluding basal cell and squamous cell carcinoma of the skin, which are allowed.*

*An autoimmune disease, including hypothyroidism without a defined non-autoimmune cause, localized or history of psoriasis.*

*An immunodeficiency of any cause.*

*Chronic kidney disease, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m<sup>2</sup>.*

5. Has an acute illness<sup>9</sup>, as determined by the participating site PI or appropriate sub-investigator, with or without fever [oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ )] within 72 hours prior to each vaccination.

*<sup>9</sup>An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the participating site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.*

6. Has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV types 1 or 2 antibodies at screening.
7. Has participated in another investigational study involving any investigational product<sup>10</sup> within 60 days, or 5 half-lives, whichever is longer, before the first vaccine administration.

*<sup>10</sup>study drug, biologic or device*

8. Currently enrolled in or plans to participate in another clinical trial with an investigational agent<sup>11</sup> that will be received during the study-reporting period.<sup>12</sup>

*<sup>11</sup>Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.*

*<sup>12</sup>13 months after the first vaccination.*

9. Has previously participated in an investigational study involving LNPs (a component of the investigational vaccine assessed in this trial).
10. Has a history of hypersensitivity or severe allergic reaction (e.g., 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 be associated with impaired immune responsiveness.<sup>13</sup>

*<sup>13</sup>Including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other similar or toxic drugs during the preceding 6-month period prior to vaccine administration (Day 1). The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.*

12. Anticipating 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. Has any blood dyscrasias or significant disorder of coagulation.
15. Has any chronic liver disease, including fatty liver.
16. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 6 months before the first vaccine administration.
17. Has a positive test result for drugs of abuse at screening or before the first vaccine administration. If cannabis is the only detected drug, inclusion is permitted.

18. Has any abnormality or permanent body art (e.g., tattoo) that would interfere with the ability to observe local reactions at the injection site (deltoid region).
19. Received or plans to receive a licensed, live vaccine within 4 weeks before or after each vaccination.
20. Received or plans to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
21. Receipt of any other SARS-CoV-2 or other experimental coronavirus vaccine at any time prior to or during the study.
22. 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. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 28 days after the last vaccination.
27. Reside in a nursing home or other skilled nursing facility or have a requirement for skilled nursing care.
28. Non-ambulatory.
29. For subjects  $\geq 56$  years of age, history of chronic smoking within the prior year.
30. For subjects  $\geq 56$  years of age, current smoking or vaping.
31. For subjects  $\geq 56$  years of age, individuals currently working with high risk of exposure to SARS-CoV-2 (e.g., active health care workers with direct patient contact, emergency response personnel).

### **5.2.1 Exclusion of Specific Populations**

This is a first-in-human trial in healthy subjects,  $\geq 18$  years of age. Because the effects on the fetus are not known, pregnant women will not be eligible for the trial. Women of childbearing potential must utilize a highly effective method of contraception and will be required to have a negative urine or serum pregnancy test within 24 hours prior to each vaccination. Children will not be included in this trial as presently there are no safety or efficacy data in adults. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

### **5.3 Inclusion of Vulnerable Subjects**

Not Applicable

### **5.4 Lifestyle Considerations**

During this study subjects are asked to:

- Refrain from consuming food or drink containing poppy seeds within 72 hours of the screening visit as this could cause a false positive urine drug screen result.
- Follow public health guidance on preventing SARS-CoV-2 infection.
- Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.

## **5.5 Screen Failures**

After the screening assessments have been completed, the participating site PI or qualified designee is to review the inclusion and exclusion criteria and determine the subject's eligibility for the study.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility. Subjects who are found to be ineligible will be told the reason for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal clinical laboratory finding may be rescreened once.

## **5.6 Strategies for Recruitment and Retention**

### **5.6.1 Recruitment**

Potential subjects will learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry and local advertisements/flyers. Screening will begin with a brief IRB-approved telephone call from study staff. Information about the study will be presented to potential subjects and questions about their health and ability to comply with the study visit schedule will be asked of potential subjects to presumptively determine eligibility. Appointments will be made at the research clinic for potential subjects who are interested in the study for further screening procedures and additional protocol-specific information.

### **5.6.2 Retention**

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participating subjects will be reminded of subsequent visits during each visit, and study staff will contact subjects prior to appointments. Study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

### **5.6.3 Compensation Plan for Subjects**

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to local IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the amount contingent on completing study procedures.

#### 5.6.4 Costs

There is no cost to subjects for the research tests, procedures/evaluations or study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party.

## 6. STUDY PRODUCT

### 6.1 Study Product(s) and Administration

#### 6.1.1 Study Product Description

##### **Product: mRNA-1273**

mRNA-1273 is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized spike protein SARS-CoV-2. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, DSPC, and PEG2000 DMG. mRNA-1273 has a total lipid content of 9.7 mg/mL and is formulated at a concentration of 0.5 mg/mL in 20 mM trometamol (Tris) buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate, at pH 7.5.

##### **Diluent: 0.9% NaCl for injection, USP**

The USP grade 0.9% NaCl or normal saline for injection is a sterile, nonpyrogenic, isotonic solution; each mL contains NaCl 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). This product should be used to dilute the vaccine to the desired concentration.

#### 6.1.2 Dosing and Administration

mRNA-1273 (0.5 mg/mL) will be diluted in 0.9% NaCl for injection, USP to obtain 10, 25, 50, 100, and 250 mcg in 0.5 mL dosages. Each dose will be administered via IM injection (0.5 mL) into the deltoid muscle on Days 1 and 29. The second dose of vaccine (0.5 mL) will be administered preferably in the same arm used for the first dose. The pharmacist will prepare a single dose (0.5 mL) for each subject based on cohort assignment.

**Table 7: Dosing and Administration**

Cohort	Product Name	Dose	Route	Frequency of Administration
1	mRNA-1273	25 mcg	IM	D1, D29
2	mRNA-1273	100 mcg	IM	D1, D29
3	mRNA-1273	250 mcg	IM	D1, D29
4	mRNA-1273	25 mcg	IM	D1, D29
5	mRNA-1273	100 mcg	IM	D1, D29
6*	mRNA-1273	250 mcg	IM	D1, D29
7	mRNA-1273	25 mcg	IM	D1, D29
8	mRNA-1273	100 mcg	IM	D1, D29
9*	mRNA-1273	250 mcg	IM	D1, D29
10	mRNA-1273	50 mcg	IM	D1, D29

Cohort	Product Name	Dose	Route	Frequency of Administration
11	mRNA-1273	50 mcg	IM	D1, D29
12	mRNA-1273	50 mcg	IM	D1, D29
13*	mRNA-1273	10 mcg	IM	D1, D29

\*Cohorts 6, 9 and 13 were not enrolled.

See the protocol-specific Manual of Procedures (MOP) for detailed information on the preparation, labeling, storage, and administration of vaccine for each cohort. Vaccine preparation will be performed by the participating site's research pharmacist on the same day of vaccine administration to the subject.

Visually inspect the mRNA-1273 upon receipt and prior to use. If the study product(s) appear(s) to have been damaged, contaminated or discolored, contain(s) visible particulate matter, or if there are any concerns regarding the integrity, do NOT use the affected study product(s). The affected study product(s) must be quarantined at appropriate storage temperature and labeled as 'Do Not Use' (until further notice). The participating site PI or responsible person should immediately contact the DMID Product Support Team at [DMIDProductSupportTeam@niaid.nih.gov](mailto:DMIDProductSupportTeam@niaid.nih.gov) and DMID Clinical Project Manager for further instructions before any additional vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If the affected study product(s) cannot be used, the participating site will receive specific instructions on how to return the affected study product(s) to the DMID Clinical Material Services (CMS) or destroy the affected study product(s) on-site. If the mRNA-1273 is unusable, study staff will use another vial from the study supply. Replacement vials may be requested by contacting DMID. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

The injection dose volume (0.5 mL each) of vaccine should be withdrawn from the final mixed vial(s) or compounding vial(s) containing the prepared dosing solution. The number of individual dosing syringes that may be filled from one mixing vial varies depending on the dosage. Doses for multiple subjects may be drawn into individual dosing syringes (0.5 mL each) from the same mixing vial within 30 minutes of completion of dosing solution preparation (10, 25, 50, and 100 mcg doses only). Gently invert the final mixed vial(s) or the compounding vial(s) 20 times until components are mixed prior to withdrawing. **Do not mix vigorously or sonicate or vortex.**

Aseptic technique will be used for the withdrawal and administration of each dose of vaccine using a disposable, sterile needle appropriate in length for each subject and a 1-mL disposable, sterile syringe.

The expiration time of the dosing syringe containing the prepared mRNA-1273 solution is **4 hours at room temperature for the 10 mcg dosage** after the solution is drawn into the dosing syringe and 8 hours at room temperature for the 25, 50, 100, and 250 mcg dosages after the solution is drawn into the dosing syringe.

### 6.1.3 Dose Escalation

[Section 4.1.](#)



#### **6.1.4 Dose Modifications**

No dose modifications.

### **6.2 Accountability/Handling/Storage/Preparation**

#### **6.2.1 Acquisition and Accountability**

##### **Product: mRNA-1273**

Will be provided by ModernaTX, Inc. via the DMID CMS.

Upon request by DMID, mRNA-1273 will be transferred to the following address:

DMID Clinical Materials Services Contract  
Fisher BioServices  
20439 Seneca Meadows Parkway  
Germantown, MD 20876  
Phone: 240-477-1350  
Fax: 240-477-1360  
Email: DMID.CMS@thermofisher.com

##### **Diluent: 0.9% NaCl for injection, USP**

Will be provided by DMID via the DMID CMS.

All study products will be shipped to the clinical research site upon request and approval from DMID.

#### **Accountability**

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Study product accountability records and dispensing logs should include, but are not limited to the following: DMID protocol number; name, dosage form, strength of the study product; capture vial numbers assigned sequentially by the pharmacists as vials/syringes are used (number uniquely, do not start over at 1 or repeat numbers), manufacturer or other source; control, lot number or other identification number; expiration or retest date; date of receipt of the study product; quantity received from supplier; subject identification number; quantity dispensed as amount or dose per subject; balance of study product currently available; disposition of study product if not dispensed to a study subject (e.g., disposed/destroyed or returned to supplier as per protocol or protocol-specific MOP or as directed by DMID); date of vaccine preparation/administration, time of vaccine preparation, expiration of vaccine preparation; and amount of vaccine withdrawn for administration. Time of vaccine administration to the subject will be recorded on the appropriate data collection form (DCF). All study product(s), including the amount of mRNA-1273, diluent (0.9% NaCl for injection, USP), and vial admixtures, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the

participating site's study product accountability records and dispensing logs per the DMID-approved clinical monitoring plan (CMP).

Once all subject dosing is complete, the pharmacy staff should retain or dispose of used study products and complete study product accountability procedures in accordance with site-specific standard operating procedures (SOPs). This applies to:

- used and unused mRNA-1273 vials
- used mixing vials
- mRNA-1273 cartons

All used supplies noted above may either be sequestered from the unused supplies and retained until study conclusion or until study product accountability has occurred by the monitor and written notification stating retention is no longer required is received, or may be destroyed in accordance with site-specific SOPs with a second pharmacy staff member's observation and verification as documented in the pharmacy log. Refer to the protocol-specific MOP for details on storing used mRNA-1273 vials, used 0.9% NaCl Injection vials and used mixing vials.

### **Destruction**

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used mRNA-1273 vials should occur as noted:

- Unused and Used mRNA-1273 vials:
  - Should be destroyed on-site following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/SOP when destroying used and unused items.
  - A certificate of destruction or documentation of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

Used syringes may be destroyed in accordance with site-specific SOPs.

### **6.2.2 Formulation, Appearance, Packaging, and Labeling**

#### **Product: mRNA-1273**

mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate, at pH 7.5.

#### **Diluent: 0.9% NaCl for injection, USP**

The USP grade 0.9% NaCl or normal saline for injection is a sterile, nonpyrogenic, isotonic solution; each mL contains NaCl 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. It is clear in appearance, and available in 10 mL vials.

Each of the study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal Law to Investigational Use."

Sterile empty vials (2-mL or 10-mL) will be provided with latex-free stoppers.

### **6.2.3 Product Storage and Stability**

#### **Product: mRNA-1273**

mRNA-1273 is stored at -70°C (-60°C to -90°C).

Stability protocols for mRNA-1273 will include at least 24-months duration at the intended storage temperature (-60°C to -90°C).

Stability and compatibility with the apparatus intended for administration for up to 8 hours after preparation were assessed. The prepared doses were stable for clinical in-use for up to 8 hours at room temperature (**Note: up to 4 hours at room temperature for 10 mcg doses**).

#### **Diluent: 0.9% NaCl for injection, USP**

0.9% NaCl for injection, USP is stored at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature.]

The temperature of the storage unit must be manually recorded daily (excluding non-business days and holidays, as applicable) and continuously monitored and recorded during the course of this trial per site-specific SOPs, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The participating site's research pharmacist must alert the participating site PI and study coordinator, if the temperature fluctuates outside of the required range. In the event the temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected study product(s) must not be administered. The participating site PI or responsible person should immediately contact the DMID Product Support Team at [DMIDProductSupportTeam@niaid.nih.gov](mailto:DMIDProductSupportTeam@niaid.nih.gov) for further instructions before any additional vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the participating site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on-site. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

mRNA-1273 must be stored in a secure area with limited access (pharmacy staff only), and must be stored frozen at -60°C to -90°C. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator; or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any mRNA-1273 that was not temperature controlled during shipment or during storage to the pharmacy staff. Such mRNA-1273 will be retained for inspection by the pharmacy staff and disposed of according to approved methods.

### **6.2.4 Preparation**

Refer to the protocol-specific MOP for details about preparation.

## **6.3 Measures to Minimize Bias: Randomization and Blinding**

### **6.3.1 Treatment Assignment Procedures**

Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6: GCP, screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the Statistical and Data Coordinating Center's (SDCC) Advantage eClinical<sup>SM</sup> (Electronic Data Capture System).

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subjects will be enrolled. Enrollment will proceed in a staged fashion. Sentinel subject dosing will begin with 4 subjects in cohort 1 (25 mcg). The 4 sentinel subjects for cohort 2 (100 mcg) will be enrolled no earlier than one day after enrollment of the last of the 4 sentinel subjects in cohort 1. If no halting rules have been met after the 8 sentinel subjects have completed Day 5, then full enrollment will proceed first with the remaining subjects in cohort 1, followed by the remaining subjects in cohort 2 without interruption. If no halting rules have been met after all subjects in cohort 2 have completed Day 8, then dosing of 4 sentinel subjects will begin in cohort 3. If no halting rules have been met after the 4 sentinel subjects in cohort 3 have completed Day 5, then full enrollment of cohort 3 will proceed.

If no halting rules have been met after all subjects in cohorts 1 and 2 have completed Day 8, dosing will begin for cohorts 4 (25 mcg; 56-70 years of age) and 5 (100 mcg; 56-70 years of age). If no halting rules have been met after all subjects in cohorts 4 and 5 have completed Day 8, dosing will begin for cohorts 7 (25 mcg;  $\geq 71$  years of age) and 8 (100 mcg;  $\geq 71$  years of age).

Based on the interim immunogenicity data available as of May 15, 2020, enrollment into cohorts 6 and 9 (250 mcg; 56-70 years of age and  $\geq 71$  years of age) will be deferred in order to explore lower dosages. Therefore, enrollment of cohorts 10-12 (50 mcg; 18-55 years of age, 56-70 years of age and  $\geq 71$  years of age) will be prioritized. Subjects will be enrolled simultaneously in cohorts 10-12; there will be no staging. To further explore dosage sparing, cohort 13 (10 mcg dose; 18-55 years of age) may be enrolled. A decision regarding the enrollment of cohorts 6, 9 and 13 will be made after review of interim immunogenicity data from cohorts 1-5, 7, 8, and 10-12.

If no halting rules have been met after all subjects in cohorts 5 and 8 have completed Day 8, dosing will begin concurrently for cohorts 10-12. If no halting rules have been met after all subjects in cohorts 3, 7 and 8 have completed Day 8, dosing may begin for cohort 6, if enrolled. If no halting rules have been met after all subjects in cohort 6 have completed Day 8, dosing may begin for cohort 9, if enrolled.

### **6.3.2 Randomization and Blinding**

This is an open-label study with sequential group enrollment so randomization and blinding will not be utilized.

### **6.3.3 Blinding and Masking Procedures**

Not Applicable

## **6.4 Study Intervention Compliance**

Each dose of study product will be administered by a member of the clinical research team that is qualified and licensed to administer the study product. Administration and date, time, and location of injection will be recorded on the appropriate DCF.

## **6.5 Concomitant Therapy**

Information about prior medications, including hormonal contraceptives, taken by the subject in the 30 days prior to providing informed consent will be recorded on the appropriate DCF.

Concomitant medications include all medications (prescription, over the counter, supplements, and vaccines received outside of the study) taken by the subject from the time the informed consent is signed through Day 394. At each study visit following dosing, including telephone calls, subjects will be queried about new concomitant medications and changes to existing medications.

Medications that might interfere with the evaluation of the investigational product should not be used by the subject during the study-reporting period (12 months after the second vaccination) unless clinically indicated as part of the subject's health care.

In the event medical conditions dictate the use of medications, subjects are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician, and inform the study Investigator as soon as practical. Any drug or vaccine used or received by the subject during the trial should be recorded on the appropriate DCF.

### **6.5.1 Rescue Medicine**

Not Applicable

### **6.5.2 Non-Research Standard of Care**

Not Applicable

## **7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL**

### **7.1 Halting Criteria and Discontinuation of Study Intervention**

#### **7.1.1 Halting Criteria**

The study will be paused if any of the following events occur:

- 1- Any subject experiences an SAE after administration of the vaccine that is considered related to vaccine.
- 2- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine that is considered related to vaccine.
- 3- Any subject experiences ulceration, abscess or necrosis at the injection site that is considered related to vaccine administration.

- 4- Two (2) or more subjects experience an allergic reaction such as generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine that is considered related to vaccine.
- 5- Three (3) or more subjects experience a Grade 3 AE (unsolicited and/or clinical laboratory abnormality), in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, that lasted at least 48 hours after administration of the vaccine and is considered related to the vaccine. Clinical laboratory abnormalities are not subject to the time window.

Study product administration and enrollments may resume only after review of the AEs that caused the pause results in a recommendation to permit further study product administration and enrollments.

### **7.1.2 Sentinel Halting Criteria**

If any of the following events occur to the sentinel subjects, the study will be paused:

- 1- Any subject experiences ulceration, abscess or necrosis at the injection site.
- 2- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine.
- 3- Any subject experiences generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine.
- 4- Any subject experiences an SAE (except for accident or trauma) after administration of the vaccine that is considered related to the vaccine.
- 5- Any 2 subjects in the same cohort experience the same Grade 3 Solicited Local AE or Systemic AE, (excluding measured grades of erythema and edema/induration alone) that lasted at least 48 hours within 7 days after administration of the vaccine.
- 6- Any 2 subjects experience the same Grade 3 AE (unsolicited and/or clinical laboratory abnormality), in the same Preferred terms based on the MedDRA coding, that lasted at least 48 hours after administration of the vaccine and is considered related to the vaccine. Clinical laboratory abnormalities are not subject to the time window.

### **7.1.3 Criteria for Continuation of Dosing and Redosing**

In the event a halting rule is met:

- an unscheduled safety analysis by the SMC will be required for approval of further enrollment, and
- further administration of the vaccine, including a second dose, is suspended for ALL subjects until an assessment by the SMC takes place.

#### **7.1.3.1 Withdrawal Criteria for Second Study Vaccination**

Prior to receiving the second vaccination, subjects will be reassessed. The following events constitute contraindications to any further administration of vaccines. If any of these events occur during the study, the subject must not receive the second vaccination but will be

encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination.

- Withdrawal of consent.
- As deemed necessary by the participating site PI or appropriate sub-investigator for non-compliance or other reasons. This may include previously undisclosed or new conditions that meet exclusion criteria.
- Any clinically significant medical condition that, in the opinion of the participating site PI or appropriate sub-investigator, poses an additional risk to the subject if he/she continues to participate in the study.
- Anaphylaxis or unexpected systemic hypersensitivity reaction following the administration of the first vaccination.
- Any SAE judged to be related to vaccine.
- Pregnancy.
- Subject is lost to follow-up.
- New information becomes available that makes further participation unsafe.
- Termination of this trial.

#### **7.1.3.2 Delay of Study Vaccination**

If any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the window specified in the SOA, or the subject may be withdrawn from dosing at the discretion of the participating site PI or appropriate sub-investigator:

- Acute moderate or severe infection with or without fever at the time of vaccination.
- Fever, defined as oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) at the time of vaccination.

Subjects with a minor illness without fever, as assessed by the participating site PI or appropriate sub-investigator, can be administered vaccines. Subjects with an oral temperature of  $38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) or higher will be re-contacted within the window specified in the SOA and re-evaluated for eligibility.

#### **7.1.4 Follow-up for Subjects that Discontinued Study Intervention**

Discontinuation of study intervention does not require discontinuation from the study, and the remaining study procedures should be completed as indicated by the SOA. If a clinically significant finding is identified, including, but not limited to, changes from baseline, after enrollment, the participating site PI or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation should include the following:

- Clinical safety laboratory evaluations.
- Complete physical examination.

- Vital signs (BP, heart rate [HR], oral temperature).
- Immunogenicity evaluations.

## 7.2 Subject Withdrawal from the Study and Replacement

Subjects are free to withdraw from participation in the study at any time upon request, without any consequence.

A study subject will be discontinued from participation in the study if any of the following reasons occur prior to initial dosing:

- Request by the subject to terminate participation.
- Vaccine is not administered.

A subject may be removed from the study for the following reasons post initial dosing; however, whenever possible the subject should be followed for safety and immunogenicity evaluations per protocol:

- Subject becomes pregnant before receiving the second dose of vaccine.
- Study non-compliance to protocol requirements that in the opinion of the participating site PI or appropriate sub-investigator poses an increased risk (e.g., missing safety labs) or compromises the validity of the data.
- Lost to follow-up.
- If the subject met an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further study participation.
- Request of primary care provider; the IRB, FDA, or NIAID.
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the participating site PI or appropriate sub-investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses.
- If any AE, clinical laboratory abnormality or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The occurrence of an SAE.

If the subject agrees, every attempt will be made to follow all AEs through resolution or stabilization.

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced.

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

The reason for subject discontinuation or withdrawal from the study will be recorded on the appropriate DCF.



### **7.3 Lost to Follow-Up**

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-mail, etc., made on separate occasions) will be made to locate or recall the subject, or at least to determine the subject's health status. These efforts will be documented in the subject's study file.

## **8. STUDY ASSESSMENTS AND PROCEDURES**

### **8.1 Screening and Immunogenicity Assessments**

#### **8.1.1 Screening Procedures**

There is a small amount of risk to subjects who report that they are in good health but have an unknown health problem at the time of screening. Screening assessments can occur up to 42 days before the subject's first vaccination (Day 1) and may occur in one or two visits. At the first visit, and prior to any other study-related activities, the participating site PI or appropriate sub-investigator will provide the subject with detailed study information and will obtain written informed consent.

Some or all of the following assessments are performed during the screening visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history.
- Review pre-study medications and therapies up to 30 days prior to the start of screening and record on the appropriate DCF.
- Review of adult vaccinations, including any other SARS-CoV-2 or other experimental coronavirus vaccines.
- Measure vital signs (HR, BP, and oral temperature) and height and weight for determination of BMI.
- Perform full physical examination which will include assessments of the following organs and organ systems: skin, head, ears, eyes, nose, and throat (HEENT), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
- Review of birth control history with female subjects.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Obtain blood and urine for clinical screening laboratory evaluations:
  - Hematology
    - WBCs
    - Hgb
    - PLTs
  - Chemistry (fasting or non-fasting)

- ALT
- AST
- ALP
- T. Bili
- Lipase
- Cr
- PT
- PTT
- Serology
  - Hepatitis B surface antigen
  - Hepatitis C virus antibody
  - HIV types 1 and 2 antigen/antibody
- Serum pregnancy test (in women of childbearing potential)
- Urine drug screen
- Review inclusion and exclusion criteria.

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected for these evaluations is presented in Table 8.

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Study subjects who qualify for inclusion will be contacted and scheduled for enrollment and first vaccination within the window for enrollment.

If a physiologic parameter, e.g., vital signs or clinical laboratory value, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or “white coat syndrome”) or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

A subject may be re-screened if there is a transient disease status (e.g., subject complained of a “cold or fever” and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (e.g., a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).

No subjects may be screened more than twice due to a screening failure result as defined above.

Subjects will be provided the results of abnormal clinical laboratory test values or abnormal clinical findings necessitating follow-up at the discretion of the participating site PI or appropriate sub-investigator. Research laboratory results will not be provided to the subject.

### **8.1.2 Screening Procedures for Leukapheresis**

For those subjects consented for leukapheresis, screening procedures, including screening laboratory evaluations, will be performed locally prior to the leukapheresis procedure. Refer to the protocol-specific MOP for details on the leukapheresis procedure.

### **8.1.3 Immunogenicity Evaluations**

#### Serological Immunogenicity Assays:

The following serological immunogenicity assays will be performed:

- IgG ELISA to the SARS-CoV-2 S (spike) protein.
- IgM and IgA ELISA to the SARS-CoV-2 S (spike) protein.
- Neutralization assay using a SARS-CoV-2 pseudovirus.
- Neutralization assay using a live wild-type SARS-CoV-2.

Preparation of blood samples and shipping instructions for serological immunogenicity assays are outlined in the protocol-specific MOP. Inability (e.g., loss of IV access) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline serum for serological immunogenicity assays is collected.

#### Cellular Immunology Assays:

This trial will also investigate T cell immune responses using multiparametric flow cytometry.

Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the protocol-specific MOP.

The volume of venous blood to be collected for immunogenicity evaluations is presented in [Table 8](#).

### **8.1.4 Samples for Genetic/Genomic Analysis**

#### **8.1.4.1 Genetic/Genomic Analysis**

Stored PBMCs, including leukocyte samples obtained by leukapheresis, may be used in secondary research for sequencing of DNA from B cells to characterize B cell receptors and monoclonal antibodies. The DNA data may be used to synthesize antigen-specific antibodies to characterize antibody binding. Secondary research samples may also be used for other genomic analysis, including, but not limited to, single nucleotide polymorphisms (SNP) arrays, human leukocyte antigen (HLA) typing, transcriptomic analysis, evaluation of the immune response to the vaccine, and/or evaluation of any AE from the vaccine.

#### **8.1.4.2 Genetic Privacy and Confidentiality**

Any genetic data generated will be kept private. Informed consent permitting data sharing will be part of the consent process. Subjects will be informed that the evolution of genomic technology

and analytical methods raises the risk of re-identification, even when specimens are de-identified. No data that may identify specific subjects will be kept with the genetic data.

### 8.1.4.3 Management of Results

All genetic testing in this protocol will be performed for research only and is not performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. Therefore, results will not be shared with the subjects.

## 8.2 Safety and Other Assessments

Study procedures are specified in the SOA. A study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator, will be responsible for all study-related medical decisions.

- Medical history:
  - A complete medical history will be obtained by interview of subjects at the screening visit. Subjects will be queried regarding a history of significant medical disorders of the head, ears, eyes, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.
  - At all subsequent visits an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit or telephone call will be noted. The interim medical history should include an assessment for new medical conditions and symptoms suggestive of Protocol Specified AESIs, MAAEs and NOCMCs.
- Physical examination:
  - A full physical examination will be performed at the screening visit and a symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the SOA.
    - A full physical examination will include assessments of the following organs and organ systems: skin, HEENT, neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system.
    - Height and weight will be measured, and BMI calculated, at the screening visit only.
  - A symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the SOA.
    - Targeted physical examinations should also include an assessment for signs suggestive of Protocol Specified AESIs, MAAEs and NOCMCs. Interim or unscheduled physical examinations will be performed at the

discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs or abnormal clinical laboratory test results.

- Reactogenicity assessments of solicited AEs occurring from the time of each vaccination through 7 days post each vaccination, will include an assessment of injection site reactions—erythema, edema/induration and pain, as well as systemic reactions—fever, fatigue, chills, myalgia (exclusive of the injection site), arthralgia, headache, and nausea. Pre-administration reactogenicity assessments will be performed immediately prior to each vaccination to establish baseline, then the vaccination will be given.
- Subjects will be observed in the clinic for at least 60 minutes post each vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AEs/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic. The vaccination site will also be examined on Days 8 and 36.
- Vital signs: Vital sign measurements will include systolic and diastolic BP, HR, and oral temperature. Vital signs will be measured at timepoints specified in the SOA. On Days 1 and 29, vital sign measurements will be collected prior to vaccine administration. Vital signs assessed on Day 1 prior to the first vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold within 10 minutes prior to taking oral temperature.
- Clinical laboratory evaluations:
  - Fasting is not required before collection of clinical laboratory evaluations.
  - Serum pregnancy test will be performed locally by the site laboratory at the screening visit, and urine or serum pregnancy test will be performed locally by the site laboratory within 24 hours prior to each vaccination on Days 1 and 29, and as needed at interim or unscheduled visits for all women of childbearing potential. Results must be confirmed as negative prior to enrollment on Day 1 and administration of each vaccination.
  - Serology: hepatitis B surface antigen, hepatitis C virus antibody, and HIV types 1 and 2 antigen/antibody at the screening visit only.
  - Urine drug screen for drugs of abuse (components per the standard panel at the site laboratory) at the screening visit only.
  - Clinical screening laboratory evaluations (WBCs, Hgb, PLTs, ALT, AST, ALP, T. Bili, Cr, Lipase, PT, and PTT) will be collected at the screening visit.
    - Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected for clinical screening laboratory evaluations is presented in Table 8.
  - Clinical safety laboratory evaluations (WBCs, Hgb, PLTs, ALT, AST, ALP, T. Bili, Cr, and Lipase) collected immediately prior to the first vaccination will serve as the baseline (Day 1), and will be repeated on Days 8, 29 and 36.

- Clinical safety laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected for clinical safety laboratory evaluations is presented in Table 8. Inability (e.g., loss of IV access) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline clinical safety laboratory evaluations is collected.
- Blood and urine will be collected at timepoints specified in the SOA.
- Memory aid:
  - All subjects will complete a Memory Aid from the time of each vaccination through 7 days post each vaccination (Days 1-8 for the first vaccination, and Days 29-36 for the second vaccination). Memory Aids will be reviewed with the subjects for any AEs (solicited injection site and systemic reactions, as well as unsolicited AEs), SAEs and concomitant medications during telephone calls on Days 2, 3, 30, and 31 and at clinic visits on Days 8 and 36.
- Telephone call:
  - Subjects will be contacted by telephone to query for safety events. AEs that have occurred since the previous clinic visit or telephone call will be solicited. Based on the information collected, subjects may be asked to return to the clinic for evaluation.
- Leukapheresis (only for those subjects consented for leukapheresis):
  - To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled in cohorts 2, 3, 5, 10, and 11 may undergo leukapheresis to collect additional samples for secondary research. If enrollment in cohort 6 proceeds, a subset of subjects in this cohort may also undergo leukapheresis.
  - Leukapheresis is an outpatient procedure during which leukocytes will be selectively harvested; red cells and other blood components will be returned to the subject. In a typical leukapheresis procedure, approximately  $1-3 \times 10^9$  cells can be isolated with only minimal loss of red blood cells. No sedation is required. The procedure will be done by trained site staff and will be done using devices and procedures that conform to standard guidelines and SOPs.
  - For those subjects consented for leukapheresis, screening procedures, including screening laboratory evaluations, will be performed locally prior to the leukapheresis procedure.
  - Refer to the protocol-specific MOP for details on the leukapheresis procedure.

**Table 8: Venipuncture Volumes**

	Screening Visit 00, Day -42 to -1	Enrollment/Baseline Visit 01, Day 1	Visit 02, Day 2 1 day post Dose 1	Visit 03, Day 3 2 days post Dose 1	Visit 04 Day 8 +/- 1 day	Visit 05 Day 15 +/- 2 days	Visit 06 Day 29 +/- 2 days	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09 <sup>4</sup> Day 36 +/- 1 day	Visit 10 <sup>4</sup> Day 43 +/- 2 days	Visit 11 <sup>4</sup> Day 57 +/- 2 days	Visit 11A <sup>1</sup> Day 71 -7/+ 21 days	Visit 12 <sup>4</sup> Day 119 +/- 7 days	Visit 13 <sup>4</sup> Day 209 +/- 7 days	Final Study Visit 14 <sup>4,5</sup> Day 394 +/- 14 days	Early Termination Visit	Total Volume of Blood Drawn (mL)	
<b>Procedures</b>		X					X												
Vaccination		X					X												
Clinical Laboratory Evaluations <sup>1</sup>	28	8			8		8			8								60	
Serum for Serological Immunogenicity Assays <sup>1</sup>		16				16	16			16	16	16		16	16	16	16	16 <sup>2</sup>	144
PBMCs for Cellular Immunology Assays		80				40	16			16	40	16		40	40			16 <sup>2</sup> or 40 <sup>2</sup>	288
Serum for Secondary Research		16				8	8			8	8	8		8	8	8	8	8 <sup>2</sup>	80
Serum for Product Assay Development		16				8	8			8	8	8		8	8	8	8	8 <sup>2</sup>	80
Leukocytes for Secondary Research (subset of subjects)													62 <sup>3</sup>						
<b>Per Visit Blood Volume Total (mL)</b>	28	136			8	72	56			56	72	48		72	72	32	-	652	
<b>Cumulative Blood Volume (mL) (prior 56 days)</b>		164			172	244	300			356	428	312		72	72	32			
<b>Running Blood Volume Total (mL)</b>	28	164			172	244	300			356	428	476		548	620	652	-		

<sup>1</sup> Inability (e.g., loss of IV access) to collect all baseline samples on Day 1 will not exclude the subject from further participation in this study as long as a minimum of baseline clinical safety laboratory evaluations and serum for serological immunogenicity assays are collected.

<sup>2</sup> These blood volumes are not included in the blood volume totals. Blood volume depends upon day of early termination visit.

<sup>3</sup> Only for those subjects consented for leukapheresis. These blood volumes are not included in the blood volume totals.

<sup>4</sup> Visits 09-14 windows should be based off the actual Visit 06 date.

<sup>5</sup> Subjects who participate in the optional third mRNA-1273 vaccination substudy will exit the Schedule of Activities for the main study between Visit 13 and the close of the window for Visit 14 and will not have Visit 14, instead will have Visit 14A and subsequent substudy visits. See [Section 12](#), [Appendix A](#) for the Schedule of Activities for the optional third mRNA-1273 vaccination substudy.



### **8.2.1 Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings**

If a physiologic parameter, e.g., vital signs, or clinical laboratory value, is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the participating site PI or appropriate sub-investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or “white coat syndrome”) or other source of error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

All abnormal clinical findings or abnormal clinical laboratory tests values that occur post vaccination will be considered AEs.

## **8.3 Adverse Events and Serious Adverse Events**

### **8.3.1 Definition of Adverse Event (AE)**

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding), symptom or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

AEs can be further divided into solicited AEs and unsolicited AEs. Solicited AEs are those for which the study team will specifically query the subject whether they occurred. Unsolicited AEs are those events that the subject report occurring without being queried about the specific event.

All AEs will be assessed for severity and relationship to study intervention ([Section 8.3.3](#)). Reporting of all AEs, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the second vaccination. After Day 57 through the end of study on Day 394, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.

All AEs, solicited and unsolicited, will be captured on the appropriate DCF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator), date of resolution, seriousness, and outcome. AEs occurring during the study-collection and reporting period will be documented appropriately regardless of relationship.

AEs will be followed to resolution or stabilization.

#### **8.3.1.1 Solicited Adverse Events**

Solicited AEs are anticipated local and systemic AEs for which consistent collection of information is desired. Study clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days.

Solicited AEs (i.e., reactogenicity) will be collected using a memory aid and recorded on the appropriate DCF from the time of each vaccination through 7 days post each vaccination (Days 1-8 for the first vaccination, and Days 29-36 for the second vaccination).

For this study, solicited AEs will be:

- Injection site Pain
- Injection site Erythema
- Injection site Edema/Induration
- Headache
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Fever
- Chills

#### **8.3.1.2 Unsolicited Adverse Events**

All AEs spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination or other diagnostic procedures must be recorded on the appropriate DCF.

Unsolicited AEs of all severities will be reported from the time of study product administration through Day 57.

After Day 57, only SAEs (as detailed in [Section 8.3.2](#)), Protocol Specified AESIs, MAAEs, and NOCMCs will be reported through the end of the study (Day 394).

#### **8.3.1.3 Possible Adverse Events Associated with Leukapheresis**

For those subjects consented for leukapheresis, the possible adverse events associated with the leukapheresis procedure are:

- Site of needle placement: pain, bruising and discomfort in the arms.
- Vasovagal episodes, characterized by transient hypotension, dizziness, nausea, and rarely syncope.
- Temporary decrease (1-2 days) in red blood cell count.
- Blood loss secondary to machine malfunction.
- Toxicity-associated anticoagulant resulting in a sour taste in the mouth, mild muscle cramps and/or tingling sensation around the mouth, feet or hands.

The risks of the leukapheresis procedure are minimal and are generally confined to the period of the actual study visit itself. In this protocol, AEs that are non-serious will not be routinely recorded in the study database.

Only SAEs that occur during or within 24 hours after the leukapheresis study visit will be recorded in the study database.

#### **8.3.1.4 Special Reporting of Adverse Events**

Not Applicable

#### **8.3.2 Definition of Serious Adverse Event (SAE)**

An SAE is defined in 21 CFR 312.32 as follows: “An AE or suspected adverse reaction is considered serious if, in the view of either the participating site PI or appropriate sub-investigator or the sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening AE,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

“Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered an SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the appropriate SAE DCF.

All SAEs will be followed through resolution or stabilization by a study clinician, licensed to make medical diagnoses and listed on the Form FDA 1572 as the participating site PI or appropriate sub-investigator.

All SAEs will be reviewed and evaluated by DMID and will be sent to the SMC (for periodic review unless related) and IRB/IEC.

#### **8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)**

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator’s Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

#### **8.3.4 Classification of an Adverse Event**

The determination of seriousness, severity and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs and classify AEs based upon medical judgment. This includes, but is not limited to, physicians, physician assistants and nurse practitioners.

#### **8.3.4.1 Severity of Adverse Events**

All AEs or SAEs will be assessed for severity, according to the toxicity grading scales in the FDA “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”.

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject’s usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate DCF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

#### **8.3.4.2 Relationship to Study Intervention**

For each reported adverse reaction, the participating site PI or qualified designee must assess the relationship of the event to the study product using the following guidelines:

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

#### **8.3.5 Time Period and Frequency for Event Assessment and Follow-Up**

For this study:

- solicited AEs will be collected from Days 1-8 (7 days post first vaccination) and Days 29-36 (7 days post second vaccination).
- unsolicited AEs will be collected from Days 1-57.

- SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from Day 1 through the end of the study (Day 394).

### **8.3.6 Adverse Event Reporting**

#### **8.3.6.1 Investigators Reporting of AEs**

Information on all AEs should be recorded on the appropriate DCF. All clearly related signs, symptoms and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a clinical laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual clinical laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

### **8.3.7 Serious Adverse Event Reporting**

#### **8.3.7.1 Investigators Reporting of SAEs**

Any AE that meets a protocol-defined criterion as an SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group  
Clinical Research Operations and Management Support (CROMS)  
6500 Rock Spring Dr. Suite 650  
Bethesda, MD 20817, USA  
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)  
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)  
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the SDCC system. Refer to the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the participating site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the participating site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

#### **8.3.7.2 Regulatory Reporting of SAEs**

Following notification from the participating site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any SUSAR in an IND safety report to the FDA and will notify all participating site PIs (i.e., all PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the

sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

### **8.3.8 Reporting Events to Subjects**

Subjects will be informed of any AEs or SAEs that occur as part of their participation in this trial.

### **8.3.9 Adverse Events of Special Interest (AESIs)**

Adverse Events of Special Interest (AESIs) represent any events for which additional data (besides the standard AE data) are desired. These may be at the request of the regulatory agency, industry partner or DMID, and driven by a regulatory requirement, or known or potential risk from the product or class. Non-structured data similar to SAEs will be collected for AESIs. AESIs encompass the following terms:

- Protocol Specified AESIs:
  - All suspected cases of myocarditis or pericarditis should be recorded. For reporting purposes, a subject who displays signs/symptoms consistent with myocarditis or pericarditis should be reported as a potential case of myocarditis or pericarditis.
- NOCMCs – defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.
- MAAEs – defined as hospitalization, an emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason.

All AESIs are assessed, recorded, and followed as described above under AEs. AESIs that meet SAE criteria will be reported on an SAE form within 24 hours to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group  
Clinical Research Operations and Management Support (CROMS)  
6500 Rock Spring Dr. Suite 650  
Bethesda, MD 20817, USA  
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)  
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)  
SAE Email Address: [PVG@dmidcroms.com](mailto:PVG@dmidcroms.com)

In addition, for documentation and medical assessment purposes AESIs that do not meet SAE criteria will also be reported on an SAE form within the period for AE reporting to the DMID Pharmacovigilance Group; however, the narrative will indicate that the AESI did not meet SAE criteria.

### **8.3.10 Reporting of Pregnancy**

Pregnancy is not an AE. However, any pregnancy that occurs during study participation (through Day 394) should be reported to the sponsor on the appropriate DCF. Pregnancy should be followed to outcome.

## **8.4 Unanticipated Problems**

### **8.4.1 Definition of Unanticipated Problems (UPs)**

The Department of Health and Human Services (DHHS) OHRP considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### **8.4.2 Unanticipated Problem Reporting**

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the SDCC/study sponsor within 24 hours of the participating site PI or appropriate sub-investigator becoming aware of the event per the above described SAE reporting process.
- UPs that are SAEs will be collected from Day 1 through the end of the study (Day 394).
- Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the participating site PI or appropriate sub-investigator becoming aware of the problem.
- UPs that are not SAEs will be collected from Days 1-57.

### **8.4.3 Reporting Unanticipated Problems to Subjects**

Subjects will be informed of any UPs that occur as part of their participation in this trial.

## 9. STATISTICAL CONSIDERATIONS

### 9.1 Statistical Hypotheses

This is a phase I, open-label, dose-ranging clinical trial and is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of mRNA-1273.

### 9.2 Sample Size Determination

Rare AEs are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs given various true event rates are presented in [Table 9](#). With the assumption that all enrolled subjects will likely complete immunizations and safety visits in this relatively short duration study, the following statistical considerations apply. With 15 subjects in each dose group (cohorts 1-3,10,13), the chance of observing at least one AE of probability 20% or more is approximately 97%. Therefore, if no AEs of a given type occur in a dose group (cohorts 1-3,10,13), we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With 60 subjects across these four dosing cohorts (1-3,10), the chance of observing at least one AE of probability 5% or more is at least 95%. Therefore, if no AEs of a given type occur across the combined doses, we can be very confident that any dosage-independent event will occur in fewer than 5% of people once the vaccine is implemented. If Cohort 13 is enrolled and there are 75 subjects across five dosing cohorts (1-3,10,13), the chance of observing at least one AE of probability 5% or more is at least 97.9%. Therefore, if no AEs of a given type occur across the combined doses, we can be very confident that any dosage-independent event will occur in fewer than 5% of people once the vaccine is implemented. With 10 subjects in each dose group (cohorts 4-9,11-12), the chance of observing at least one AE of probability 20% or more is approximately 89.3%. Therefore, if no AEs of a given type occur in a dose group (cohorts 4-9,11-12), we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented in the older population. With 30 subjects across each of the two older subject dosing cohorts (i.e., cohorts 4,5,11 and 7,8,12), the chance of observing at least one AE of probability 5% or more is at least 78.5%. Therefore, if no AEs of a given type occur across the combined doses, we can be very confident that any dosage-independent event will occur in fewer than 5% of older people once the vaccine is implemented. If Cohorts 6 and 9 are enrolled and there are 40 subjects across each of the two older subject dosing cohorts (i.e., cohorts 4,5,6,11 and 7,8,9,12), the chance of observing at least one AE of probability 5% or more is at least 87.1%. Therefore, if no AEs of a given type occur across the combined doses, we can be very confident that any dosage-independent event will occur in fewer than 5% of older people once the vaccine is implemented.

**Table 9: Probability of Observing an Adverse Event for Various Event Rates**

N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)
15	0.1%	1.5	60	0.1%	5.8	75	0.1%	7.2
	0.5%	7.2		0.5%	26.0		0.5%	31.3
	1.0%	14.0		1.0%	45.3		1.0%	52.9



N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)
	2.0%	26.1		2.0%	70.2		2.0%	78.0
	3.0%	36.7		3.0%	83.9		3.0%	89.8
	4.0%	45.8		4.0%	91.4		4.0%	95.3
	5.0%	53.7		5.0%	95.4		5.0%	97.9
	10.0%	79.4		10.0%	99.8		10.0%	>99.9
	15.0%	91.3		15.0%	>99.9		15.0%	>99.9
	20.0%	96.5		20.0%	>99.9		20.0%	>99.9
N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)	N	“True” Event Rate	Probability of Observation (%)
10	0.1%	1.0	30	0.1%	3.0	40	0.1%	3.9
	0.5%	4.9		0.5%	14.0		0.5%	18.2
	1.0%	9.6		1.0%	26.0		1.0%	33.1
	2.0%	18.3		2.0%	45.5		2.0%	55.4
	3.0%	26.3		3.0%	59.9		3.0%	70.4
	4.0%	33.5		4.0%	70.6		4.0%	80.5
	5.0%	40.1		5.0%	78.5		5.0%	87.1
	10.0%	65.1		10.0%	95.8		10.0%	98.5
	15.0%	80.3		15.0%	99.2		15.0%	99.8
	20.0%	89.3		20.0%	99.9		20.0%	>99.9

### 9.3 Populations for Analyses

The Safety Analysis population for the main study includes all subjects who received one dose of vaccine. Analyses for the primary safety population will include safety reported through the end of the main study. A modified primary safety population analysis will also be performed that excludes safety data collected after subjects receive either the third mRNA-1273 vaccination in the optional substudy or non-study EUA vaccine, if applicable.

The modified intent-to-treat (mITT) population includes all subjects who received one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood samples for immunogenicity testing for which valid results were reported.

In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The per protocol (PP) population will then be defined – and this includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent for the protocol deviations that are considered to affect the science.

- Data from any visit that occurs substantially out of window.

## 9.4 Statistical Analyses

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

The final analysis will be performed after the final data lock (through Day 394) and clinical study report (CSR) completed when all primary safety endpoint data and all secondary immunogenicity endpoint data are available and received by the SDCC. Any available data from the exploratory immunogenicity endpoints may also be included in the CSR. Remaining exploratory immunogenicity endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report(s). Abbreviated analysis plans that describe planned analyses to facilitate dissemination of study data for public health reasons, including manuscript publication(s), will be developed by the SDCC. A full statistical analysis plan (SAP) will be developed by the SDCC and finalized prior to the primary data lock.

### 9.4.1 General Approach

Unless otherwise noted in the SAP, continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

### 9.4.2 Analysis of the Primary Endpoint(s)

[Section 9.4.4](#) describes the analyses of Safety which is the primary endpoint of this protocol.

### 9.4.3 Analysis of the Secondary Endpoint(s)

Summaries and analysis of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a per-protocol (PP) analysis may also be performed.

Seroconversion is defined as a 4-fold increase in antibody titer over baseline.

Seroconversion rates, GMFR and GMT for SARS-CoV-2 as measured by IgG ELISA will be calculated at Days 1 (GMT only) and 57 by cohort and will be summarized graphically. Seroconversion rates, GMFR and GMT will be presented with their corresponding 95% confidence interval (CI) estimates at each timepoint and overall peak GMT, and the pair-wise differences between seroconversion rates by cohort will be summarized by study day along with 95% CIs.

### 9.4.4 Safety Analyses

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Solicited AEs will be summarized by severity for each day post vaccination (Days 1-8) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence

intervals (CI), to summarize the proportion of subjects reporting each symptom, any application site symptom, and any systemic symptom.

Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after the second vaccination. Unsolicited AEs will be coded by MedDRA for preferred term and system organ class (SOC). SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first vaccination through the end of the study (Day 394). The numbers of SAEs and MAAEs will be reported by detailed listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

Clinical laboratory data will be summarized by severity for each visit, and as the maximum over all post-vaccination visits. Graphical presentations may include box plots and shift plots.

#### **9.4.5 Baseline Descriptive Statistics**

Summaries of demographic variables such as age, sex, ethnicity, and race will be presented by cohort and overall. Summaries of baseline clinical laboratory values will be presented by cohort and overall.

#### **9.4.6 Planned Interim and Early Analyses**

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community. Early analyses will include safety and immunogenicity as described in [Sections 9.4.6.1, 9.4.6.2 and 9.4.6.3](#). Further, the protocol team will review data periodically to confirm no halting criteria have been met as described in [Section 10.1.6.1](#).

Cumulative safety information, study status, and primary endpoint results may be published, presented at a public forum, or presented as summaries aggregated by study arm at the discretion of the sponsor while the main study is ongoing. Any ad-hoc analyses, jointly developed by the SDCC and/or the VRC, other participating laboratories and ModernaTX, Inc., will be executed by the SDCC as needed. None of the interim analyses will include any formal statistical hypothesis testing; therefore, p value adjustment will not be made to any analyses.

##### **9.4.6.1 Interim Safety Analyses**

Given the need for rapid review and dissemination of study data for public health reasons, AEs and SAEs may be reviewed as necessary outside of SMC reviews. The SMC will not need to meet (unless halting rules are met), and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

The SMC will review cumulative AE data after all subjects in cohorts 1 and 2 have completed Day 8. In addition, cumulative AE data will be provided to the SMC after all subjects in cohorts 3, 4, 5, 7, and 8 have completed Day 8. Cumulative AE data will also be provided to the SMC after all subjects in all cohorts have completed Day 57. Documentation of review and any concerns noted will be solicited electronically.

#### **9.4.6.2 Interim Immunogenicity Review**

For public health reasons there will be several immunogenicity reviews. The following reviews are anticipated once data are available:

- Sentinel subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- Sentinel subjects in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohorts 4, 5, 7 and 8, ELISA IgG data through Day 29;
- All subjects in cohorts 10-12, ELISA IgG data through Day 29;
- All subjects in cohort 13, ELISA IgG data through Day 29 (if cohort is enrolled);
- All subjects in cohorts 6 and 9, ELISA IgG data through Day 29 (if cohorts are enrolled);
- Sentinel subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinel subjects in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohorts 4, 5, 7 and 8, ELISA IgG data through Day 57;
- All subjects in cohorts 10-12, ELISA IgG data through Day 57;
- All subjects in cohort 13, ELISA IgG data through Day 57 (if cohort is enrolled)
- All subjects in cohorts 6 and 9, ELISA IgG data through Day 57 (if cohorts are enrolled).
- Additional data review of immunogenicity may be performed to inform public health decisions.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

#### **9.4.6.3 Interim Immunogenicity and Safety Review**

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

#### **9.4.7 Sub-Group Analyses**

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

#### **9.4.8 Tabulation of Individual Subject Data**

In general, all data will be listed, sorted by cohort and subject, and when appropriate by visit number within subject.

### **9.4.9 Exploratory Analyses**

Summaries and analysis of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

Seroconversion is defined as a 4-fold increase in antibody titer over baseline.

Seroconversion rates, GMFR and GMT for SARS-CoV-2 as measured by IgG, IgA and IgM ELISA, neutralization assay using SARS-CoV-2 pseudovirus and neutralization assay using a live wild-type SARS-CoV-2 will be calculated for specified timepoints by cohort and will be summarized graphically. Seroconversion rates, GMFR and GMT will be presented with their corresponding 95% CI estimates at each timepoint and overall peak GMT, and the pair-wise differences between seroconversion rates by cohort will be summarized by study day along with 95% CI.

Summaries and analysis of cellular assay data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

The magnitude, phenotype and percentage of cytokine producing S protein-specific T cells will be summarized at each timepoint by vaccination group.

## **10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **10.1 Regulatory, Ethical, and Study Oversight Considerations**

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Subjects), and the ICH E6(R2).

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment materials, and handouts or surveys intended for the subjects, prior to the recruitment, screening and enrollment of subjects. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable.

Each institution engaged in this research will hold an OHRP-approved FWA.

Any amendments to the protocol or informed consent documents will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The participating site PI will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

DMID must receive the documentation that verifies IRB approval for this protocol, informed consent documents and associated documents, prior to the recruitment, screening and enrollment of subjects, and any IRB approvals for continuing review or amendments as required by the DMID.

#### **10.1.1 Informed Consent Process**

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed. The participating site PI or other study staff may obtain oral or written information for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject if the process is approved by the IRB.

At the first study visit, informed consent will be obtained and documented before any study procedures are performed. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, risks and discomforts, the expected duration of the subject's participation in the trial, any expected benefits to the subject, and alternative treatments and procedures that may be available to the subject. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the participating site PI) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled. Subjects will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed, even if identifiers are removed, that information collected from this research and/or specimens may be used for secondary research, including the sharing of deidentified data.

Subjects will be informed that the monitor(s), auditor(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.

New information will be communicated by the participating site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

#### **10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)**

Not Applicable

#### **10.1.1.2 Other Informed Consent Procedures**

The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times. The consent process, including relevant language in the ICF, will provide an explanation of the potential risks to the individual study subjects and their families. Clinical metadata, genomic, or other datasets or a subset of the clinical and other metadata that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified.

Subjects will be asked for consent to collect additional blood, the use of residual specimens, and the sharing of genetic information and samples for secondary research. This extra/residual blood and corresponding serum, plasma and PBMCs will be used as back-up specimens for PP defined assays or designated for secondary research use and stored indefinitely at a designated storage facility.

Subjects will be asked to consent specifically to genetic testing, including DNA sequencing. DNA sequencing data will be kept private. DNA data may be used to produce commercial antibody-based therapeutics. Subjects will not share in profits or commercial rights to those products.

To support development of diagnostics, therapeutics and vaccines, a subset of subjects enrolled in cohorts 2, 3, 5, 10, and 11, and possibly cohort 6, if enrolled, will also be asked to consent for leukapheresis to collect additional samples for secondary research, which will be stored indefinitely at a designated storage facility.

If subjects choose not to provide permission for extra blood and secondary research use, they will not be eligible for enrollment into the study. However, consent for leukapheresis is not required for study participation.

Collection of extra/residual samples during the course of the study will help facilitate rapid follow-on analyses, if warranted, to provide more comprehensive scientific insights into the impact (safety and immunological) of the vaccine on the host response to vaccination. To maintain statistical power in follow-on analyses it is important that extra blood collection and secondary research use be included in as many subjects as possible, due to the limited sample size per treatment arm, with the exception of leukapheresis.

The stored samples will be labeled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed, however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples designated for secondary research use may be used for additional immunological assessments that may include but are not limited to antibody epitope mapping, B and T cell repertoire determination, non-traditional immune assay development, determination of innate immune factors and the ability of vaccine-induced antibodies to cross-react to different proteins and virus strains. These blood samples might be used in new or different immunological laboratory tests, to provide information for the development of new vaccines or therapeutics, or for the studies of nCoV or other infections. Secondary research using DNA may also be warranted to understand genetic factors involved in vaccination failures.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from the secondary research. No results from secondary research will be entered into the subject's medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Risks are associated with the additional volume of blood collected, such as anemia. Risks for loss of privacy and confidentiality are described below.

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the participating site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples. Subjects who withdraw consent before the last visit will not have the extra blood drawn for secondary use.

### **Human Genetic Testing**

The research staff will seek the subjects' consent for extra and residual specimens to be stored and used for secondary research, including genetic research, evaluating human genomic and phenotypic markers. The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times.

The consent process will include an explanation of the potential risks to the individual subjects and their families associated with data submitted to an NIH data repository and subsequent sharing. Data that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified. The consent will include whether individual subject data will be shared through a NIH controlled access data repository. Data for genomic or phenotypic research will be submitted to a controlled access data repository, therefore, informed consent permitting the data sharing must be documented, even if the specimens are de-identified.

#### **10.1.2 Study Termination and Closure**

In [Section 7](#), Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including, but not limited to:



- Determination of unexpected, significant, or unacceptable risk to subjects
- Results of interim analysis
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities

If the study is prematurely terminated, the PI will promptly inform study subjects and the IRB as applicable. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. The PI will assure appropriate follow-up for the subjects, as necessary.

The sponsor will notify regulatory authorities as applicable.

### **10.1.3 Confidentiality and Privacy**

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples and genetic tests, and all other information generated during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the participating site PI, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating site will permit access to such records.

All source records, including electronic data, will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the participating site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the participating site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize subjects, their families, or groups. In addition, there may be unknown risks.

As this research is funded by the NIH, it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality (COC). By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA.

A COC does not prevent subjects from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The COC does not prevent the researchers from reporting, without the subject's consent, information that would identify the subject as a subject in the research project in the case of matters that must be legally reported, including child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or that the release is in compliance with applicable Federal regulations governing the protection of human subjects in research.

#### **10.1.4 Secondary Use of Stored Specimens and Data**

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other "primary" or "initial" activity, such as the data and samples collected in this protocol. This section will detail the samples and data available for secondary research. Any use of the sample or data, however, will be presented in a separate protocol and require separate IRB approval.

##### **10.1.4.1 Samples for Secondary Research**

The following types of samples will be stored and used for secondary research:

- Residual Research Sample: Any leftover Primary Research Sample after the laboratory testing specified in this protocol is completed will be stored for future studies with the subject's consent.
- Repository Research Sample: Samples will be collected with the subject's consent in this protocol with the intent to store for additional research (i.e., samples collected beyond those needed for primary research) and will be used in future studies. Amendments to this protocol with additional assays may use repository research samples.

Samples will be stored indefinitely at a DMID-designated storage facility. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur, however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

Residual/Repository Research Samples, upon written request and approval from DMID and any approvals required by the site or network, may be shared for secondary research with investigators at the participating site, with researchers at other Infectious Disease Clinical Research Consortium (IDCRC) sites or other institutions, or company-designated research

laboratories. The samples will not be sold or used directly for production of any commercial product. DMID will authorize shipment from the DMID CMS.

Reports from secondary research will not be kept in the subjects' health records or shared with subjects, unless required by law. Reports will not be sent to the specimen repository.

The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. To participate in this study, subjects must consent for storage of samples for secondary use. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

#### **10.1.4.2 Data Sharing for Secondary Research**

Data from this study may be used for secondary research. All of the individual subject data collected during this study will be made available after de-identification. The SAP and Analytic Code will also be made available. Data will be available immediately following publication, with no end date. Upon written request, with provision of a methodologically sound proposal, and approval from DMID and any approvals required by the site or network, data may be shared for secondary research with investigators/researchers. The data will be available for only the purpose outlined in the approved proposal.

For access to genomic data in the NIH designated controlled access database, an investigator (or data requestor) must submit a Data Access Request which certifies adherence to the NIH Security Best Practices for Controlled-Access data subject to the NIH Genomic Data Sharing (GDS) Policy.

The participating site PI may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved.

#### **10.1.5 Key Roles and Study Governance**

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating site (PI), DMID (sponsor), VRC, and ModernaTX, Inc. Key Roles are noted in the protocol-specific MOP.

#### **10.1.6 Safety Oversight**

##### **10.1.6.1 Protocol Team Oversight**

The protocol team will meet at the following timepoints to review AE data and to ensure no halting rules have been met:

- after the four 25 mcg (cohort 1) and the four 100 mcg (cohort 2) sentinel subjects have completed Day 5.
- after the full cohorts 1 and 2 have completed Day 8.
- after the four 250 mcg (cohort 3) sentinel subjects have completed Day 5.
- after the full cohorts 1 and 2 have completed Day 29 (prior to beginning Dose 2 vaccinations in cohort 3).
- after the full cohort 3 has completed Day 8.

- after the full cohorts 4 and 5 have completed Day 8.
- after the full cohorts 7 and 8 have completed Day 8.
- after the full cohort 6, if enrolled, has completed Day 8.

#### **10.1.6.2 Safety Monitoring Committee (SMC)**

The SMC is an independent group of at least 2-3 experts that monitors subject safety and advises DMID. SMC members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

The SMC will hold an organizational meeting prior to enrollment. At this meeting, the SMC will review the charter, protocol, ICF, IB, and safety report templates.

Given the frequency and urgency to review data, the SMC will not need to meet (unless halting rules are met), and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

The SMC will review cumulative AE data after all subjects in cohorts 1 and 2 have completed Day 8. In addition, cumulative AE data will be provided to the SMC after all subjects in cohorts 3, 4, 5, 7, and 8 have completed Day 8. Cumulative AE data will also be provided to the SMC after all subjects in all cohorts have completed Day 57. Documentation of review and any concerns noted will be solicited electronically.

The SMC does not need to meet for dose escalation to 250 mcg (cohorts 3, 6 and 9) or for initiation of the optional third mRNA-1273 vaccination substudy.

The SMC will meet when trial or optional third mRNA-1273 vaccination substudy halting criteria are met, or as requested by the sponsor or PI.

Ad hoc reviews will occur when trial halting criteria are met, or as requested by the sponsor or PI.

The SMC will have a final review meeting at the end of the trial, defined as the end of the optional third mRNA-1273 vaccination substudy.

Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the SMC charter.

Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial.

#### **10.1.7 Clinical Monitoring**

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/

amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a CMP. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, electronic case report forms (eCRFs), ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study staff and all study documentation according to the DMID-approved CMP. Study monitors will meet with all participating site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

### **10.1.8 Quality Control (QC) and Quality Assurance (QA)**

To ensure the reliability of study data, the participating site will develop a Clinical Quality Management Plan (CQMP). The CQMP will describe:

- routine internal quality control (QC) and QA activities
  - for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
  - independent of sponsor site monitoring.
- a process for addressing data quality issues (i.e., collecting, recording), and reporting findings in a timely manner); systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation and evaluation of Corrective and Preventative Action Plan (CAPA) procedures.

### **10.1.9 Data Handling and Record Keeping**

#### **10.1.9.1 Data Collection and Management Responsibilities**

Data collection is the responsibility of the study staff at the participating site under the supervision of the participating site PI. The participating site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation, including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will be entered by the participating site into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID.

#### **10.1.9.2 Study Record Retention**

Study-related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records, should be maintained for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

#### **10.1.9.3 Source Records**

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

#### **10.1.10 Protocol Deviations**

A protocol deviation is any non-compliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP or GCP requirements, or any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

The non-compliance may be either on the part of the subject, the participating site PI or the study staff. Following a deviation(s), corrective actions should be developed by the participating site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the participating site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The participating site PI and study staff are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

#### **10.1.11 Publication and Data Sharing Policy**

Analyses will be conducted as data become available while the study is ongoing at the discretion of the sponsor. Analyses of data will be available for publication to inform the scientific community. Data will be available immediately following publication, with no end date, with data sharing at the discretion of the PI. Publication of manuscripts may occur at the discretion of the sponsor in accordance with DMID's Expanded Distribution of Clinical Research Endpoint Data Policy.

#### **10.1.12 Human Data Sharing Plan**

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

#### **10.1.13 Genomic Data Sharing (GDS) Plan**

This study will comply with the NIH GDS Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), SNP arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

#### **10.1.14 Publication**

At intervals throughout the study at the discretion of the sponsor and following completion of the study, the lead PI is expected to publish the results of this research in a scientific journal. This study will adhere to the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. As such, the final peer-reviewed journal manuscripts will be accessible to the public on PubMed Central no later than 12 months after publication.

#### **10.1.15 Conflict of Interest Policy**

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to

have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 10.2 Additional Considerations

### 10.2.1 Research Related Injuries

For any potential research related injury, the participating site PI or designee will assess the subject. Study staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. As needed, referrals to appropriate health care facilities will be provided to the subject. The participating site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

If it is determined by the participating site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study staff will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the vaccine. No financial compensation will be provided to the subject by NIAID, NIH, the vaccine manufacturer, or the participating site for any injury suffered due to participation in this trial.

For this protocol, the study vaccine, mRNA-1273, manufactured by ModernaTX, Inc. is covered under the PREP Act, as described in [Section 2.1.1](#).

## 10.3 Abbreviations

**Table 10: Abbreviations**

2019-nCov	2019-novel Coronavirus
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
BP	Blood Pressure
°C	Degrees Celsius
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
CMV	Cytomegalovirus



COC	Certificate of Confidentiality
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CQMP	Clinical Quality Management Plan
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DSPC	1,2-distearoyl- <i>sn</i> -glycero-3-phosphocholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EUA	Emergency Use Authorization
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GWAS	Genome-Wide Association Studies
hDPP4	Dipeptidyl Peptidase 4
HEENT	Head, Ears, Eyes, Nose, and Throat
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HKU1	Human Coronavirus HKU1
HLA	Human Leukocyte Antigen
hMPV	Human Metapneumovirus
HR	Heart Rate
HRSA	Health Resources and Services Administration
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDCRC	Infectious Disease Clinical Research Consortium
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LNP	Lipid Nanoparticle
m	Meter
MAAE	Medically-Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mg	Milligrams
MI	Myocardial Infarction
min	Minute
mITT	Modified Intent-To-Treat
mL	Milliliter
mm Hg	Millimeter of Mercury
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Number (typically refers to subjects)
NaCl	Sodium Chloride
nCoV	Novel Coronavirus
NDA	New Drug Application
Neut	Neutralizing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	No-Observed-Adverse-Effect-Level
NOCMC	New-Onset Chronic Medical Condition
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PEG	Polyethylene Glycol
PHI	Protected Health Information
PI	Principal Investigator
PIV3	Parainfluenza Virus Type 3
PLT	Platelet
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	SARS Coronavirus
SARS-CoV-2	SARS Coronavirus 2
SDCC	Statistical and Data Coordinating Center
SDSP	Study Data Standardization Plan
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T. Bili	Total Bilirubin
Th	T helper
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
VRC	Vaccine Research Center
WBC	White Blood Cell
WHO	World Health Organization
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

## 10.4 Protocol Amendment History

**Table 11: Protocol Amendment History**

Version, Date	Section	Description of Change	Brief Rationale
2.0, March 13, 2020	Throughout	Administrative.	Advanced version and date.
	Throughout	Clarifications and modifications to resolve inconsistencies.	To address Pre-IND, IND non-hold and PI comments.
	Sect. 1.1, Page 7	Updated COVID-19 case counts.	
	Sect. 2.1, Page 14	Updated COVID-19 status.	
	Sect. 4.1, Page 22	Enrollment will occur at <u>up to three</u> <del>one</del> domestic <u>clinical research sites</u> .	Revised language to add clinical research sites.
	Sect. 1.2, Table 4 and Sect. 8.2, Table 9	Adjusted visit windows.	

Version, Date	Section	Description of Change	Brief Rationale
	Sect. 5.1, Page 26	Added Inclusion Criterion #16:  The subject must agree to refrain from donating blood or plasma during the study (outside of this study).	Moved from Exclusion Criterion #22.
	Sect. 5.2, Page 28	Revised Exclusion Criterion #21:  Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.	Increased duration from 2 weeks to 30 days from known contact.
	Sect. 5.2, Page 28	Deleted Exclusion Criterion #22:  <del>Has traveled to countries/regions with known widespread community transmission of SARS-CoV-2 (e.g., China, regions in Italy, South Korea, Iran, or other countries based on the most updated epidemiology at the time of study enrollment) within 30 days before the first vaccination.</del>	Addressed in revision to Exclusion Criterion #21.
	Sect. 5.4, Page 29	Revised lifestyle considerations.	
	Sect. 6.1.2, Page 31	Revised dosing and administration instructions.	
	Sect. 6.2.1, Page 33	Revised product destruction and storage instructions.	
	Sect. 7.1, Page 36	Revised halting and sentinel halting criteria.  Halting Criterion #5 revised: Three (3) or more subjects experience a Grade 3 AE ( <u>unsolicited systemic</u> and/or clinical laboratory abnormality), in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding, that lasted at least 48 hours after	

Version, Date	Section	Description of Change	Brief Rationale
		administration of the vaccine and is considered related to the vaccine.	
	Sect. 7.1.3, Page 37	Revised dosing and redosing criteria	
	Sect. 8.1.2, Page 42	Added research laboratory location and contact information	
	Sect. 8.2, Table 9	Adjusted blood volumes.	
	Sect. 8.3.9	Clarified AESIs reporting.	
	Sect. 2.1.1	Added PREP Act.	
3.0, March 30, 2020	Throughout	Administrative.	Advanced version and date.
	Sect. 2.1.1	Revised PREP Act language.	To address Office of General Counsel comments.
	Sect. 5.1 and 5.2	Refined eligibility criteria.	To address PI comments.
	Sect. 8.1.3	Removed previous Table 8: Testing Laboratories.	Details moved to protocol-specific MOP.
	Throughout	Included cohorts >55 years of age.	To rapidly assess clinical safety of novel vaccines in this vulnerable population as early as possible, based on currently available information and clinical experience suggesting that older adults may be at higher risk for severe illness from COVID-19.
	Throughout	Included leukapheresis for a subset of subjects.	To support development of diagnostics, therapeutics and vaccines.
4.0, May 20, 2020	Throughout	Administrative.	Advanced version and date.
	Sect. 2.1	Updated SARS-CoV-2 case counts, deaths and status.	To be current as of May 14, 2020.
	Sect. 2.1	Updated animal data.	To include additional immune response data in mice.
	Sect. 2.2.1, Risks of mRNA-1273	Included animal data.	To add non-GLP toxicity data in rats.

Version, Date	Section	Description of Change	Brief Rationale
	Sect. 2.2.1, Risks of mRNA-1273	Included preliminary safety data from this ongoing phase I clinical trial.	To advise study design changes.
	Sect. 2.2.1, Risks of mRNA-1273	Updated non SARS-CoV-2 clinical studies.	To be consistent with updated IB v2.0, 18 May 2020.
	Sect. 2.2.1, Risks of mRNA-1273	Deleted duplicate paragraph on risks.	Same text already included in this section.
	Sect. 2.2.1, Risks of mRNA-1273	Updated enhanced immunopathology data in animals.	To include immune response data in mice.
	Throughout and Sect. 4.1.	Included 10 and 50 mcg dosage cohorts and updated the number of cohorts and subjects.	To further explore dose-ranging.
	Throughout and Sect. 4.1	Revised timing and added conditions for enrollment of cohorts 6 and 9.	Based on preliminary safety data from this ongoing phase I clinical trial.
	Throughout and Sect. 4.1	Included timing and added conditions for enrollment of cohorts 10-13.	To be consistent with study design changes.
	Throughout and Sect. 4.1	Updated/included timing of early and Day 57 data reviews for cohorts, 6 and 9-13.	To be consistent with study design changes.
	Throughout and Sect. 4.1	Revised cohorts eligible for leukapheresis.	To be consistent with study design changes.
	Sect. 5	Updated estimated time from initiation of enrollment to complete enrollment in this clinical trial from approximately 12 to 16 weeks.	To compensate for the inclusion of additional cohorts.
	Sect. 5.1	Updated Inclusion Criteria for BMI and Systolic BP.	Per Letter of Amendment dated April 10, 2020.
	Sect. 5.1.1	Updated Leukapheresis Inclusion Criteria for cohorts eligible for leukapheresis.	To be consistent with study design changes.
	Sect. 5.2	Updated Exclusion Criteria for chronic kidney disease eGFR value, as well as for subjects $\geq 56$ years of age - history of	Per Letter of Amendment dated April 10, 2020.

Version, Date	Section	Description of Change	Brief Rationale
		chronic smoking, current smoking or vaping and individuals currently working with high risk of exposure to SARS-CoV-2.	
	Throughout and Sect. 6.1.2, Table 7	Updated dosing and administration to include 10 and 50 mcg dosage cohorts.	To further explore dose-ranging and be consistent with study design changes.
	Sect. 6.1.2	Added/updated the expiration time of the dosing syringe containing the prepared mRNA-1273 solution to 4 hours at room temperature for the 10 mcg dosage after the solution is drawn into the dosing syringe and 8 hours at room temperature for the 25, 50, 100, and 250 mcg dosages after the solution is drawn into the dosing syringe.	To be consistent with updated pharmacy manual.
	Sect. 6.2.1	Updated study product accountability and destruction instructions for used and unused mRNA-1273 vials, used mixing vials and mRNA-1273 cartons.	To allow for study product accountability and destruction in accordance with site-specific SOPs and with second verification as well as documentation to include a certificate of destruction or document of destruction.
	Sect. 6.2.3	Added stability of prepared 10 mcg doses – up to 4 hours at room temperature.	To be consistent with updated pharmacy manual.
	Sect. 6.3.1	Updated/added Treatment Assignment Procedures for cohorts 6 and 9-13.	To be consistent with study design changes.
	Throughout	Changed participant(s) to subject(s).	To be consistent.
	Sect. 9.2	Updated Sample Size Determination.	To be consistent with study design changes.
	Sect. 9.4.6	Added “ <u>other participating laboratories</u> ” to the list of those involved in jointly developing ad-hoc analyses.	To be consistent with current practice.

Version, Date	Section	Description of Change	Brief Rationale
	Sect. 9.4.6.1 and 10.1.6.2.	Updated Interim Safety Analyses to clarify: <u>“Cumulative AE data will also be provided to the SMC after all subjects in all cohorts have completed Day 36.”</u>	To be consistent with study design changes and current practice.
	Sect. 9.4.6.3	Updated Interim Immunogenicity and Safety Review for additional separate interim analyses through Day 57 to be conducted as needed.	To be consistent with study design changes and current practice.
	Sect.10.1.1.1.4	Updated Publication with: <u>“At intervals throughout the study at the discretion of the sponsor and...”</u>	To allow for additional publications of results in scientific journals before the completion of the study.
	Throughout and Sect. 10.3, Table 10	Updated abbreviations.	
	Sect. 11	Updated references.	
	Protocol Summary	Updated anticipated duration of entire study from 18 to 20 months (from start of screening to last subject last visit).	To compensate for the inclusion of additional cohorts.
5.0, December 4, 2020	Throughout	Administrative.	Advanced version and date.
	Protocol Summary	50 mcg dosage added.	Inadvertently not included in previous amendment.
	Protocol Summary and Sect. 3	“3” dosages changed to “5”.	Inadvertently not included in previous amendment.
	Protocol Summary, Sect. 3, 4.1, 8.1.3, 8.1.4.1, and 9.4.9	Exploratory objective, endpoints and supportive text for B cell analyses removed.	To be considered for secondary research instead of primary research.
	Sect. 6.4	Changed “entered into the electronic case report form eCRF)” to “recorded on the appropriate DCF.”	Administrative.
	Sect. 9.4, 9.4.6.2 and 9.4.6.3	Interim Immunogenicity and Safety Review revised.	To align with what was or will be done in the study.



Version, Date	Section	Description of Change	Brief Rationale
	Sect. 9.4	Summary of Statistical Analyses (interim and final analyses as well as final data lock timing) and CSR plans revised.	To align with what was or will be done in the study.
	Sect. 9.4.6.1 and 10.1.6.2	SMC meeting plan for Interim Safety Analyses revised.	To align with what was done in the study.
	Sect. 10.1.1. and 10.1.1.2	Consenting specifically to genetic testing, including DMD sequencing removed from primary research and added to secondary research.	Genetic testing will not be included as primary research. No change to ICF needed, because genetic testing is already included as secondary research and not included as primary research in the ICF.
	Sect. 10.1.6.2	Number of SMC members changed from “3” to “2-3”.	To align with what was done in the study.
	Sect. 10.1.6.2	Clarified that SMC materials will be provided electronically.	To align with what was done in the study.
	Sect. 10.1.6.2	Removed “The SMC will review blinded aggregate data in the open session of the SMC meetings.”	To align with what was done in this open-label study.
	Sect. 10.1.7	Abbreviation for electronic case reports forms added.	Administrative.
6.0, January 28, 2021	Throughout	Administrative.	Advanced version and date.
	Throughout	<u>*Cohorts 6, 9 and 13 were not enrolled.</u>	Updates to the study.
	Throughout	<del>One</del> <u>Up to one</u>	Administrative.
	Throughout	<del>last</del> <u>second</u>	Administrative.
	Throughout	<u>Based on interim immunogenicity and reactogenicity data, Cohorts 6, 9 and 13 were not enrolled.</u>	Updates to the study.
	Throughout	<u>main study</u>	Administrative.
	Protocol Summary, Study Design	Added text.	Updates to the study, including added the Optional Third mRNA-1273 Vaccination SubStudy.

Version, Date	Section	Description of Change	Brief Rationale
	Protocol Summary, Study Duration	<u>The duration of the optional third mRNA-1273 vaccination substudy is anticipated to be 12 months from the last subject vaccinated with the third mRNA-1273 vaccination.</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Protocol Summary, Subject Duration	<u>The duration for each individual subject in the optional third mRNA-1273 vaccination substudy is approximately 26 months (from first contact to last visit).</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Protocol Summary, Safety	<u>See Section 12, Appendix A for halting rules for the optional third mRNA-1273 vaccination substudy.</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Protocol Summary, Safety	<u>The SMC does not need to meet for dose escalation or for initiation of the optional third mRNA-1273 vaccination substudy.</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Sect. 1.2, Table 4	<u>g) Subjects who participate in the optional third mRNA-1273 vaccination substudy will exit the Schedule of Activities for the main study between Visit 13 and the close of the window for Visit 14 and will not have Visit 14, instead will have Visit 14A and subsequent substudy visits. See Section 12, Appendix A for the Schedule of Activities for the optional third mRNA-1273 vaccination substudy.</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Sect. 2.2.1, Risks of mRNA-1273	Added and deleted text.	Updates to the study and added new information.
	Sect. 2.2.2	<u>As outlined in Section 12.2, data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE) suggests 94.1% efficacy of the vaccine when administered at 100 mcg</u>	Updates to the study and added new information.

Version, Date	Section	Description of Change	Brief Rationale
		<u>versus placebo against SARS-CoV-2 infection when assessed on November 25, 2020 (Baden LR et al, 2020). The efficacy of other doses of mRNA-1273 (e.g., 25, 50, or 250 mcg) is not known. Although declines in binding and neutralizing antibodies are observed over time, 100 mcg of mRNA-1273 has the potential to provide durable humoral immunity (Widge AT et al, 2020).</u>	
	Sect. 4.4	Added new section.	Optional Third mRNA-1273 Vaccination SubStudy.
	Sect. 8.2, Table 8	<u><sup>5</sup> Subjects who participate in the optional third mRNA-1273 vaccination substudy will exit the Schedule of Activities for the main study between Visit 13 and the close of the window for Visit 14 and will not have Visit 14, instead will have Visit 14A and subsequent substudy visits. See Section 12, Appendix A for the Schedule of Activities for the optional third mRNA-1273 vaccination substudy.</u>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Sect. 9.3	<u>The Safety Analysis population for the main study includes all subjects who received one dose of vaccine. Analyses for the primary safety population will include safety reported through the end of the main study. A modified primary safety population analysis will also be performed that excludes safety data collected after subjects receive either the third mRNA-1273 vaccination in the optional substudy or non-study EUA vaccine, if applicable.</u>	Updated for main study and substudy.

Version, Date	Section	Description of Change	Brief Rationale
	Sect. 10.1.6.2	<p>The SMC does not need to meet for dose escalation to 250 mcg (cohorts 3, 6 and 9) <u>or for initiation of the optional third mRNA-1273 vaccination substudy.</u></p> <p>The SMC will meet when trial <u>or optional third mRNA-1273 vaccination substudy halting criteria are met, or as requested by the sponsor or PI.</u></p> <p><u>Ad hoc reviews will occur when trial halting criteria are met, or as requested by the sponsor or PI.</u></p> <p>The SMC will have a final review meeting at the end of the <u>study trial, defined as the end of the optional third mRNA-1273 vaccination substudy.</u></p>	Added the Optional Third mRNA-1273 Vaccination SubStudy.
	Sect. 10.3, Table 10	Abbreviations for emergency use authorization (EUA) and polyethylene glycol (PEG) added.	Administrative.
	Sect. 11	Added references.	Updates to the study.
	Sect. 12, Appendix A	Added new section.	Optional Third mRNA-1273 Vaccination SubStudy.
7.0, July 30, 2021	Throughout	Administrative.	Advanced version and date.
	Throughout	Added protocol specified adverse events of special interest (AESIs).	Myocarditis and pericarditis classified as protocol specified AESIs to address Manufacturer surveillance request..
	Protocol Summary, Safety	<del>Deleted: See Section 12, Appendix A for halting rules for the optional third mRNA-1273 vaccination substudy.</del>	No special halting rules for the Optional Third mRNA-1273 Vaccination Substudy.
	Sect. 2.2.1	Myocarditis and pericarditis added to the risks of mRNA-1273.	Per updated Moderna COVID-19 EUA Vaccine Fact Sheet.

## 11. REFERENCES

1. Anderson, E. J., Roupshael, N. G., Widge, A. T., Jackson, L. A., Roberts, P. C., Makhene, M., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Corbett, K. S., Swanson, P. A., 2nd, Padilla, M., Neuzil, K. M., ... mRNA-1273 Study Group (2020). Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *The New England Journal of Medicine*, 383(25), 2427–2438. <https://doi.org/10.1056/NEJMoa2028436>.
2. Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Roupshael, N., Creech, C. B., McGettigan, J., Kehtan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., ... COVE Study Group (2020). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *The New England Journal of Medicine*, 10.1056/NEJMoa2035389. Advance online publication. <https://doi.org/10.1056/NEJMoa2035389>.
3. Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Paredes, R., Sweeney, D. A., Short, W. R., Touloumi, G., ... ACTT-1 Study Group Members (2020). Remdesivir for the Treatment of Covid-19 - Final Report. *The New England Journal of Medicine*, 383(19), 1813–1826. <https://doi.org/10.1056/NEJMoa2007764>.
4. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*. Jan 24. pii: S0140-6736(20)30154-9. doi: 10.1016/S0140-6736(20)30154-9.
5. Chen, P., Nirula, A., Heller, B., Gottlieb, R. L., Boscia, J., Morris, J., Huhn, G., Cardona, J., Mocherla, B., Stosor, V., Shawa, I., Adams, A. C., Van Naarden, J., Custer, K. L., Shen, L., Durante, M., Oakley, G., Schade, A. E., Sabo, J., Patel, D. R., ... BLAZE-1 Investigators (2020). SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *The New England Journal of Medicine*, NEJMoa2029849. Advance online publication. <https://doi.org/10.1056/NEJMoa2029849>.
6. Chen, Yingzhu, Shuai Lu, Hao Jia, Yao Deng, Jianfang Zhou, Baoying Huang, Yueyang Yu, Jiaming Lan, Wenling Wang, Yongliang Lou, Kun Qin, and Wenjie Tan. 2017. 'A novel neutralizing monoclonal antibody targeting the N-terminal domain of the MERS-CoV spike protein', *Emerging Microbes & Infections*, 6: e37.
7. Corbett, K. S., Edwards, D. K., Leist, S. R., Abiona, O. M., Boyoglu-Barnum, S., Gillespie, R. A., Himansu, S., Schäfer, A., Ziwawo, C. T., DiPiazza, A. T., Dinno, K. H., Elbashir, S. M., Shaw, C. A., Woods, A., Fritch, E. J., Martinez, D. R., Bock, K. W., Minai, M., Nagata, B. M., Hutchinson, G. B., ... Graham, B. S. (2020). SARS-CoV-2 mRNA vaccine design

- enabled by prototype pathogen preparedness. *Nature*, 586(7830), 567–571.  
<https://doi.org/10.1038/s41586-020-2622-0>.
8. Corbett, K. S., Flynn, B., Foulds, K. E., Francica, J. R., Boyoglu-Barnum, S., Werner, A. P., Flach, B., O'Connell, S., Bock, K. W., Minai, M., Nagata, B. M., Andersen, H., Martinez, D. R., Noe, A. T., Douek, N., Donaldson, M. M., Nji, N. N., Alvarado, G. S., Edwards, D. K., Flebbe, D. R., ... Graham, B. S. (2020). Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *The New England Journal of Medicine*, 383(16), 1544–1555. <https://doi.org/10.1056/NEJMoa2024671>.
  9. Corti, Davide, Jincun Zhao, Mattia Pedotti, Luca Simonelli, Sudhakar Agnihothram, Craig Fett, Blanca Fernandez-Rodriguez, Mathilde Foglierini, Gloria Agatic, Fabrizia Vanzetta, Robin Gopal, Christopher J. Langrish, Nicholas A Barrett, Federica Sallusto, Ralph S. Baric, Luca Varani, Maria Zambon, Stanley Perlman, and Antonio Lanzavecchia. 2015. 'Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus', *Proceedings of the National Academy of Sciences*, 112: 10473-78.
  10. Garg, S., Kim, L., Whitaker, M., O'Halloran, A., Cummings, C., Holstein, R., Prill, M., Chai, S. J., Kirley, P. D., Alden, N. B., Kawasaki, B., Yousey-Hindes, K., Niccolai, L., Anderson, E. J., Openo, K. P., Weigel, A., Monroe, M. L., Ryan, P., Henderson, J., Kim, S., ... Fry, A. (2020). Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR. Morbidity and mortality weekly report*, 69(15), 458–464.  
<https://doi.org/10.15585/mmwr.mm6915e3>.
  11. Hartley, G.E., Edwards E.S.J, Aui P.M., et al. Rapid generation of durable B cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 and convalescence. *Science Immunology* 2020;5:eabf8891.
  12. Ibarondo, F. J., Fulcher, J. A., Goodman-Meza, D., Elliott, J., Hofmann, C., Hausner, M. A., Ferbas, K. G., Tobin, N. H., Aldrovandi, G. M., & Yang, O. O. (2020). Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. *The New England Journal of Medicine*, 383(11), 1085–1087. <https://doi.org/10.1056/NEJMc2025179>.
  13. Jackson, L. A., Anderson, E. J., Roupheal, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A., Flach, B., Doria-Rose, N. A., Corbett, K. S., Morabito, K. M., O'Dell, S., Schmidt, S. D., Swanson, P. A., 2nd, Padilla, M., ... mRNA-1273 Study Group (2020). An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *The New England Journal of Medicine*, 383(20), 1920–1931. <https://doi.org/10.1056/NEJMoa2022483>.
  14. Johnson, Reed F., Ulas Bagci, Lauren Keith, Xianchun Tang, Daniel J. Mollura, Larry Zeitlin, Jing Qin, Louis Huzella, Christopher J. Bartos, Natasha Bohorova, Ognian Bohorov, Charles Goodman, Do H. Kim, Michael H. Pauly, Jesus Velasco, Kevin J. Whaley, Joshua C. Johnson, James Pettitt, Britini L. Ork, Jeffrey Solomon, Nicholas Oberlander, Quan Zhu, Jiusong Sun, Michael R. Holbrook, Gene G. Olinger, Ralph S. Baric, Lisa E. Hensley, Peter

- B. Jahrling, and Wayne A. Marasco. 2016. '3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012', *Virology*, 490: 49-58.
15. Kalil, A. C., Patterson, T. F., Mehta, A. K., Tomashek, K. M., Wolfe, C. R., Ghazaryan, V., Marconi, V. C., Ruiz-Palacios, G. M., Hsieh, L., Kline, S., Tapson, V., Iovine, N. M., Jain, M. K., Sweeney, D. A., El Sahly, H. M., Branche, A. R., Regalado Pineda, J., Lye, D. C., Sandkovsky, U., Luetkemeyer, A. F., ... Beigel, J. H. (2020). Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *The New England Journal of Medicine*, NEJMoa2031994. Advance online publication. <https://doi.org/10.1056/NEJMoa2031994>.
16. Kim, Y., H. Lee, K. Park, S. Park, J. H. Lim, M. K. So, H. M. Woo, H. Ko, J. M. Lee, S. H. Lim, B. J. Ko, Y. S. Park, S. Y. Choi, D. H. Song, J. Y. Lee, S. S. Kim, and D. Y. Kim. 2019. 'Selection and Characterization of Monoclonal Antibodies Targeting Middle East Respiratory Syndrome Coronavirus through a Human Synthetic Fab Phage Display Library Panning', *Antibodies (Basel)*. Jul 31;8(3). pii: E42. doi: 10.3390/antib8030042.
17. Lumley, S. F., O'Donnell, D., Stoesser, N. E., Matthews, P. C., Howarth, A., Hatch, S. B., Marsden, B. D., Cox, S., James, T., Warren, F., Peck, L. J., Ritter, T. G., de Toledo, Z., Warren, L., Axten, D., Cornall, R. J., Jones, E. Y., Stuart, D. I., Screamon, G., Ebner, D., ... Oxford University Hospitals Staff Testing Group (2020). Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *The New England Journal of Medicine*, NEJMoa2034545. Advance online publication. <https://doi.org/10.1056/NEJMoa2034545>.
18. Martin, J. E., M. K. Louder, L. A. Holman, I. J. Gordon, M. E. Enama, B. D. Larkin, C. A. Andrews, L. Vogel, R. A. Koup, M. Roederer, R. T. Bailer, P. L. Gomez, M. Nason, J. R. Mascola, G. J. Nabel, B. S. Graham, and V. R. C. Study Team. 2008. 'A SARS DNA vaccine induces neutralizing antibody and cellular immune responses in healthy adults in a Phase I clinical trial', *Vaccine*, 26: 6338-43.
19. Modjarrad, K., C. C. Roberts, K. T. Mills, A. R. Castellano, K. Paolino, K. Muthumani, E. L. Reuschel, M. L. Robb, T. Racine, M. D. Oh, C. Lamarre, F. I. Zaidi, J. Boyer, S. B. Kudchodkar, M. Jeong, J. M. Darden, Y. K. Park, P. T. Scott, C. Remigio, A. P. Parikh, M. C. Wise, A. Patel, E. K. Duperret, K. Y. Kim, H. Choi, S. White, M. Bagarazzi, J. M. May, D. Kane, H. Lee, G. Kobinger, N. L. Michael, D. B. Weiner, S. J. Thomas, and J. N. Maslow. 2019. 'Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial', *Lancet Infect Dis*, 19: 1013-22.
20. Pallesen, Jesper, Nianshuang Wang, Kizzmekia S. Corbett, Daniel Wrapp, Robert N. Kirchdoerfer, Hannah L. Turner, Christopher A. Cottrell, Michelle M. Becker, Lingshu Wang, Wei Shi, Wing-Pui Kong, Erica L. Andres, Arminja N. Kettenbach, Mark R. Denison, James D. Chappell, Barney S. Graham, Andrew B. Ward, and Jason S. McLellan. 2017. 'Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen', *Proceedings of the National Academy of Sciences*, 114: E7348-E57.

21. Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. V., Cooper, D., Frenck, R. W., Jr, Hammitt, L. L., Türeci, Ö., ...C4591001 Clinical Trial Group (2020). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *The New England Journal of Medicine*, 383(27), 2603–2615. <https://doi.org/10.1056/NEJMoa2034577>.
22. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *The New England Journal of Medicine*. 2020 Jul 17;NEJMoa2021436. doi: 10.1056/NEJMoa2021436. Epub ahead of print. PMID: 32678530; PMCID: PMC7383595.
23. Slaoui, M., & Hepburn, M. (2020). Developing Safe and Effective Covid Vaccines - Operation Warp Speed's Strategy and Approach. *The New England Journal of Medicine*, 383(18), 1701–1703. <https://doi.org/10.1056/NEJMp2027405>.
24. Wang, Lingshu, Wei Shi, M. Gordon Joyce, Kayvon Modjarrad, Yi Zhang, Kwanyee Leung, Christopher R. Lees, Tongqing Zhou, Hadi M. Yassine, Masaru Kanekiyo, Zhi-yong Yang, Xuejun Chen, Michelle M. Becker, Megan Freeman, Leatrice Vogel, Joshua C. Johnson, Gene Olinger, John P. Todd, Ulas Bagci, Jeffrey Solomon, Daniel J. Mollura, Lisa Hensley, Peter Jahrling, Mark R. Denison, Srinivas S. Rao, Kanta Subbarao, Peter D. Kwong, John R. Mascola, Wing-Pui Kong, and Barney S. Graham. 2015. 'Evaluation of candidate vaccine approaches for MERS-CoV', *Nature Communications*, 6: 7712.
25. Wang L, Shi W, Chappell JD, Joyce MG, Zhang Y, Kanekiyo M, Becker MM, van Doremalen N, Fischer R, Wang N, Corbett KS, Choe M, Mason RD, Van Galen JG, Zhou T, Saunders KO, Tatti KM, Haynes LM, Kwong PD, Modjarrad K, Kong WP, McLellan JS, Denison MR, Munster VJ, Mascola JR, Graham BS. 2016. 'Importance of Neutralizing Monoclonal Antibodies Targeting Multiple Antigenic Sites on the Middle East Respiratory Syndrome Coronavirus Spike Glycoprotein To Avoid Neutralization Escape', *J Virol*. 2018 Apr 27;92(10). pii: e02002-17. doi: 10.1128/JVI.02002-17.
26. Widge, A. T., Roupahel, N. G., Jackson, L. A., Anderson, E. J., Roberts, P. C., Makhene, M., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Neuzil, K. M., Bennett, H., Leav, B., Makowski, M., ... mRNA-1273 Study Group (2021). Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *The New England Journal of Medicine*, 384(1), 80–82. <https://doi.org/10.1056/NEJMc2032195>.
27. Widjaja, Ivy, Chunyan Wang, Rien van Haperen, Javier Gutiérrez-Álvarez, Brenda van Dieren, Nisreen M. A. Okba, V. Stalin Raj, Wentao Li, Raul Fernandez-Delgado, Frank Grosveld, Frank J. M. van Kuppeveld, Bart L. Haagmans, Luis Enjuanes, Dubravka Drabek, and Berend-Jan Bosch. 2019. 'Towards a solution to MERS: protective human monoclonal



antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein', *Emerging Microbes & Infections*, 8: 516-30. World Health Organization (WHO). <https://www.who.int>. Accessed May 15, 2020.

28. Yu, Xiaojuan, Senyan Zhang, Liwei Jiang, Ye Cui, Dongxia Li, Dongli Wang, Nianshuang Wang, Lili Fu, Xuanlin Shi, Ziqiang Li, Linqi Zhang, and Xinquan Wang. 2015. 'Structural basis for the neutralization of MERS-CoV by a human monoclonal antibody MERS-27', *Scientific Reports*, 5: 13133.

## 12. APPENDIX A: OPTIONAL THIRD mRNA-1273 VACCINATION SUBSTUDY

All aspects of the main study apply to this substudy unless otherwise specified in [Section 12, Appendix A](#).

### 12.1 Overview

All subjects in this clinical trial were scheduled to receive two mRNA-1273 vaccinations, 28 days apart, at dosages of 25, 50, 100, or 250 mcg (see [Table 1](#)), with the last scheduled follow-up visit occurring at 365 days after the second vaccination (see [Table 4](#)). During the course of the main study, interim efficacy data from a Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE), administered as 2 doses of 100 mcg given 28 days apart, demonstrated vaccine efficacy of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic, confirmed COVID-19 (Baden, LR, et al. 2020). After review of the interim safety and efficacy data from that clinical trial, the FDA granted on December 18, 2020 an Emergency Use Authorization (EUA) for the mRNA-1273 vaccine in adults 18 years of age and older.

To potentially enhance and extend the duration of protection provided by the 2-dose vaccination schedule of mRNA-1273 administered in the main study, and to gain an understanding of the immune responses to a third dose of mRNA-1273, subjects in the main study may participate in an optional third mRNA-1273 vaccination substudy, detailed in [Section 12, Appendix A](#).

Substudy subjects will receive a third mRNA-1273 vaccination, administered via an IM injection at a dosage of 100 mcg/0.5 mL, given six to twelve months after receipt of their second vaccination in the main study. Substudy subjects will be followed for safety, reactogenicity, and immunogenicity endpoints through 12 months post third vaccination (Substudy Day 366).

To be eligible to participate in the substudy, subjects must have received both the first and second mRNA-1273 vaccinations in the main study. Other eligibility criteria are specified in [Appendix A](#). Subjects who received only one mRNA-1273 vaccination in the main study will be advised to receive an FDA authorized or approved COVID-19 vaccine, according to the recommended schedule, when available to them outside of this trial, unless they have a contraindication to COVID-19 vaccines that are available.

Subjects who elect not to participate in the optional third mRNA-1273 vaccination substudy or are not eligible for the substudy will continue to be followed according to the Schedule of Activities for the main study (see [Table 4](#)) with the Final Study Visit 14 occurring at Day 394 ( $\pm 14$  days).

Dosing for the optional third mRNA-1273 vaccination substudy is found in [Table 13](#).

Schedule of assessments for the optional third mRNA-1273 vaccination substudy is found in [Table 14](#).

Statistical Considerations for the optional third mRNA-1273 vaccination substudy are found in [Section 12.11](#).

### 12.2 Background and Scientific Rationale

See [Section 2.1](#) for additional background information.

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia that was ultimately identified as a novel pathogen named SARS-CoV-2. The disease caused by SARS-CoV-2 is called Coronavirus disease 2019 (COVID-19). On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. On March 11, 2020 the WHO declared COVID-19 a pandemic. As of January 10, 2021, the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University ([systems.jhu.edu](http://systems.jhu.edu)) reports a global tally of 89,960,893 cases and 1,931,083 deaths and a total of 22,227,722 cases and 373,331 deaths in the United States. Morbidity and mortality have disproportionately affected older adults, and racial and ethnic minority populations (Garg S et al, 2020).

Despite success in developing a novel antiviral – remdesivir (Beigel JH et al, 2020), use of steroids and other novel immunomodulators (Kalil AC et al, 2020; Recovery Collaborative Group et al, 2020), and use of monoclonal antibodies (Chen P et al, 2020) for prevention and treatment of SARS-CoV-2 infection and COVID-19 disease, mortality remains substantial. Therefore, there is an urgent public health need for vaccines against SARS-CoV-2. Currently, there are over 170 vaccines in preclinical development and 60 vaccines that have entered into clinical trials (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>). In the US, 2 mRNA vaccines [Moderna (mRNA-1273), Pfizer-BioNTech (BNT162b2)] received FDA EUA in December 2020.

Studies of mRNA-1273 have been conducted in both mice and nonhuman primates (rhesus macaques) (Corbett KS et al, *N Engl J Med* 2020). A single dose of mRNA-1273 in mice elicited robust S protein binding antibody titers, but with no virus neutralization activity observed (Corbett KS et al, *Nature* 2020). Mice from this study were challenged with mouse-adapted SARS-CoV-2 virus, and preliminary results indicate that mRNA-1273-induced immunity is protective after challenge. Similarly, rhesus macaques also had a dose-dependent response to vaccination (Corbett KS et al, *N Engl J Med* 2020). The mRNA-1273 vaccine candidate induced antibody levels exceeding those in human convalescent-phase serum. Vaccination induced type 1 helper T cell (Th1)–biased CD4 T cell responses and low or undetectable Th2 or CD8 T cell responses. Viral replication was not detectable in BAL fluid by day 2 after challenge in seven of eight animals in both vaccinated groups. No viral replication was detectable in the nose of any of the eight animals in the 100- $\mu$ g dose group by day 2 after challenge, and limited inflammation or detectable viral genome or antigen was noted in lungs of animals in either vaccine group.

This phase I clinical trial is evaluating safety and immunogenicity of variable doses of Moderna’s mRNA-1273 in healthy adults across the age spectrum ( $\geq 18$  years of age). Cohorts now include subjects who received two doses of 25, 50, and 100 mcg in all 3 age ranges, and 250 mcg in those 18-55 years of age. A total of 120 subjects have been enrolled to assess the safety, reactogenicity, and immunogenicity of the mRNA-1273. To date, no serious adverse events have occurred, and no safety concerns have been identified (Jackson LA et al, 2020; Anderson EJ et al, 2020; Widge AT et al, 2020). Dose-dependent reactogenicity has occurred, with reactogenicity generally being greater with the second dose. This was typically mild-moderate in severity, and usually resolved within a few days. The second 250 mcg dose had increased reactogenicity in the 18-55 year old cohort and given high binding and neutralizing antibodies with lower doses, a dose of 50 or 100 mcg was chosen for the Phase 2 placebo-controlled, dose-

confirmation clinical trial of mRNA-1273 (Jackson LA et al, 2020). Binding and neutralizing antibodies, and T cell responses were dose-dependent (Jackson LA et al, 2020; Anderson EJ et al, 2020). Responses at 1 month after the second dose were generally greater than those observed in sera of patients convalescing from COVID-19. A CD4 cytokine response occurred particularly among type 1 helper T cells.

Although declines in binding and neutralizing antibodies are observed by 3 months after the boost dose, recipients that had received 100 mcg of mRNA-1273 still had binding and neutralizing antibody titers that were similar to or exceeded that of convalescent sera (Jackson LA et al, 2020; Anderson EJ et al, 2020; Widge AT et al, 2020). Data through 6 months after the boost dose are pending.

A Phase 2 placebo-controlled, dose-confirmation clinical trial of mRNA-1273 (NCT04405076) is being conducted in adults using a prime-boost regimen of 50 mcg, 100 mcg, or placebo in 18- <55 year old and  $\geq$ 55 year old subjects. This trial is ongoing, but publicly available data are limited.

A Phase 3 placebo-controlled clinical trial of mRNA-1273 (NCT04470427, the COVE study) was initiated at almost 100 sites in the United States that enrolled 30,420 adults and administered two doses of either 100 mcg of mRNA-1273 or placebo (saline) (Baden LR et al, 2020). Risks to subjects receiving mRNA-1273 were primarily mild to moderate injection site reactions, particularly pain. Delayed injection-site reactions (those with onset on or after day 8) were noted in 244 subjects (0.8%) after the first dose and in 68 subjects (0.2%) after the second dose. Systemic reactions were transient and included fever, fatigue, chills, headache, myalgias, and arthralgias. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (54.9%, vs. 42.2%) and the second dose (79.4%, vs. 36.5%). The severity of the solicited systemic events increased after the second dose in the mRNA-1273 group, with an increase in proportions of grade 2 events (from 16.5% after the first dose to 38.1% after the second dose) and grade 3 events (from 2.9% to 15.8%). Solicited systemic adverse events in the mRNA-1273 group lasted a mean of 2.6 days and 3.1 days after the first and second doses, respectively. Both solicited injection-site and systemic adverse events were more common among younger subjects (18 to <65 years of age) than among older subjects ( $\geq$ 65 years of age). Serious adverse events were rare, and the incidence was similar in the two groups. The frequency of grade 3 adverse events in the placebo group (1.3%) was similar to that in the vaccine group (1.5%), as were the frequencies of medically attended adverse events (9.7% vs. 9.0%) and serious adverse events (0.6% in both groups). Hypersensitivity reactions were reported in 1.5% and 1.1% of subjects in the vaccine and placebo groups, respectively.

In the primary efficacy analysis of the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE), 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%;  $P < 0.001$ ) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. Findings were similar across key secondary analyses, including assessment starting 14 days after dose 1. Thirty subjects in the trial had severe COVID-19; all 30 were in the placebo group (indicating vaccine efficacy against severe COVID-19 of 100% [95% CI, could not be estimated to 1.0]), and one death among these subjects was attributed to COVID-19. The vaccine

efficacy to prevent COVID-19 was consistent across subgroups stratified by demographic and baseline characteristics.

It has been observed that antibodies may decline in patients previously infected with mild SARS-CoV-2 and that reinfection can occur (although perhaps infrequently symptomatic) (Ibarrondo FJ et al, 2020; Lumley SF et al, 2020). T cells and memory B cells are established after initial infection and remain present through 6 months after initial infection (Hartley GE et al, 2020). Additionally, the correlate or correlates of protection against COVID-19-related disease are not known, although active investigations are underway. Samples obtained from the Phase 3 clinical trials may provide insight into the correlate or correlates of protection.

The durability of the immune response to mRNA-1273 remains uncertain beyond 3 months after the second vaccination (Widge AT et al, 2020). Immune responses after vaccination in general are known to wane, sometimes to the point where wild-type disease can occur. Since immunity after natural SARS-CoV-2 infection is not lifelong and no correlate of protection has been identified yet, a study to assess the safety, reactogenicity, and immunogenicity of a third dose of mRNA-1273 is warranted. Additionally, some subjects in this trial have received less (25 and 50 mcg) than the 100 mcg dosage utilized in the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE) that resulted in the EUA for mRNA-1273. These subjects could directly benefit from an additional vaccination that might boost their serological and cellular responses. Since T cells and memory B cells are established after initial infection through at least 6 months, it is likely that SARS-CoV-2 revaccination will result in robust serological responses, even among those that received less than the authorized dose (e.g., 25 mcg, 50 mcg) of mRNA-1273.

### **12.2.1 Justification for Dose**

It is not known whether a third mRNA-1273 vaccination will elicit immune responses or enhance immunity elicited by the 2-dose vaccination schedule of mRNA-1273 administered in the main study. If such responses can be induced, the optimal number of doses and interval between vaccinations is also not known. The EUA was granted for the 2-dose 100 mcg regimen evaluated in the Phase 3 placebo-controlled clinical trial of mRNA-1273 (NCT04470427, the COVE study), and 100 mcg is the dosage likely to be used in the future if additional mRNA-1273 vaccinations are recommended. Therefore, the 100 mcg dosage was selected for evaluation in this substudy.

## **12.3 Risk/Benefit Assessment**

### **12.3.1 Known Potential Risks**

The potential risks of participating in this substudy are those associated with having blood drawn, IM injection, possible reactions to mRNA-1273, and breach of confidentiality. These and additional risks are described in [Section 2.2.1](#).

A third vaccination of mRNA-1273 has not been evaluated in humans. The risks are expected to be similar to the risks associated with the first and second mRNA-1273 vaccinations in the main study but it is possible that there may be unanticipated risks with the third mRNA-1273 vaccination.

In a prior Phase 1 dose-ranging study of CMV vaccines (mRNA-1647 and mRNA-1443) with doses administered at 0, 1, and 6 months (NCT03382405), no safety issues were identified after the late third dose of mRNA vaccine (at 6 months after initial dose).

### 12.3.2 Known Potential Benefits

As outlined in [Section 12.2](#), data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE) suggests 94.1% efficacy of the vaccine when administered at 100 mcg versus placebo against SARS-CoV-2 infection when assessed on November 25, 2020 (Baden LR et al, 2020). The efficacy of other doses of mRNA-1273 (e.g., 25, 50, or 250 mcg) is not known. Although declines in binding and neutralizing antibodies are observed over time, 100 mcg of mRNA-1273 has the potential to provide durable humoral immunity (Widge AT et al, 2020).

Administration of a third dose of 100 mcg of mRNA-1273 vaccine might boost cellular responses and binding and neutralizing antibody titers in prior mRNA-1273 recipients. This could provide a boost in immune responses in subjects that received a lower vaccine dose (i.e., 25 mcg, 50 mcg) than that used in the Phase 3 placebo-controlled clinical trial of mRNA-1273 (COVE). Additionally, this third mRNA-1273 vaccination of prior 100 mcg or 250 mcg 2-dose recipients could boost the immune responses directed against the Spike protein of SARS-CoV-2. It is unknown as to whether a third mRNA-1273 vaccination will provide additional protection against SARS-CoV-2 infection.

There is potential benefit to society as a result of information gained from participation in this optional third mRNA-1273 vaccination substudy. Data on the safety and immunogenicity of a third mRNA-1273 vaccination of mRNA-1273 could provide key insights to inform the response to the ongoing threat imposed by the SARS-CoV-2 pandemic.

## 12.4 Objectives and Endpoints

**Table 12: Objectives and Endpoints (Outcome Measures)**

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
<ul style="list-style-type: none"> <li>To evaluate the safety and reactogenicity of a third mRNA-1273 vaccination, at a dosage of 100 mcg.</li> </ul>	<ul style="list-style-type: none"> <li>Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post third mRNA-1273 vaccination.</li> <li>Frequency and grade of any unsolicited AEs during the 28-day follow-up period post third mRNA-1273 vaccination.</li> <li>Frequency of any SAEs, Protocol Specified AESIs, NOCMCs, and MAAEs from Substudy Day 1 to Substudy Day 366.</li> </ul>
Secondary	

<b>OBJECTIVES</b>	<b>ENDPOINTS (OUTCOME MEASURES)</b>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a third mRNA-1273 vaccination, at a dosage of 100 mcg, at all timepoints after the third mRNA-1273 vaccination.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of antibody at each timepoint after the third mRNA-1273 vaccination.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> <li>The GMFR in IgG titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> </ul>
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by pseudovirus neutralization and other viral neutralization assays following a third mRNA-1273 vaccination, at a dosage of 100 mcg.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of Neut antibody at each timepoint after the third mRNA-1273 vaccination.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> <li>The GMFR Neut antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> </ul>

<b>OBJECTIVES</b>	<b>ENDPOINTS (OUTCOME MEASURES)</b>
<ul style="list-style-type: none"> <li>To evaluate the immunogenicity as measured by live SARS-CoV-2 neutralization following a third mRNA-1273 vaccination, at a dosage of 100 mcg.</li> </ul>	<ul style="list-style-type: none"> <li>GMT of Neut antibody at each timepoint after third mRNA-1273 vaccination.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> <li>The GMFR in Neut antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> </ul>
<ul style="list-style-type: none"> <li>To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.</li> </ul>	<ul style="list-style-type: none"> <li>Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at timepoints pre- and post-third mRNA-1273 vaccination.</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate using a multiplex assay IgG ELISA to SARS-CoV-2 S protein and SARS-CoV-2 N protein.</li> </ul>	<p>For each antigen,</p> <ul style="list-style-type: none"> <li>GMT of antibody at each timepoint after the third mRNA-1273 vaccination.</li> <li>Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> <li>The GMFR in IgG titer from the pre-third mRNA-1273 dose baseline (Substudy Day 1) at each post-vaccination timepoint and pre-first mRNA-1273 dose baseline (Main Study Day 1).</li> </ul>

## 12.5 Study Design



This is a substudy to a phase I, open-label, dose-ranging clinical trial to assess a third mRNA-1273 vaccination, administered via an IM injection at a dosage of 100 mcg/0.5 mL, in subjects, 18 years of age and older, who received both the first and second mRNA-1273 vaccinations in the main study (see [Table 13](#)) and meet all other substudy eligibility criteria. This optional third mRNA-1273 vaccination substudy is designed to assess safety, reactogenicity, and immunogenicity through 12 months post third vaccination (Substudy Day 366). Subjects who participate in this substudy are from the same three domestic clinical research sites that enrolled into the main study.

**Table 13: Treatment Arms and Substudy Dosing**

Cohort	Sample Size**	Stratum (Years of Age)	First and Second Dose in Main Study	Optional Third Dose in Substudy
1	15	18-55	25 mcg mRNA-1273	100 mcg mRNA-1273
2	15	18-55	100 mcg mRNA-1273	100 mcg mRNA-1273
3	15	18-55	250 mcg mRNA-1273	100 mcg mRNA-1273
4	10	56-70	25 mcg mRNA-1273	100 mcg mRNA-1273
5	10	56-70	100 mcg mRNA-1273	100 mcg mRNA-1273
6*	10	56-70	250 mcg mRNA-1273	n/a
7	10	≥71	25 mcg mRNA-1273	100 mcg mRNA-1273
8	10	≥71	100 mcg mRNA-1273	100 mcg mRNA-1273
9*	10	≥71	250 mcg mRNA-1273	n/a
10	15	18-55	50 mcg mRNA-1273	100 mcg mRNA-1273
11	10	56-70	50 mcg mRNA-1273	100 mcg mRNA-1273
12	10	≥71	50 mcg mRNA-1273	100 mcg mRNA-1273
13*	15	18-55	10 mcg mRNA-1273	n/a

\*Cohorts 6, 9 and 13 were not enrolled.

\*\*\*Four subjects did not receive the second dose of mRNA-1273 in the main study. Three subjects discontinued due to an AE (hives on lower extremities judged related to the first mRNA-1273 vaccination [cohort 1], sore throat [cohort 3], and maculopapular rash [cohort 5]); the other subject discontinued treatment due to quarantine for a COVID-19 exposure (cohort 1).

The third mRNA-1273 vaccination will be offered to subjects who received 2 doses of 25 or 50 mcg (cohorts 1, 4, 7, 10, 11, and 12), which are lower than the EUA mRNA-1273 dosage of 100

mcg, as soon as feasible after their Main Study Day 209 visit, and also will be offered to subjects who received 2 doses of 100 and 250 mcg (cohorts 2, 3, 5, and 8) no later than the close of the window for their originally scheduled Main Study Day 394 visit.

Subjects who receive the third mRNA-1273 vaccination will exit the Schedule of Activities for the main study and will enter the Schedule of Activities for the optional third mRNA-1273 vaccination substudy (see [Table 14](#)). Substudy follow-up visits will occur 1, 2 and 4 weeks post the third mRNA-1273 vaccination (Substudy Days 8, 15, and 29), as well as 3, 6 and 12 months after the third mRNA-1273 vaccination (Substudy Days 91, 181 and 366). Blood will be drawn at these substudy visits for immunogenicity assays. As with prior mRNA-1273 vaccinations, reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of the third mRNA-1273 vaccination through 7 days after the third mRNA-1273 vaccination. Unsolicited non-serious AEs will be collected from the time of the third mRNA-1273 vaccination through 28 days after the third mRNA-1273 vaccination. SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first mRNA-1273 vaccination through 12 months after the third mRNA-1273 vaccination.

Subjects who do not participate in this substudy, including those who are not eligible to participate in the substudy due to their prior receipt of an FDA authorized (under an EUA) or approved COVID-19 vaccine outside of this clinical trial, will continue, with their permission, to be followed according to the Schedule of Activities for the main study (see [Table 4](#)).

Interim safety and immunogenicity data from this substudy may be reviewed as needed, at the discretion of the study team, to inform public health decisions and to assess the adequacy of the immune responses in the 25 and 50 mcg dose cohorts compared with the 100 mcg dose cohort. Information from interim data reviews may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

Evaluation of immunogenicity will include quantitation of antibodies to the SARS-CoV-2 S protein at multiple timepoints post third mRNA-1273 vaccination as measured by ELISA and virus neutralization assays. In addition, exploratory studies to characterize T cell responses are planned.

Subjects who participate in the optional third mRNA-1273 vaccination substudy will exit the Schedule of Activities for the main study between Visit 13 and the close of the window for Visit 14 and will not have Visit 14, instead will have Visit 14A and subsequent substudy visits (see [Table 14](#)).

**Table 14: Schedule of Activities for the Optional Third mRNA-1273 Vaccination Substudy**

<b>Optional Third mRNA-1273 Vaccination Substudy Schedule Day</b>		<b>D1</b>	<b>D8</b>	<b>D15</b>	<b>D29</b>	<b>D91</b>	<b>D181</b>	<b>D366</b>
<b>SubStudy Visit Window (± number of days)</b>		<b>n/a</b>	<b>2d</b>	<b>2d</b>	<b>4d</b>	<b>10d</b>	<b>12d</b>	<b>30d</b>
<b>Optional Third mRNA-1273 Vaccination Substudy Visit</b>		<b>V14A</b>	<b>V15</b>	<b>V16</b>	<b>V17</b>	<b>V18</b>	<b>V19</b>	<b>V20</b>
Clinical Evaluations and Procedures	Tube							
Review eligibility criteria for the third mRNA-1273 vaccination		X						
Review medical history and con meds		X	X	X	X	X	X	X
Vital signs		X	X	X	X	{X}	{X}	{X}
<b>Third mRNA-1273 Vaccination<sup>1</sup></b>		<b>X</b>						
Targeted physical exam		{X}	{X}	{X}	{X}	{X}	{X}	{X}
Evaluate vaccination site		X	X					
Review memory aid			X					
Solicited AEs		X	X					
Unsolicited AEs and SAEs		X	X	X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>
Pregnancy test (urine) <sup>3</sup>		X						
Serum for humoral immunogenicity assays (mL)	SST	24	24	24	24	24	24	24
Serum for secondary research (mL)	SST	8	8	8	8	8	8	8
PBMC isolation for cellular immunology assays and plasma (mL)	NaCit CPT	40		30	30	30	30	40
PBMC isolation and plasma for secondary research	NaCit CPT	48	40	18	34	34	34	40
<b>Total volume per visit (mL)</b>		<b>120</b>	<b>72</b>	<b>80</b>	<b>96</b>	<b>96</b>	<b>96</b>	<b>112</b>
<b>Maximum cumulative blood volume<sup>4</sup> (mL) (prior 56 days)</b>		<b>192</b>	<b>264</b>	<b>344</b>	<b>440</b>	<b>96</b>	<b>96</b>	<b>112</b>

{ } Required at this substudy visit only if clinically indicated.

- 1) 0.5 mL of the mRNA-1273 vaccine will be injected IM in the deltoid muscle. After the injection, subjects will be observed for 60 minutes. The injection site will be evaluated, and vital signs obtained, during that period and before the subject leaves the clinic.
- 2) After Substudy Day 29 through the end of the substudy (Substudy Day 366), only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.
- 3) For women of childbearing potential. Must be confirmed as negative prior to the third mRNA-1273 vaccination. The visit will also include review of contraceptive/menstrual history and pregnancy avoidance counselling.

- 4) For purposes of estimating the maximum possible cumulative blood volume over the prior 56 days, this calculation assumes that the blood draw (72 mL) for Main Study Day 209 occurs on the day prior to Substudy Day 1.

## 12.6 Eligibility Criteria

### 12.6.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in this substudy:

1. Enrolled in the main study and received both the first and second mRNA-1273 vaccinations.
2. Provides written informed consent for the third mRNA-1273 vaccination.
3. Agrees to the collection of venous blood per substudy.
4. Must agree to have samples stored for secondary research.
5. Women of childbearing potential have had a negative urine pregnancy test within 24 hours before the third mRNA-1273 vaccination.
6. Women of childbearing potential<sup>1</sup> must agree to use or have practiced true abstinence<sup>2</sup> or use at least one acceptable primary form of contraception.<sup>3,4</sup>

*Note: These criteria are applicable to females in a heterosexual relationship and child-bearing potential (i.e., the criteria do not apply to subjects in a same sex relationship).*

<sup>1</sup>*Not of childbearing potential – post-menopausal females (defined as having a history of amenorrhea for at least one year) or a documented status as being surgically sterile (hysterectomy, bilateral oophorectomy, tubal ligation/salpingectomy, or Essure® placement).*

<sup>2</sup>*True abstinence is 100% of time no sexual intercourse (male's penis enters the female's vagina). (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).*

<sup>3</sup>*Acceptable forms of primary contraception include monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more prior to the subject's first vaccination, intrauterine devices, birth control pills, and injectable/implantable/insertable hormonal birth control products.*

<sup>4</sup>*Must use at least one acceptable primary form of contraception for at least 30 days prior to the third mRNA-1273 vaccination and for at least 30 days after the third mRNA-1273 vaccination.*

### 12.6.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from participation in this substudy.

1. Anaphylaxis or other systemic hypersensitivity reaction following a mRNA-1273 or any other vaccination.
2. Immediate allergic reaction of any severity after mRNA-1273 or any of its components.<sup>5</sup>

<sup>5</sup>Including polyethylene glycol (PEG)

3. Immediate allergic reaction of any severity to polysorbate.<sup>6</sup>

<sup>6</sup>Due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG

4. History of an SAE judged related to mRNA-1273 vaccine.
5. Female subject who is breastfeeding or plans to breastfeed from the time of the third mRNA-1273 vaccination through 30 days after the third mRNA-1273 vaccination.
6. Has an acute illness<sup>7</sup>, as determined by the participating site PI or appropriate sub-investigator, with or without fever [oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ )], within 72 hours prior to the third mRNA-1273 vaccination.

<sup>7</sup>An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the participating site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the substudy.

7. Has received any approved, authorized or investigational COVID-19 vaccine outside of this trial.
8. Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the subject from vaccination.
9. History of documented COVID-19 infection.
10. Has any medical disease or condition that, in the opinion of the participating site PI or appropriate sub-investigator, precludes substudy participation.
11. Received or plans to receive a licensed vaccine, other than a COVID-19 vaccine, within 2 weeks before or after the third mRNA-1273 vaccination.

## 12.7 Study Product

### 12.7.1 Study Product Description

#### **Product: mRNA-1273**

For the optional third mRNA-1273 vaccination substudy, mRNA-1273 is provided by ModernaTX, Inc. via the DMID CMS as a sterile solution for injection in a 10 dose multidose vial formulated at a concentration of 0.2mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM acetate, at pH 7.5 and presented in 10R USP Type I borosilicate glass vials with PLASCAP vial seal containing a 20 mm FluroTec-coated plug stopper and aluminum flip-off crimp seals with a nominal fill volume of 6.3 mL/vial.

There is no preservative in the mRNA-1273 solution. Hence, all ten (10) doses must be withdrawn into individual dosing syringes in quick succession, one after the other once the vial is breached.

Dilution is not required for the third mRNA-1273 vaccination. Each multidose vial contains ready-to-use solution and does not require further dilution or preparation. It will be administered as a single 0.5 mL IM injection of 100 mcg into the deltoid muscle.

See the protocol-specific MOP for detailed information:

- 20 (minimum) to 30 (maximum) minutes are required for the mRNA-1273 vials to equilibrate to room temperature (20°C to 25°C).
- A maximum of 30 minutes is allowed between completion of equilibration and completion of dosing syringes fill.
- Ten (10) dosing syringes must be prepared from each mRNA-1273 vial.
- All dosing syringes must be filled in quick succession, one after the other.
- Filled dosing syringes must be held at room temperature (20°C to 25°C) and will expire (eight) 8 hours after being filled.
- Withdrawal of mRNA-1273 from the vial into the dosing syringes should be completed within 30 minutes after the vial has equilibrated to room temperature (20°C to 25°C).

### 12.7.2 Dose Modifications

It is unknown whether subjects in the 25 mcg and 50 mcg cohorts from the main study have been optimally primed to respond to the third mRNA-1273 vaccination. In the event that the responses to a third mRNA-1273 vaccination in either or both of those cohorts are judged to be suboptimal in comparison to the responses in the 100 mcg cohorts, the study team will inform the subjects and consider a protocol amendment to administer another mRNA-1273 vaccination at a dosage of 100 mcg.

### 12.7.3 Product Storage and Stability

#### **Product: mRNA-1273**

For the optional third mRNA-1273 vaccination substudy, mRNA-1273 must be stored in a secure area with limited access (pharmacy staff only), and must be stored locally under refrigerated conditions (2°C to 8°C [36°F to 46°F]). The refrigerator should have an automated temperature recording and alert system. There must be an available back-up refrigerator. The refrigerators must be connected to a back-up generator; or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of refrigerator malfunctioning.

Prepared doses should remain at ambient temperatures (20°C to 25°C) and should not be shaken or allowed to roll during transport. Avoid exposing to direct sunlight while the syringe is in route to the injection administration location. If the prepared doses require transportation to a separate facility, ensure there are appropriate transport procedures in place. Under all circumstances, the time from preparation, transportation and administration of mRNA-1273 must occur within maximum (nine) 9 hours from the time the vials are removed from the refrigerator.

- A minimum of 20 minutes and a maximum of 30 minutes are allowed for equilibration of vial to room temperature (20°C to 25°C) after removal from refrigerator.
- A maximum of 30 minutes is allowed between completion of equilibration and completion of dosing syringes fill. However, all dosing syringes (10) must be filled in quick succession once the vial is breached.

- A maximum of 8 (eight) hours is allowed for holding dosing solution in dosing syringes prior to completion of administration.
- Note that the multi-dose vial does not contain a preservative and must be discarded 6 hours after the first penetration of the sterile septum.

## 12.8 Concomitant Therapy

Information about prior medications, including hormonal contraceptives, taken by the subject in the 30 days prior to providing informed consent for the substudy will be recorded on the appropriate DCF.

Concomitant medications include all medications (prescription, over the counter, supplements, and vaccines received outside of the study) taken by the subject from the time the substudy informed consent is signed through Substudy Day 366. At each substudy visit following the third mRNA-1273 vaccination, subjects will be queried about new concomitant medications and changes to existing medications.

Medications that might interfere with the evaluation of the investigational product should not be used by the subject during the study-reporting period (12 months after the third mRNA-1273 vaccination) unless clinically indicated as part of the subject's health care.

In the event medical conditions dictate the use of medications, subjects are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician, and inform the study Investigator as soon as practical. Any drug or vaccine used or received by the subject during the study-reporting period (12 months after the third mRNA-1273 vaccination) should be recorded on the appropriate DCF.

## 12.9 Immunogenicity Evaluations

### Serological Immunogenicity Assays:

The following serological immunogenicity assays may be performed on specimens collected on the day of and following the third mRNA-1273 vaccination:

- IgG ELISA to the SARS-CoV-2 S (spike) protein(s) and SARS-CoV-2 N protein.
- Pseudovirus and live SARS-CoV-2 neutralization assays.

### Cellular Immunology Assays:

This substudy will also investigate T cell immune responses using multiparametric flow cytometry.

The volume of venous blood to be collected at each substudy visit for immunogenicity evaluations is presented in [Table 14](#).

## 12.10 Adverse Events and Serious Adverse Events

### 12.10.1 Reporting of Adverse Events

Reporting of all AEs, solicited and unsolicited, will occur during the period from administration of the third mRNA-1273 vaccine on Substudy Day 1 through Substudy Day 29.

Solicited AEs (i.e., reactogenicity) will be collected using a memory aid and recorded on the appropriate DCF from the time of the third mRNA-1273 vaccination through 7 days post third mRNA-1273 vaccination (Substudy Days 1-8).

Unsolicited AEs of all severities will be reported from the time of the third mRNA-1273 vaccination on Substudy Day 1 through Substudy Day 29.

After Substudy Day 29 through the end of the substudy (Substudy Day 366), only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.

SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from Substudy Day 1 through the end of the substudy (Substudy Day 366).

### **12.10.2 Reporting of Pregnancy**

Pregnancy is not an AE. However, any pregnancy that occurs during substudy participation (through Substudy Day 366 post third mRNA-1273 vaccination) should be reported to the sponsor on the appropriate DCF. Pregnancy should be followed to outcome.

### **12.10.3 Unanticipated Problem Reporting**

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the SDCC/study sponsor within 24 hours of the participating site PI or appropriate sub-investigator becoming aware of the event per the above described SAE reporting process.
- UPs that are SAEs will be collected from Substudy Day 1 through the end of the substudy (Substudy Day 366).
- Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the participating site PI or appropriate sub-investigator becoming aware of the problem.
- UPs that are not SAEs will be collected from Substudy Days 1-29.

## **12.11 Statistical Considerations**

### **12.11.1 Statistical Hypotheses**

This is a substudy to a phase I, open-label, dose-ranging clinical trial and is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of a third mRNA-1273 vaccination between 6 months and 12 months post second mRNA-1273 vaccination.

### **12.11.2 Sample Size Determination**

Rare AEs are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs given various true event rates are presented in [Table 9](#) and apply to the substudy as well. Statistical assumptions described in [Section 9.2](#) apply to the substudy as well. It is possible that not all subjects will receive a third mRNA-1273 vaccination, assuming 5 subjects in a cohort receive a third mRNA-1273 vaccination the chance of observing at least one



AE of probability 20% or more is approximately 67%. Assuming all subjects receive a third mRNA-1273 vaccination the following additional statistical consideration applies. With 120 subjects across all cohorts the chance of observing at least one AE of probability 3% or more is approximately 97%.

### **12.11.3 Populations for Analyses**

The Safety Analysis population includes all subjects who received the third mRNA-1273 vaccination.

The modified intent-to-treat (mITT) population includes all subjects who received of the third mRNA-1273 vaccination and contributed both pre- and at least one post-third mRNA-1273 vaccination venous blood samples for immunogenicity testing for which valid results were reported.

In the final analysis, protocol deviations will be reviewed to determine which protocol deviations may affect the analysis. The per protocol (PP) population will then be defined – and this includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at the time of the third mRNA-1273 vaccination.
- Data from all substudy visits subsequent for the protocol deviations that are considered to affect the science.
- Data from any substudy visit that occurs substantially out of window.

### **12.11.4 Statistical Analyses**

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

The final substudy analysis will be performed after the final data lock (through Substudy Day 366) and reported as an addendum to the clinical study report (CSR). The addendum will be completed when all primary safety endpoint data and all secondary immunogenicity endpoint data are available and received by the SDCC. Any available data from the exploratory immunogenicity endpoints may also be included in the addendum. Remaining exploratory immunogenicity endpoint data may be included in a further addendum to the CSR, publication of manuscript(s), or other report(s). Abbreviated analysis plans that describe planned analyses to facilitate dissemination of study data for public health reasons, including manuscript publication(s), will be developed by the SDCC. A full statistical analysis plan (SAP) will be developed by the SDCC and finalized prior to the final data lock.

### **12.11.5 General Approach**

Unless otherwise noted in the SAP, continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

### **12.11.6 Analysis of the Primary Endpoint(s)**

Section 12.11.8 describes the analyses of Safety which is the primary endpoint of this substudy.

### **12.11.7 Analysis of the Secondary Endpoint(s)**

Summaries and analysis of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a per-protocol (PP) analysis may also be performed.

GMFR and seroconversion analyses will be done using two definitions of baseline. Baseline 1 will be considered Main Study Day 1 prior to the first mRNA-1273 vaccination (pre-first mRNA-1273 dose baseline) and baseline 2 will be considered Substudy Day 1 prior to the third mRNA-1273 vaccination (pre-third mRNA-1273 dose baseline).

Seroconversion is defined as a 4-fold increase in antibody titer over baseline.

Seroconversion rates, GMFR and GMT for SARS-CoV-2 as measured by IgG ELISA will be calculated at Substudy Days 1, 8, 15, 29, 91, 181 and 366 post third mRNA-1273 vaccination by cohort and will be summarized graphically. Seroconversion rates, GMFR and GMT will be presented with their corresponding 95% confidence interval (CI) estimates at each post-vaccination timepoint and overall peak GMT.

### **12.11.8 Safety Analyses**

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Solicited AEs will be summarized by severity for each day post third mRNA-1273 vaccination (Substudy Days 1-8) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period and using standard techniques, such as exact confidence intervals (CI), to summarize the proportion of subjects reporting each symptom, any application site symptom, and any systemic symptom.

Unsolicited non-serious AEs will be collected from the time of the third mRNA-1273 vaccination through 28 days after the third mRNA-1273 vaccination. Unsolicited AEs will be coded by MedDRA for preferred term and system organ class (SOC). SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first mRNA-1273 vaccination through 12 months after the third mRNA-1273 vaccination. The numbers of SAEs and MAAEs will be reported by detailed listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

Clinical laboratory data will be summarized by severity for each substudy visit, and as the maximum over all post-vaccination substudy visits. Graphical presentations may include box plots and shift plots.

### **12.11.9 Baseline Descriptive Statistics**

Summaries of demographic variables such as age, sex, ethnicity, and race will be presented by cohort and overall. Summaries of baseline clinical laboratory values will be presented by cohort and overall.

### **12.11.10 Planned Interim and Early Analyses**

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

Cumulative safety information, study status, and primary endpoint results may be published, presented at a public forum, or presented as summaries aggregated by study arm at the discretion of the sponsor while the main study is ongoing. Any ad-hoc analyses, jointly developed by the SDCC and/or the VRC, other participating laboratories and ModernaTX, Inc., will be executed by the SDCC as needed. None of the interim analyses will include any formal statistical hypothesis testing; therefore, p value adjustment will not be made to any analyses.

#### **12.11.10.1 Interim Safety Analyses**

Given the need for rapid review and dissemination of study data for public health reasons, AEs and SAEs may be reviewed as necessary outside of SMC reviews. The SMC will not need to meet (unless halting rules are met), and materials will be provided electronically. Documentation of review and any concerns noted will be solicited electronically.

#### **12.11.10.2 Interim Immunogenicity Review**

For public health reasons there may be several immunogenicity reviews as needed.

Data may be disseminated to public health officials and partners as needed and included in publications and presentations to inform the global scientific community.

#### **12.11.10.3 Interim Immunogenicity and Safety Review**

Interim analyses of safety, reactogenicity, and immunologic response data may be done, as needed.

### **12.11.11 Sub-Group Analyses**

The protocol does not define any formal subgroup analyses, and the substudy is not adequately powered to perform subgroup analyses.

### **12.11.12 Tabulation of Individual Subject Data**

In general, all data will be listed, sorted by cohort and subject, and when appropriate by substudy visit number within subject.

### **12.11.13 Exploratory Analyses**

Summaries and analysis of immunogenicity data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

GMFR and seroconversion analyses will be done using two definitions of baseline. Baseline 1 will be considered Main Study Day 1 prior to the first mRNA-1273 vaccination (pre-first mRNA-1273 dose baseline) and baseline 2 will be considered Substudy Day 1 prior to the third mRNA-1273 vaccination (pre-third mRNA-1273 dose baseline).

Seroconversion is defined as a 4-fold increase in antibody titer over baseline.

Seroconversion rates, GMFR and GMT for SARS-CoV-2 as measured by IgG ELISA, neutralization assay using SARS-CoV-2 pseudovirus, neutralization assay using live SARS-CoV-2, and multiplex assay IgG ELISA to the SARS-CoV-2 S proteins and SARS-CoV-2 N protein will be calculated for all post third mRNA-1273 timepoints by cohort and will be summarized graphically. Seroconversion rates, GMFR and GMT will be presented with their corresponding 95% CI estimates at each post-vaccination timepoint and overall peak GMT.

Summaries and analysis of cellular assay data will be presented for the mITT population. If there are protocol deviations which may affect the analysis, a PP analysis may also be performed.

The magnitude, phenotype and percentage of cytokine producing S protein-specific T cells will be summarized at each post-vaccination timepoint by vaccination group.

## **12.12 Regulatory, Ethical, and Study Oversight Considerations**

Informed consent for the substudy will be obtained in accordance with [Section 10.1.1](#).

As per [Section 10.1.1.2](#), the rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times.

If subjects choose not to provide permission for extra blood and secondary research use, they will not be eligible for participation in the optional third mRNA-1273 vaccination substudy.

Subjects may withdraw permission to use substudy samples for secondary use at any time. They will need to contact the participating site and the samples will be removed from the study repository after this substudy is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples. Subjects who withdraw consent before the last substudy visit will not have the extra blood drawn for secondary use.