Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2022483

This supplement contains the following items:

1. Original protocol v1.0 (redacted), final protocol v.20 (redacted), and summary of changes (Table 14 protocol v2.0)
2. Original, and only, statistical analysis plan.

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)

Version Number: 1.0

14 February 2020

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: _____

Lisa A. Jackson, MD, MPH
Senior Investigator, Kaiser Permanente Washington
Health Research Institute

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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 24,000 confirmed cases and 492 deaths as of February 5, 2020. There is currently no vaccine against the 2019-novel Coronavirus (2019-nCoV). 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 2019-nCoV (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 2019-nCoV S protein.

Study Design

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, 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 2019-nCoV. Enrollment will occur at one domestic site.

Table 1: Treatment Arms

Cohort	Sample Size	First and Second Dose
1	15	25 mcg mRNA-1273
2	15	100 mcg mRNA-1273
3	15	250 mcg mRNA-1273

Forty-five subjects will be enrolled into one of three cohorts (25 microgram [mcg], 100 mcg, 250 mcg). Subjects will receive an intramuscular (IM) injection (0.5 milliliter [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 study, 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.

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), new-onset chronic medical conditions (NOCMCs) and medically-attended adverse events (MAAEs) will be collected through 12 months after the last 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).

Objectives and Endpoints

Table 2: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination. • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination. • Frequency of any SAEs, NOCMCs and MAAEs from Day 1 to Day 394.
Secondary	
• To evaluate the immunogenicity as measured by Immunoglobulin G (IgG)	• Geometric mean titer (GMT) of antibody at Day 57.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
enzyme-linked immunosorbent assay ELISA to the 2019-nCoV S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.	• Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline. • The geometric mean fold rise (GMFR) in IgG titer from baseline.
Exploratory	
• To evaluate the immunogenicity as measured by IgG ELISA to the 2019-nCoV S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.	• GMT of antibody at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgG titer from baseline for each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by Immunoglobulin M (IgM) and Immunoglobulin A (IgA) ELISA to the 2019-nCoV S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of neutralizing (Neut) antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by live 2019-nCoV neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.
• To assess, in at least a subset of samples, the 2019-nCoV S protein-specific T cell responses.	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.
• To determine, in at least a subset of samples, the epitopes recognized by B cells and antibodies generated in response to mRNA-1273.	• Change in magnitude and phenotype of S protein-specific B cells as measured by flow cytometry at different timepoints post vaccination relative to baseline. • Determination of major antigenic sites and amino acid residues on 2019-nCoV S protein recognized by representative B cell clones and corresponding sequences of B cell receptors and monoclonal antibodies generated by vaccination.

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, 18 to 55 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, 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. Oral temperature is less than 100.0°F (37.8°C).
8. Pulse no greater than 100 beats per minute.
9. Systolic blood pressure (BP) is 85 to 150 mmHg, inclusive.
10. 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.

11. 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 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 site PI or appropriate sub-investigator, with or without fever [oral temperature >38.0°C (100.4^0F)] 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.

Study Phase

- 1

Study Population

Forty-five (45) males and non-pregnant females, 18 to 55 years of age, inclusive, who are in good health and meet all eligibility criteria will be enrolled.

Sites

- Single Infectious Disease Clinical Research Consortium (IDCRC) site - Kaiser Permanente Washington Health Research Institute

Study Intervention:

- mRNA-1273 is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized spike protein 2019-nCoV. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, [redacted], and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.
- mRNA-1273 (0.5 mg/mL) will be diluted in 0.9% Sodium Chloride (NaCl) for injection, United States Pharmacopeia (USP) to obtain 25, 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 participant 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

Study Duration

- The duration of the entire study is anticipated to be 16 months (from start of screening to last subject last visit).

Subject Duration

- The duration for each individual subject is approximately 14 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.

1.2 Schedule of Activities (SOA)

Table 4: Schedule of Activities

Procedures	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 day	Visit 06 Day 29 +/- 1 day	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09 Day 36 +/- 2 days	Visit 10 Day 43 +/- 2 days	Visit 11 Day 57 +/- 2 days	Visit 12 Day 119 +/- 7 days	Visit 13 Day 209 +/-7 days	Final Study Visit 14 Day 394 +/- 14 days	Unscheduled Visit	Early Termination Visit
Informed Consent	X																
Review Eligibility Criteria	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 Exam[a]	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 Body Mass Index [BMI])	X																
Hematology[b]	X	X			X		X			X							
Chemistry[b]	X	X			X		X			X							
Serology[b]	X																
Pregnancy Test[c]	X	X					X										
Urine Drug Screen	X																
Memory Aid: Solicited AEs		Days 1-8					Days 29-36										
Unsolicited AEs		Days 1-57															
SAEs, 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[d]		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

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 randomization 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.

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) has been abbreviated as 2019-nCoV and is now 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 24,000 confirmed cases and 492 deaths as of February 5, 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). Most of the infections outside China have been traveler-associated cases in those who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people. Global efforts to evaluate novel antivirals and therapeutic strategies to treat 2019-nCoV severe infections have intensified, but no proven therapeutic currently exists. There is currently no vaccine against the 2019-nCoV virus. 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. 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 2019-nCoV. mRNA-1273 is a novel LNP mRNA-based vaccine that encodes for the full-length spike (S) protein of 2019-nCoV, 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 2019-nCoV S protein. The VRC and collaborators found that the stabilized 2019-nCoV 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 2019-nCoV S protein stabilized with the 2P mutation. HEK293 cells transfected with mRNA expressing the 2019-nCoV S-2P protein successfully expressed the protein.

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).

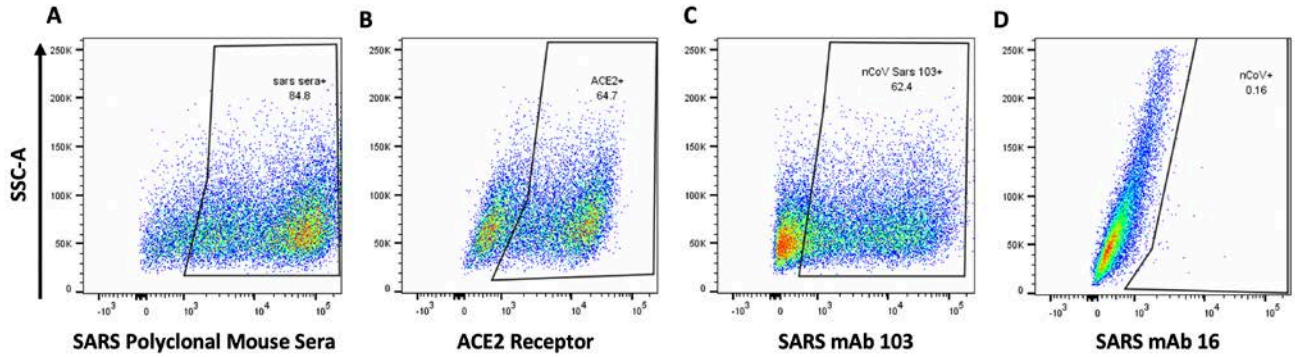

Figure 1. The 2019-nCoV full-length stabilized spike protein (S-2P) delivered by mRNA is expressed on the cell surface. HEK293T cells were transfected with mRNA encoding for the 2019-nCoV S-2P protein. After 24hrs, cell flow cytometry was used to measure surface expression by staining with (A) mouse 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 2019-nCoV S-2P; (D) a SARS S protein-specific monoclonal antibody (mAb 16) that does not bind 2019-nCoV was used as a negative control.

The expressed prefusion, stabilized S protein binds to the 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 2019-nCoV S protein.

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, the IM injection, 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.

Preclinical evaluations will occur in parallel with this phase I study. However, in support of the development of mRNA-1273 for prophylaxis against 2019-nCoV infection, nonclinical immunogenicity, Good Laboratory Practice (GLP)-compliant repeat dose toxicology study, biodistribution, and genotoxicity studies have been completed with similar mRNA-based vaccines formulated in [redacted]-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 [redacted] 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 [redacted]-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, [redacted], 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 [redacted]-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.

mRNA-1273 has not yet been administered to humans. Thus, information on possible risks and adverse reactions associated with IM administration of mRNA-1273 is derived from animal studies with mRNA-1273 and the LNP components or animal and human studies of similar mRNA-based vaccines (mRNA-1647 and mRNA-1653).

Risk to subjects receiving mRNA-1273 is expected to primarily involve mild to moderate injection site reactions, which have been observed in animal studies and are generally observed and expected for other IM-administered vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible systemic reactions, which are also transient, may include fever, fatigue, chills, headache, myalgias, and arthralgias. 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.

Based on the clinical experience to date with similar mRNA-based vaccines, mRNA-1273 should not be administered to individuals with a known hypersensitivity to any component of the study product.

Overall there have been 8 clinical studies initiated across Moderna's infectious disease vaccine platform with 895 subjects dosed with either vaccine or placebo, as of Feb 2020, under Moderna's sponsorship. mRNA vaccines with [redacted]-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV and HMPV/PIV3, and ZIKA. In three Phase 1 studies as of January 6, 2020, approximately 365 subjects were dosed with either an [redacted]-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 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, 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 the 8 subjects with arthralgia, and 4 of the 7 subjects with myalgia. There were no related SAEs reported in the Phase 1 CMV, HMPV/PIV3 or ZIKA studies.

Risk to participants receiving mRNA-1273 is expected to be low and primarily involve mild to moderate injection site reactions, which have been observed in animal studies and are generally observed and expected for other IM-administered vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible mild to moderate systemic reactions, which are also transient, may include fever, fatigue, chills, headache, myalgias, and arthralgias. 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.

There is also a potential risk of hypersensitivity reactions following the administration of any study product, including mRNA-1273.

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 IDCRC 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 IDCRC 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 2019-nCoV outbreak. Vaccination using mRNA-1273 may or may not provide protection against infection by 2019-nCoV. The duration of any such protection is currently unknown.

3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination. • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination. • Frequency of any SAEs, NOCMCs and MAAEs from Day 1 to Day 394.
Secondary	
• To evaluate the immunogenicity as measured by IgG ELISA to the 2019-nCoV S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.	• GMT of antibody at Day 57. • Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline. • The GMFR in IgG titer from baseline.
Exploratory	
• To evaluate the immunogenicity as measured by IgG ELISA to the 2019-nCoV S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.	• GMT of antibody at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgG titer from baseline for each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by IgM and IgA ELISA to the 2019-nCoV S (spike) protein following a	• GMT at each timepoint. • Percentage of subjects who seroconverted at each timepoint.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by live 2019-nCoV neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.
• To assess, in at least a subset of samples, the 2019-nCoV S protein-specific T cell responses.	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.
• To determine, in at least a subset of samples, the epitopes recognized by B cells and antibodies generated in response to mRNA-1273.	• Change in magnitude and phenotype of S protein-specific B cells as measured by flow cytometry at different timepoints post vaccination relative to baseline. • Determination of major antigenic sites and amino acid residues on 2019-nCoV S protein recognized by representative B cell clones and corresponding sequences of B cell receptors and monoclonal antibodies generated by vaccination.

4. STUDY DESIGN

4.1 Overall Design

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, 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 2019-nCoV. Enrollment will occur at one domestic site.

Table 6: Treatment Arms

Cohort	Sample Size	First and Second Dose
1	15	25 mcg mRNA-1273
2	15	100 mcg mRNA-1273
3	15	250 mcg mRNA-1273

Forty-five subjects will be enrolled into one of three cohorts (25 mcg, 100 mcg, 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 study, 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.

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

- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 29;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- Sentinels in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohort 3, ELISA IgG data through Day 29;

- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.
- 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 data can be reviewed when applicable.

Data may be disseminated to public health officials and partners as needed.

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, NOCMCs and MAAEs, will be collected through 12 months after the last 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 2019-nCoV S protein at multiple timepoints post vaccination as measured by ELISA, pseudovirus and live virus neutralization assays. In addition, exploratory studies to characterize T and B cell responses, as well as determination of major antigenic sites and amino acid residues on the 2019-nCoV S protein recognized by B cell clones are planned. Venous blood will also be collected at multiple timepoints post vaccination for the secondary research use of serum, plasma and PBMCs.

After the IND is in effect, IRB review and approval, and site activation, the 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 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 can be found in **Section 1.2, Schedule of Activities.**

Dose escalation or dose-ranging details are found in **Section 6.1.2, Dosing and Administration.**

Full details of interim analysis are found in **Section 9.4.6, Planned Interim and Early Analysis.**

4.2 Scientific Rationale for Study Design

This study 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 study. 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 (25 mcg, 100 mcg, 250 mcg) are within the range of previous trials. However, in support of development of mRNA-1273 for prophylaxis against 2019-nCoV infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in [redacted]-containing LNPs.

5. STUDY POPULATION

Forty-five (45) males and non-pregnant females, 18 to 55 years of age inclusive, who are in good health and meet all eligibility criteria will be enrolled at a single IDCRC site. The target population should reflect the community at large. The estimated time from initiation of enrollment to complete enrollment in this trial is approximately 6 weeks. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the 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 IDCRC 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, 18 to 55 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, at screening.
6. Women of childbearing potential[1] must agree to use or have practiced true abstinence[2] or use at least one acceptable primary form of contraception.[3,4]

   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).

   [1]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).

[2]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).

[3]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.

[4]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[5]: use of condoms to ensure effective contraception with a female partner from first vaccination until 3 months after the last vaccination.

   [5]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 3 months after the last vaccination.
10. Oral temperature is less than 100.0°F (37.8°C).
11. Pulse no greater than 100 beats per minute.
12. Systolic BP is 85 to 150 mmHg, inclusive.
13. 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.
14. Must agree to have samples stored for secondary research.
15. Agrees to adhere to Lifestyle Considerations (defined in Section 5.4) throughout study duration.

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 site PI or appropriate sub-investigator, precludes study participation.[6]

[6]*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).[7]

   [7]*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) or history of myocarditis or pericarditis as an adult.

   Neurological or neurodevelopmental conditions (e.g., migraines, epilepsy, stroke, seizures in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis or transverse myelitis).

   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.

5. Has an acute illness[8], as determined by the site PI or appropriate sub-investigator, with or without fever [oral temperature >38.0°C (100.4°F)] within 72 hours prior to each vaccination.

   [8]*An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the 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[9] within 60 days, or 5 half-lives, whichever is longer, before the first vaccine administration.

   [9]*study drug, biologic or device*

8. Currently enrolled in or plans to participate in another clinical trial with an investigational agent[10] that will be received during the study-reporting period.[11]

   [10]*Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.*

[11] *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.[12]

    [12] *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. 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.
13. Has any blood dyscrasias or significant disorder of coagulation.
14. Has any chronic liver disease, including fatty liver.
15. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 6 months before the first vaccine administration.
16. 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.
17. 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).
18. Received or plans to receive a licensed, live vaccine within 4 weeks before or after each vaccination.
19. Received or plans to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
20. Receipt of any other 2019-nCoV or other experimental coronavirus vaccine at any time prior to or during the study.
21. Known close contact of anyone known to have 2019-nCoV infection within 2 weeks prior to vaccine administration.
22. Has traveled to China within 30 days before the first vaccination.
23. Current use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the investigator.
24. The subject must agree to refrain from donating blood or plasma during the study.
25. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 28 days after the second vaccination.

5.2.1 Exclusion of Specific Populations

This is a first-in-human trial in healthy subjects, 18 to 55 years of age, inclusive. 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.
- Abstain from travel to areas known to be endemic with 2019-nCoV until 13 months after the last vaccination.
- 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 IDCRC 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 IDCRC 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 2019-nCoV. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, [redacted], 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 [redacted]

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 25, 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 participant 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

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 IDCRC 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 IDCRC site PI or responsible person should immediately contact the DMID Product Support Team at 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 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.

Only one- 0.5 mL dose of vaccine should be withdrawn from the final mixed vial(s) or compounding vials containing the prepared dosing solution. Gently invert the final mixed vial(s) or the compounding vials 20 times until components are mixed. **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 8 hours 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 Preparation/Handling/Storage/Accountability

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 IDCRC site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating IDCRC site PI may delegate to the participating IDCRC site's research pharmacist responsibility for study product accountability. The participating IDCRC 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 retuned 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 IDCRC site's study product accountability records and dispensing logs per the DMID-approved site monitoring plan.

The following must be retained for study product accountability:

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

- mRNA-1273 cartons

All used supplies noted above must 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. 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 returned to the sponsor or 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/standard operating procedure (SOP) when destroying used and unused items.
    - A certificate 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 [redacted]

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 (-60ºC to -90ºC).

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.

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 IDCRC site's research pharmacist must alert the participating IDCRC 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 IDCRC site PI or responsible person should immediately contact the DMID Product Support Team at 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 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 (unblinded pharmacy staff only), protected from moisture and light, and be stored 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., the unblinded 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., unblinded pharmacy staff) should have access to the product used in this study. The site is responsible for reporting any mRNA-1273 that was not temperature controlled during shipment or during storage to the unblinded site (pharmacy) monitor. Such mRNA-1273 will be retained for inspection by the unblinded monitor 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 IDCRC 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[SM] (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.

6.3.2 Randomization and Blinding

This is an open-label trial 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 entered into the electronic case report form (eCRF).

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 last 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 within 28 days 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 (systemic 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 within 28 days after administration of the vaccine and is considered related to the vaccine.

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 more than two body parts) within 72 hours after administration of vaccine.

4- Any subject experiences an SAE (except for accident or trauma) within 28 days 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 within 28 days after administration of the vaccine and is considered related to the vaccine. Clinical laboratory abnormalities are not subject to the time window.

In case of a sentinel halting rule, Table 8 describes the actions to follow.

Table 8: Halting Rules for Sentinel Subjects

Halting rule occurrence (YES/NO)*			
Cohort 1 (25 mcg)	**Cohort 2 (100 mcg)**	**Cohort 3 (250 mcg)**	**Action**
YES	NO	-	Halt the Study for SMC assessment.
NO	YES	-	Halt enrollment in cohort 2, Continue cohort 1.
YES	YES	-	Halt the study for SMC assessment.
NO	NO	YES	Continue study, including second dose for cohorts 1 and 2. SMC assessment for cohort 3.

* For any hypersensitivity reaction due to the vaccine, all cohorts and future doses will be halted pending SMC review.

7.1.3 Criteria for Redosing

In the event of any of the above-mentioned occurrences, an unscheduled safety analysis by the SMC will be required for approval of further enrollment. The pause is only for enrollment and vaccination of new subjects; in a given cohort, any subject who tolerated the first vaccination will be allowed to receive the second vaccination.

7.1.3.1 Withdrawal Criteria for Second Study Vaccination

Prior to receiving the second vaccination, participants will be reassessed. The following events constitute contraindications to any further administration of vaccines. If any of these events occur during the study, the participant must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after the last vaccination.

- Withdrawal of consent.
- As deemed necessary by the participating IDCRC 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 IDCRC site PI or appropriate sub-investigator, poses an additional risk to the participant 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 participant may be vaccinated at a later date, within the window specified in the SOA, or the participant may be withdrawn from dosing at the discretion of the participating IDCRC 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 ≥ 38.0°C (100.4°F) at the time of vaccination.

Participants with a minor illness without fever, as assessed by the participating IDCRC site PI or appropriate sub-investigator, can be administered vaccines. Participants with an oral temperature of 38.0°C (100.4°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 IDCRC 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 exam.
- 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 IDCRC 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 IDCRC 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 IDCRC 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 2019-nCoV 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 and 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 10.

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 IDCRC 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 IDCRC site PI or appropriate sub-investigator. Research laboratory results will not be provided to the subject.

8.1.2 Immunogenicity Evaluations

Serological Immunogenicity Assays:

The following serological immunogenicity assays will be performed:

- IgG ELISA to the 2019-nCoV S (spike) protein.
- IgM and IgA ELISA to the 2019-nCoV S (spike) protein.
- Neutralization assay using a 2019-nCoV pseudovirus.
- Neutralization assay using a wild-type 2019-nCoV.

Table 9: Testing Laboratories

Assay	Research Laboratory

	Location and Contact Information
IgG ELISA to the 2019-nCoV S protein	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
IgM and IgA ELISA to the 2019-nCoV S protein	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
Neutralization assay using a 2019-nCoV pseudovirus	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
Neutralization assay using a wild-type 2019-nCoV	TBD

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 and B cell immune responses using multiparametric flow cytometry, as well as identification of major antigenic sites and amino acid residues on the 2019-nCoV S protein recognized by B cell clones.

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 10.

8.1.3 Samples for Genetic/Genomic Analysis

8.1.3.1 Genetic/Genomic Analysis

DNA obtained from B-cells may be sequenced to identify B cell receptors and monoclonal antibodies. The DNA data may be used to synthesize antigen-specific antibodies to characterize antibody binding.

Additionally, stored PBMCs may be used in secondary research for testing, including, but not limited to, other genomic analysis 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.

8.1.3.2 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.

8.1.3.3 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 IDCRC 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 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 MAAEs and NOCMCs. Interim or unscheduled physical examinations will be performed at the discretion of the participating IDCRC 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 first 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 randomization 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) 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 10.
  - 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 10. 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.

Table 10: Venipuncture Volumes

Procedures	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 day	Visit 06 Day 29 +/- 1 day	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09 Day 36 +/- 2 days	Visit 10 Day 43 +/- 2 days	Visit 11 Day 57 +/- 2 days	Visit 12 Day 119 +/- 7 days	Visit 13 Day 209 +/- 7 days	Final Study Visit 14 Day 394 +/-14 days	Early Termination Visit	Total Volume of Blood Drawn (mL)
Vaccination		X					X										
Clinical Laboratory Evaluations[1]	28	6			6		6			6							52
Serum for Serological Immunogenicity Assays[1]		16				16	16			16	16	16	16	16	16	16[2]	144
PBMCs for Cellular Immunology Assays		80				40	16			16	40	16	40	40		16[2] or 40[2]	288
Serum for Secondary Research		16				8	8			8	8	8	8	8	8	8[2]	80
Serum for Product Assay Development		16				8	8			8	8	8	8	8	8	8[2]	80
Per Visit Blood Volume Total (mL)	28	134			6	72	54			54	72	48	72	72	32	-	644
Running Blood Volume Total (mL)	28	162			168	240	294			348	420	468	540	612	644	-	

[1] 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.

[2] These blood volumes are not included in the blood volume totals. Blood volume depends upon day of early termination visit.

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 IDCRC 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 Day 57, 28 days after the last vaccination. After Day 57 through the end of study on Day 394, only SAEs, 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 IDCRC 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), MAAEs and NOCMCs will be reported through the end of the study (Day 394).

8.3.1.3 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 IDCRC 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 IDCRC 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 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 IDCRC 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, 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. Please see 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 IDCRC site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the participating IDCRC 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 IDCRC 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 IDCRC 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:

- 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. In addition, the AESI 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

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 IDCRC site PI or appropriate sub-investigator becoming aware of the event per the above describe SAE reporting process.
- Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the participating IDCRC site PI or appropriate sub-investigator becoming aware of the problem.

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 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 11. 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, 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 cohort, we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With 45 subjects across the three dosing cohorts, the chance of observing at least one AE of probability 5% or more is at least 90%. 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.

Table 11: Probability of Observing an Adverse Event for Various Event Rates

N	"True" Event Rate	Probability of Observation (%)	N	"True" Event Rate	Probability of Observation (%)

15	0.1%	1.5	45	0.1%	4.4
	0.5%	7.2		0.5%	20.2
	1.0%	14.0		1.0%	36.4
	2.0%	26.1		2.0%	59.7
	3.0%	36.7		3.0%	74.6
	4.0%	45.8		4.0%	84.1
	5.0%	53.7		5.0%	90.1
	10.0%	79.4		10.0%	99.1
	15.0%	91.3		15.0%	99.9
	20.0%	96.5		20.0%	>99.9

9.3 Populations for Analyses

The Safety Analysis population includes all subjects who received one dose of vaccine.

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

The final analysis will be performed and clinical study report (CSR) completed when all primary safety endpoint data and all secondary and exploratory immunogenicity endpoint data are available. The CSR will be completed after the final data lock (through Day 394) and when all endpoint data are received by the SDCC. A formal 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 2019-nCoV 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 last vaccination. Unsolicited AEs will be coded by MedDRA® for preferred term and system organ class (SOC). All SAEs, 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. Early analyses will include safety and immunogenicity as described in Sections 9.4.6.1, 9.4.6.2and 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.

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 maybe reviewed as necessary outside of SMC reviews.

The SMC will review cumulative AE data after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Given the 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 will be solicited electronically.

9.4.6.2 Interim Immunogenicity Review

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

- For sentinel subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For all subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For sentinel subjects in cohort 3, the ELISA IgG data through Day 29;
- For all subjects in cohort 3, the ELISA IgG data through Day 29;
- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.
- 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.

9.4.6.3 Interim Immunogenicity and Safety Review

An interim analysis of safety, reactogenicity, and immunologic response data is planned once all subjects (cohorts 1-3) have completed Day 57 and the data are entered in the database, validated and monitored according to the clinical monitoring plan (CMP).

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 2019-nCoV as measured by IgG, IgA and IgM ELISA, neutralization assay using 2019-nCoV pseudovirus and neutralization assay using a wildtype 2019-nCoV 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.

The magnitude and phenotype of S protein-specific B cells will be summarized at each timepoint by vaccination group.

B-cell receptor sequence analysis to identify representative B cell clones and associated major antigenic sites and amino acid residues will be described.

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 material, 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 IDCRC 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 IDCRC 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, probability for random assignment to treatment groups, 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 IDCRC 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.

Subject 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.

Subjects will be informed that the monitor(s), auditors(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 IDCRC 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. If they choose to not provide permission for extra blood and secondary use, they will not be eligible for enrollment into the study. 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.

Extra blood will be drawn for secondary research during each visit (x10) when a study blood samples are obtained. 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.

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 study 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 genetic research in this study, and for extra and residual specimens to be stored and used for secondary 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 IDCRC site PI, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating IDCRC 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 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 clinical 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 IDCRC, may be shared for secondary research with investigators at the participating IDCRC site, with researchers at other 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 the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This 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 IDCRC, data may be shared for secondary research with investigators. 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 IDCRC 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

The study is sponsored by DMID. Decisions related to the study will be made by the protocol team, which includes representatives from the IDCRC 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).

10.1.6.2 Safety Monitoring Committee (SMC)

The SMC is an independent group of at least 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, and safety report template.

Given the frequency and urgency to review data, the SMC will not need to meet unless halting rules are met. Cumulative AE data will be provided to the SMC after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Documentation of review and any concerns noted will be solicited electronically.

The SMC does not need to meet for dose escalation to 250 mcg (cohort 3).

The SMC will meet 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 study.

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. The SMC will review blinded aggregate data in the open session of the SMC meetings.

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, 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 IDCRC site, study staff and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with all participating IDCRC 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 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 IDCRC site under the supervision of the participating IDCRC site PI. The participating IDCRC 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 IDCRC 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 IDCRC 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 IDCRC site PI, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the participating IDCRC 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 IDCRC 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

Following completion of the study, the PI retains the rights to publish the results of this research in a scientific journal. Data will be available immediately following publication, with no end date, with data sharing at the discretion of the PI.

10.1.12Human 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.

10.1.13Genomic 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

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 IDCRC 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 IDCRC 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 IDCRC 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 IDCRC 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 IDCRC 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 IDCRC site for any injury suffered due to participation in this trial.

10.3 Abbreviations

Table 12: Abbreviations

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
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
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-*sn*-glycero-3-phosphocholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
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
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
LNP	Lipid nanoparticle
MAAE	Medically-Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mITT	Modified Intent-To-Treat

mL	Milliliter
MOP	Manual of Procedures
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
PHI	Protected Health Information
PI	Principal Investigator
PIV3	Parainfluenza Virus Type 3
PLT	Platelet
PP	Per Protocol
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
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
VRC	Vaccine Research Center
WBC	White Blood Cell
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

10.4 Protocol Amendment History

Table 13: Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

11. REFERENCES

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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)

Version Number: 2.0

13 March 2020

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: _____

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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 WHO declared COVID-19 a pandemic. There is currently no vaccine against the 2019-novel Coronavirus (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.

Study Design

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, 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 sites.

Table 1: Treatment Arms

Cohort	Sample Size	First and Second Dose
1	15	25 mcg mRNA-1273
2	15	100 mcg mRNA-1273
3	15	250 mcg mRNA-1273

Forty-five subjects will be enrolled into one of three cohorts (25 microgram [mcg], 100 mcg, 250 mcg). Subjects will receive an intramuscular (IM) injection (0.5 milliliter [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 study, 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.

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), new-onset chronic medical conditions (NOCMCs) and medically-attended adverse events (MAAEs) will be collected through 12 months after the last 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).

Objectives and Endpoints

Table 2: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination. • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination. • Frequency of any SAEs, NOCMCs and MAAEs from Day 1 to Day 394.
Secondary	
• To evaluate the immunogenicity as measured by Immunoglobulin G (IgG)	• Geometric mean titer (GMT) of antibody at Day 57.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
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.	• Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline. • The geometric mean fold rise (GMFR) in IgG titer from baseline.
Exploratory	
• 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.	• GMT of antibody at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgG titer from baseline for each post-vaccination timepoint.
• 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.	• GMT at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of neutralizing (Neut) antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by live SARS-CoV-2 neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.
• To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.
• To determine, in at least a subset of samples, the epitopes recognized by B cells and antibodies generated in response to mRNA-1273.	• Change in magnitude and phenotype of S protein-specific B cells as measured by flow cytometry at different timepoints post vaccination relative to baseline. • Determination of major antigenic sites and amino acid residues on SARS-CoV-2 S protein recognized by representative B cell clones and corresponding sequences of B cell receptors and monoclonal antibodies generated by vaccination.

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, 18 to 55 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, 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. Oral temperature is less than 100.0°F (37.8°C).
8. Pulse no greater than 100 beats per minute.
9. Systolic blood pressure (BP) is 85 to 150 mmHg, inclusive.
10. 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.

11. 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 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 site PI or appropriate sub-investigator, with or without fever [oral temperature ≥38.0°C (100.4^0F)] 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.

Study Phase

- 1

Study Population

Forty-five (45) males and non-pregnant females, 18 to 55 years of age, inclusive, who are in good health and meet all eligibility criteria will be enrolled.

Sites

Up to three 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, [redacted], and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.
- mRNA-1273 (0.5 mg/mL) will be diluted in 0.9% Sodium Chloride (NaCl) for injection, United States Pharmacopeia (USP) to obtain 25, 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 participant 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

Study Duration

- The duration of the entire study is anticipated to be 16 months (from start of screening to last subject last visit).

Subject Duration

- The duration for each individual subject is approximately 14 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.

1.2 Schedule of Activities (SOA)

Table 4: Schedule of Activities

Procedures	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 day	Visit 06 Day 29 +/- 2 day	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09[e] Day 36 +/- 1 day	Visit 10[e] Day 43 +/- 2 days	Visit 11[e] Day 57 +/- 2 day	Visit 12[e] Day 119 +/- 7 days	Visit 13[e] Day 209 +/-7 days	Final Study Visit 14[e] Day 394 +/- 14 days	Unscheduled Visit	Early Termination Visit
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[a]	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 Body Mass Index [BMI])	X																
Hematology[b]	X	X			X		X			X							
Chemistry[b]	X	X			X		X			X							
Serology[b]	X																
Pregnancy Test[c]	X	X					X										
Urine Drug Screen	X																
Memory Aid: Solicited AEs		Days 1-8					Days 29-36										
Unsolicited AEs		Days 1-57															
SAEs, 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[d]		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

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) Visits 09-14 windows should be based off the actual Visit 06 date.

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.

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.

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.

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).

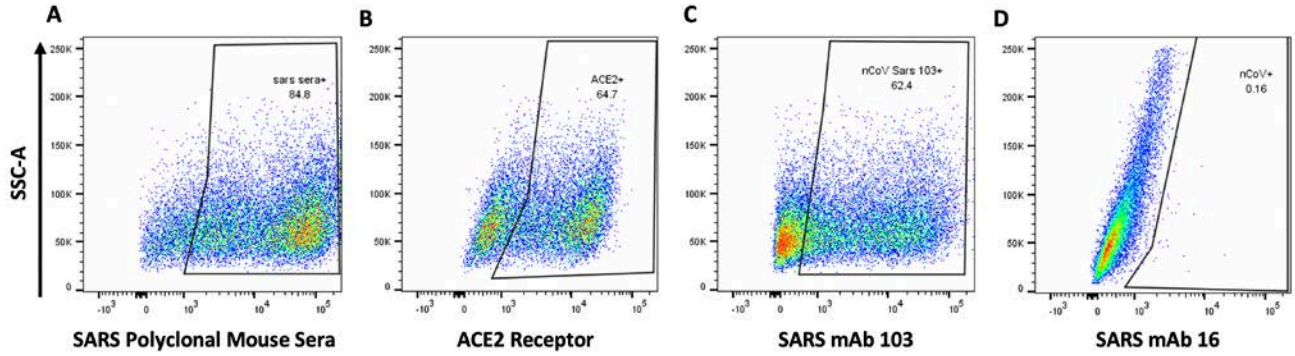

Figure 1. The SARS-CoV-2 full-length stabilized spike protein (S-2P) delivered by mRNA is expressed on the cell surface. HEK293T cells were transfected with mRNA encoding for the SARS-CoV-2 S-2P protein. After 24hrs, cell flow cytometry was used to measure surface expression by staining with (A) mouse 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 the 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

For this protocol, the study product, mRNA-1273 manufactured by ModernaTX, Inc. and the clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act). Under the PREP Act, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer or dispense the mRNA-1273) are immune from liability actions brought from the administration, manufacture or use of a covered countermeasure that is the subject of a declaration. The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries 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 administration or use of the countermeasure. Requests would go to the Health Resources and Services Administration (HRSA) Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/). Compensation may then be available for medical benefits, lost wages and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary of HRSA. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from administration and use of the mRNA-1273 may request benefits from the CICP. A serious physical injury means an injury that is life-threatening or results in, or requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to body structure. 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, and the Department of Veterans Affairs or Workers' Compensation programs do not have an obligation to pay.

If no funds have been appropriated to the compensation program, the Secretary of HRSA 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, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. 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, the IM injection, 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.

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

mRNA-1273 has not yet been administered to humans. Thus, information on possible risks and adverse reactions associated with IM administration of mRNA-1273 is derived from animal studies with mRNA-1273 and the LNP components or animal and human studies of similar mRNA-based vaccines (mRNA-1647 and mRNA-1653).

Risk to subjects receiving mRNA-1273 is expected to primarily involve mild to moderate injection site reactions, which have been observed in animal studies and are generally observed and expected for other IM-administered vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible systemic reactions, which are also transient, may include fever, fatigue, chills, headache, myalgias, and arthralgias. 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.

Based on the clinical experience to date with similar mRNA-based vaccines, mRNA-1273 should not be administered to individuals with a known hypersensitivity to any component of the study product.

Overall there have been 8 clinical studies initiated across Moderna's infectious disease vaccine platform with 895 subjects dosed with either vaccine or placebo, as of Feb 2020, under Moderna's sponsorship. mRNA vaccines with [redacted]-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV and HMPV/PIV3, and ZIKA. In three Phase 1 studies as of January 6, 2020, approximately 365 subjects were dosed with either an [redacted]-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 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, 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 the 8 subjects with arthralgia, and 4 of the 7 subjects with myalgia. There were no related SAEs reported in the Phase 1 CMV, HMPV/PIV3 or ZIKA studies.

Risk to participants receiving mRNA-1273 is expected to be low and primarily involve mild to moderate injection site reactions, which have been observed in animal studies and are generally observed and expected for other IM-administered vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible mild to moderate systemic reactions, which are also transient, may include fever, fatigue, chills, headache, myalgias, and arthralgias. 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.

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 response or elicited antibodies that had poor neutralizing activity against the virus. The relevance of these observations to mRNA vaccines in humans is unknown. Notably, 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.

There is also a potential risk of hypersensitivity reactions following the administration of any study product, including mRNA-1273.

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.

3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination. • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination. • Frequency of any SAEs, NOCMCs and MAAEs from Day 1 to Day 394.
Secondary	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.	• GMT of antibody at Day 57. • Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline. • The GMFR in IgG titer from baseline.
Exploratory	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-	• GMT of antibody at each timepoint. • Percentage of subjects who seroconverted at each timepoint.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.	• The GMFR in IgG titer from baseline for each post-vaccination timepoint.
• 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.	• GMT at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by live SARS-CoV-2 neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.
• To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.
• To determine, in at least a subset of samples, the epitopes recognized by B	• Change in magnitude and phenotype of S protein-specific B cells as measured by

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
cells and antibodies generated in response to mRNA-1273.	flow cytometry at different timepoints post vaccination relative to baseline. • Determination of major antigenic sites and amino acid residues on SARS-CoV-2 S protein recognized by representative B cell clones and corresponding sequences of B cell receptors and monoclonal antibodies generated by vaccination.

4. STUDY DESIGN

4.1 Overall Design

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, 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 sites.

Table 6: Treatment Arms

Cohort	Sample Size	First and Second Dose
1	15	25 mcg mRNA-1273
2	15	100 mcg mRNA-1273
3	15	250 mcg mRNA-1273

Forty-five subjects will be enrolled into one of three cohorts (25 mcg, 100 mcg, 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 study, 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.

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

- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 29;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- Sentinels in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohort 3, ELISA IgG data through Day 29;
- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.
- 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 data can be reviewed when applicable.

Data may be disseminated to public health officials and partners as needed.

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, NOCMCs and MAAEs, will be collected through 12 months after the last 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 virus neutralization assays. In addition, exploratory studies to characterize T and B cell responses, as well as determination of major antigenic sites and amino acid residues on the SARS-CoV-2 S protein recognized by B cell clones are planned. Venous blood will also be collected at multiple timepoints post vaccination for the secondary research use of serum, plasma and PBMCs.

After the IND is in effect, IRB review and approval, and site activation, the 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 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 can be found in **Section 1.2, Schedule of Activities.**

Dose escalation or dose-ranging details are found in **Section 6.1.2, Dosing and Administration.**

Full details of interim analysis are found in **Section 9.4.6, Planned Interim and Early Analysis.**

4.2 Scientific Rationale for Study Design

This study 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 study. 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 (25 mcg, 100 mcg, 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 [redacted]-containing LNPs.

5. STUDY POPULATION

Forty-five (45) males and non-pregnant females, 18 to 55 years of age inclusive, 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 trial is approximately 6 weeks. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the 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, 18 to 55 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, at screening.
6. Women of childbearing potential[1] must agree to use or have practiced true abstinence[2] or use at least one acceptable primary form of contraception.[3,4]

   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).

   [1]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).

   [2]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).

   [3]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.

   [4]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[5]: use of condoms to ensure effective contraception with a female partner from first vaccination until 3 months after the last vaccination.

   [5]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 3 months after the last vaccination.
10. Oral temperature is less than 100.0°F (37.8°C).
11. Pulse no greater than 100 beats per minute.
12. Systolic BP is 85 to 150 mmHg, inclusive.
13. 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.

14. Must agree to have samples stored for secondary research.
15. Agrees to adhere to Lifestyle Considerations (defined in Section 5.4) throughout study duration.
16. The subject must agree to refrain from donating blood or plasma during the study (outside of this study).

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 site PI or appropriate sub-investigator, precludes study participation.[6]

   [6]*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).[7]

   [7]*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) or history of myocarditis or pericarditis as an adult.

   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 or transverse myelitis).

   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.
5. Has an acute illness[8], as determined by the site PI or appropriate sub-investigator, with or without fever [oral temperature ≥38.0°C (100.4°F)] within 72 hours prior to each vaccination.

[8]*An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the 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[9] within 60 days, or 5 half-lives, whichever is longer, before the first vaccine administration.

   [9]*study drug, biologic or device*
8. Currently enrolled in or plans to participate in another clinical trial with an investigational agent[10] that will be received during the study-reporting period.[11]

   [10]*Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.*

   [11]*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.[12]

    [12]*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. 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.
13. Has any blood dyscrasias or significant disorder of coagulation.
14. Has any chronic liver disease, including fatty liver.
15. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 6 months before the first vaccine administration.
16. 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.
17. 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).
18. Received or plans to receive a licensed, live vaccine within 4 weeks before or after each vaccination.

19. Received or plans to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
20. Receipt of any other SARS-CoV-2 or other experimental coronavirus vaccine at any time prior to or during the study.
21. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.
22. .Current use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the investigator.
23. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 28 days after the second vaccination.

5.2.1 Exclusion of Specific Populations

This is a first-in-human trial in healthy subjects, 18 to 55 years of age, inclusive. 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, [redacted], 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 [redacted].

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 25, 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 participant 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

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 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 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 (25 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 8 hours 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 Preparation/Handling/Storage/Accountability

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 retuned 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 site monitoring plan.

The following must be retained for study product accountability:

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

All used supplies noted above must 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. 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/standard operating procedure (SOP) when destroying used and unused items.
    - A certificate 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 [redacted]

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 (-60ºC to -90ºC).

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.

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 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 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 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^{SM} (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.

6.3.2 Randomization and Blinding

This is an open-label trial 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 entered into the electronic case report form (eCRF).

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 last 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, participants will be reassessed. The following events constitute contraindications to any further administration of vaccines. If any of these events occur during the study, the participant must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after the 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 participant 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 participant may be vaccinated at a later date, within the window specified in the SOA, or the participant 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 ≥ 38.0°C (100.4°F) at the time of vaccination.

Participants with a minor illness without fever, as assessed by the participating site PI or appropriate sub-investigator, can be administered vaccines. Participants with an oral temperature of 38.0°C (100.4°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 and 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 9.

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 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 wild-type SARS-CoV-2.

Table 8: Testing Laboratories

Assay	**Research Laboratory Location and Contact Information**
IgG ELISA to the SARS-CoV-2 S protein	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
IgM and IgA ELISA to the SARS-CoV-2 S protein	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
Neutralization assay using a SARS-CoV-2 pseudovirus	VRC, NIAID, NIH. Bethesda, MD. Barney S. Graham, M.D., Ph.D. 301-594-8468 bgraham@nih.gov
Neutralization assay using a wild-type SARS-CoV-2	Vanderbilt University Medical Center Mark R. Denison, M.D. 615-343-9881 mark.denison@vumc.org

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 and B cell immune responses using multiparametric flow cytometry, as well as identification of major antigenic sites and amino acid residues on the SARS-CoV-2 S protein recognized by B cell clones.

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 9.

8.1.3 Samples for Genetic/Genomic Analysis

8.1.3.1 Genetic/Genomic Analysis

DNA obtained from B-cells may be sequenced to identify B cell receptors and monoclonal antibodies. The DNA data may be used to synthesize antigen-specific antibodies to characterize antibody binding.

Additionally, stored PBMCs may be used in secondary research for testing, including, but not limited to, other genomic analysis 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.

8.1.3.2 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.

8.1.3.3 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 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 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) 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 9.
    - 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 9. 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.

Table 9: Venipuncture Volumes

Procedures	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 day	Visit 06 Day 29 +/- 1 day	Visit 07, Day 30 1 day post Dose 2	Visit 08, Day 31 2 days post Dose 2	Visit 09[3] Day 36 +/- 1 day	Visit 10[3] Day 43 +/- 2 days	Visit 11[3] Day 57 +/- 1 day	Visit 12[3] Day 119 +/- 7 days	Visit 13[3] Day 209 +/- 7 days	Final Study Visit 14[3] Day 394 +/-14 days	Early Termination Visit	Total Volume of Blood Drawn (mL)
Vaccination		X					X										
Clinical Laboratory Evaluations[1]	28	8			8		8			8							60
Serum for Serological Immunogenicity Assays[1]		16				16	16			16	16	16	16	16	16	16[2]	144
PBMCs for Cellular Immunology Assays		80				40	16			16	40	16	40	40		16[2] or 40[2]	288
Serum for Secondary Research		16				8	8			8	8	8	8	8	8	8[2]	80
Serum for Product Assay Development		16				8	8			8	8	8	8	8	8	8[2]	80
Per Visit Blood Volume Total (mL)	28	136			8	72	56			56	72	48	72	72	32	-	652
Running Blood Volume Total (mL)	28	164			172	244	300			356	428	476	548	620	652	-	

[1] 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.

[2] These blood volumes are not included in the blood volume totals. Blood volume depends upon day of early termination visit.

[3] Visits 09-14 windows should be based off the actual Visit 06 date.

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 last vaccination. After Day 57 through the end of study on Day 394, only SAEs, 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), MAAEs and NOCMCs will be reported through the end of the study (Day 394).

8.3.1.3 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 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, 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. Please see 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:

- 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

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 describe SAE reporting process.
- 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.

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 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 10. 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, 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 cohort, we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With 45 subjects across the three dosing cohorts, the chance of observing at least one AE of probability 5% or more is at least 90%. 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.

Table 10: Probability of Observing an Adverse Event for Various Event Rates

N	"True" Event Rate	Probability of Observation (%)	N	"True" Event Rate	Probability of Observation (%)
15	0.1%	1.5	45	0.1%	4.4
	0.5%	7.2		0.5%	20.2
	1.0%	14.0		1.0%	36.4
	2.0%	26.1		2.0%	59.7
	3.0%	36.7		3.0%	74.6
	4.0%	45.8		4.0%	84.1
	5.0%	53.7		5.0%	90.1
	10.0%	79.4		10.0%	99.1
	15.0%	91.3		15.0%	99.9
	20.0%	96.5		20.0%	>99.9

9.3 Populations for Analyses

The Safety Analysis population includes all subjects who received one dose of vaccine.

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

The final analysis will be performed and clinical study report (CSR) completed when all primary safety endpoint data and all secondary and exploratory immunogenicity endpoint data are available. The CSR will be completed after the final data lock (through Day 394) and when all endpoint data are received by the SDCC. A formal 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 last vaccination. Unsolicited AEs will be coded by MedDRA® for preferred term and system organ class (SOC). All SAEs, 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. 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.

Cumulative safety information, study status, and primary endpoint results may be presented at a public forum in a blinded manner or presented as summaries aggregated by study arm at the discretion of the sponsor while the primary study is ongoing. While the primary study is ongoing no data will be released that is unblinding at an individual subject level, and caution will be taken to ensure that data summarized by treatment arm does not identify the treatment assignment of any individual subject. Any ad-hoc analyses, jointly developed by the SDCC and/or the VRC 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 maybe reviewed as necessary outside of SMC reviews.

The SMC will review cumulative AE data after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Given the 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 will be solicited electronically.

9.4.6.2 Interim Immunogenicity Review

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

- For sentinel subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For all subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For sentinel subjects in cohort 3, the ELISA IgG data through Day 29;
- For all subjects in cohort 3, the ELISA IgG data through Day 29;
- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.

- 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.

9.4.6.3 Interim Immunogenicity and Safety Review

An interim analysis of safety, reactogenicity, and immunologic response data is planned once all subjects (cohorts 1-3) have completed Day 57 and the data are entered in the database, validated and monitored according to the clinical monitoring plan (CMP).

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 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.

The magnitude and phenotype of S protein-specific B cells will be summarized at each timepoint by vaccination group.

B-cell receptor sequence analysis to identify representative B cell clones and associated major antigenic sites and amino acid residues will be described.

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.

Subject 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.

Subjects will be informed that the monitor(s), auditors(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. If they choose to not provide permission for extra blood and secondary use, they will not be eligible for enrollment into the study. 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.

Extra blood will be drawn for secondary research during each visit (x10) when a study blood samples are obtained. 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.

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 study 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 genetic research in this study, and for extra and residual specimens to be stored and used for secondary 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 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 clinical 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 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 the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This 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. 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

The study is sponsored by DMID. Decisions related to the 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).

10.1.6.2 Safety Monitoring Committee (SMC)

The SMC is an independent group of at least 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. Cumulative AE data will be provided to the SMC after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Documentation of review and any concerns noted will be solicited electronically.

The SMC does not need to meet for dose escalation to 250 mcg (cohort 3).

The SMC will meet 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 study.

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. The SMC will review blinded aggregate data in the open session of the SMC meetings.

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, 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 site monitoring plan. 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 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 site staff. Following a deviation(s), corrective actions should be developed by the 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 clean and monitored data will be immediately 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.

10.1.13Genomic 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

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 product mRNA-1273 manufactured by ModernaTX, Inc. is covered under the PREP Act, as described in Section 2.1.1.

10.3 Abbreviations

Table 11: Abbreviations

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
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
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-*sn*-glycero-3-phosphocholine
EC	Ethics Committee
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
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
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
LNP	Lipid nanoparticle
MAAE	Medically-Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mITT	Modified Intent-To-Treat
mL	Milliliter
MOP	Manual of Procedures
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
PHI	Protected Health Information
PI	Principal Investigator
PIV3	Parainfluenza Virus Type 3
PLT	Platelet
PP	Per Protocol
PREP	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
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 12: Protocol Amendment History

Version/ Date	Section	Description of Change	Brief Rationale
2.0, March 13, 2020	Throughout	Administrative	Advanced to 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 case counts,	
	Sect 2.1, page 14	Updated COVID-19 status	
	Sect 4.1, Page22	Enrollment will occur at <u>up to three</u> ~~one~~ domestic site<u>s</u>.	Revised language to add clinical sites,
	Sect. 1.2, page 13	Adjusted visit windows	
	Sect. 5.1, page 26	Added Inclusion criterion	Moved from Exclusion criteria

		#16. The subject must agree to refrain from donating blood or plasma during the study (outside of this study).	
	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. 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.~~	Addressed in revision to 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</u> ~~systemic~~ 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.	

	Sect. 7.1.3, Page 37	Revised dosing and redosing criteria	
	Sect.8.1.2, Page 42	Added research laboratory location and contact information	
		Adjusted blood volumes,	
		AESIs reporting	
		Added Prep Act	

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CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 20-0003

Study Title:

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

NCT04283461

Version 1.0

DATE: 16-JUN-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol:20-0003**
Development Phase:	Phase 1
Products:	
Form/Route:	Injection
Indication Studied:	2019-nCoV
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	03MAR2020
Clinical Trial Completion Date:	Ongoing
Date of the Analysis Plan:	16 June 2020
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
C	Celsius
CI	Confidence Interval
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
F	Fahrenheit
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LLN	Lower Limit of Normal
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
N	Number (typically refers to subjects)
NIH	National Institutes of Health
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
S-2P	S Protein in its Prefusion Conformation
SAE	Serious Adverse Event
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class

SOP	Standard Operating Procedures
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults" (DMID Protocol 20-0003) describes and expands upon the statistical information presented in the protocol. This document is an abbreviated analysis plan and describes planned analyses to facilitate manuscript publication and is based on version 2.0 of the protocol. This document contains a review of the study design, general statistical considerations, and statistical analysis methods for efficacy and safety outcomes. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

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.

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.

2.1. Purpose of the Analyses

These analyses will assess the immunogenicity and safety of mRNA-1273 vaccine at 3 different doses 25mcg, 100 mcg and 250 mcg.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults.	• Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination. • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination. • Frequency of any SAEs, NOCMCs and MAAEs from Day 1 to Day 394.
Secondary	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.	• GMT of antibody at Day 57. • Percentage of subjects who seroconverted, defined as a 4-fold change in antibody titer from baseline. • The GMFR in IgG titer from baseline.
Exploratory	
• To evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S (spike) protein following a 2-dose vaccination schedule of mRNA-1273 at all timepoints, other than Day 57.	• GMT of antibody at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgG titer from baseline for each post-vaccination timepoint.
• 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.	• GMT at each timepoint. • Percentage of subjects who seroconverted at each timepoint. • The GMFR in IgM and IgA titer from baseline at each post-vaccination timepoint.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• To evaluate the immunogenicity as measured by pseudovirus neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR Neut antibody titer from baseline at each post-vaccination timepoint.
• To evaluate the immunogenicity as measured by live SARS-CoV-2 neutralization following a 2-dose vaccination schedule of mRNA-1273 given 28 days apart.	• GMT of Neut antibody at each timepoint. • Percentage of subjects who seroconverted, defined as a 4-fold change in Neut antibody titer from baseline at each timepoint. • The GMFR in Neut antibody titer from baseline at each post-vaccination timepoint.
• To assess, in at least a subset of samples, the SARS-CoV-2 S protein-specific T cell responses.	• Magnitude, phenotype, and percentage of cytokine producing S protein-specific T cells, as measured by flow cytometry at different timepoints post vaccination relative to baseline.
• To determine, in at least a subset of samples, the epitopes recognized by B cells and antibodies generated in response to mRNA-1273.	• Change in magnitude and phenotype of S protein-specific B cells as measured by flow cytometry at different timepoints post vaccination relative to baseline. • Determination of major antigenic sites and amino acid residues on SARS-CoV-2 S protein recognized by representative B cell clones and corresponding sequences of B cell receptors and monoclonal antibodies generated by vaccination.

3.2. Study Definitions and Derived Variables

The baseline value will be defined as the last value obtained prior to the first vaccination of study product. Vaccination group and Cohort will be used interchangeably.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase I, open-label, dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age, inclusive, 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 sites.

Forty-five subjects will be enrolled into one of three cohorts (25 mcg, 100 mcg, 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 study, 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.

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

- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 29;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 29;
- Sentinels in cohort 3, ELISA IgG data through Day 29;
- All subjects in cohort 3, ELISA IgG data through Day 29;
- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.
- 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 data can be reviewed when applicable.

Data may be disseminated to public health officials and partners as needed.

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, NOCMCs and MAAEs, will be collected through 12 months after the last 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 virus neutralization assays. In addition, exploratory studies to characterize T and B cell responses, as well as determination of major antigenic sites and amino acid residues on the SARS-CoV-2 S protein recognized by B cell clones are planned. Venous blood will also be collected at multiple timepoints post vaccination for the secondary research use of serum, plasma and PBMCs.

4.2. Discussion of Study Design, Including the Choice of Control Groups

This study 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.

No human trials of mRNA-1273 have been conducted to date. Preclinical evaluations will occur in parallel with this phase I study. 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 (25 mcg, 100 mcg, 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 [redacted]-containing LNPs.

4.3. Selection of Study Population

Forty-five (45) males and non-pregnant females, 18 to 55 years of age inclusive, 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 trial is approximately 6 weeks. Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the 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.

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, 18 to 55 years of age, inclusive, at time of enrollment.
5. Body Mass Index 18-35 kg/m^2, inclusive, at screening.
6. Women of childbearing potential[1] must agree to use or have practiced true abstinence[2] or use at least one acceptable primary form of contraception.[3,4]

   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).

   [1]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).

   [2]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).

   [3]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.

   [4]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[5]: use of condoms to ensure effective contraception with a female partner from first vaccination until 3 months after the last vaccination.

   [5]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 3 months after the last vaccination.

10. Oral temperature is less than 100.0°F (37.8°C).
11. Pulse no greater than 100 beats per minute.
12. Systolic BP is 85 to 150 mmHg, inclusive.
13. 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.
14. Must agree to have samples stored for secondary research.
15. Agrees to adhere to Lifestyle Considerations (defined in Section 5.4 of the protocol) throughout study duration.
16. The subject must agree to refrain from donating blood or plasma during the study (outside of this study).

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 site PI or appropriate sub-investigator, precludes study participation.[6]

   [6]*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).[7]

   [7]*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) or history of myocarditis or pericarditis as an adult.

   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 or transverse myelitis).

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.

5. Has an acute illness[8], as determined by the site PI or appropriate sub-investigator, with or without fever [oral temperature ≥38.0°C (100.4°F)] within 72 hours prior to each vaccination.

   [8]An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the 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[9] within 60 days, or 5 half-lives, whichever is longer, before the first vaccine administration.

   [9]study drug, biologic or device

8. Currently enrolled in or plans to participate in another clinical trial with an investigational agent[10] that will be received during the study-reporting period.[11]

   [10]Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.

   [11]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.[12]

    [12]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. 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.

13. Has any blood dyscrasias or significant disorder of coagulation.

14. Has any chronic liver disease, including fatty liver.

15. Has a history of alcohol abuse or other recreational drug (excluding cannabis) use within 6 months before the first vaccine administration.
16. 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.
17. 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).
18. Received or plans to receive a licensed, live vaccine within 4 weeks before or after each vaccination.
19. Received or plans to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
20. Receipt of any other SARS-CoV-2 or other experimental coronavirus vaccine at any time prior to or during the study.
21. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.
22. Current use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the investigator.
23. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 28 days after the second vaccination.

Exclusion of Specific Populations

This is a first-in-human trial in healthy subjects, 18 to 55 years of age, inclusive. 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.

4.4. Treatments

4.4.1. Treatments Administered

Two doses of mRNA-1273 will be administered at 3 dose levels on Days 1 and 29.

4.4.2. Identity of Investigational Product(s)

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 a proprietary ionizable lipid 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 [redacted].

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.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

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

4.4.4. Selection of Doses in the Study

No human trials of mRNA-1273 have been conducted to date. Preclinical evaluations will occur in parallel with this phase I study. 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 (25 mcg, 100 mcg, 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 [redacted]-containing LNPs.

4.4.5. Prior and 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 last 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.

4.4.6. Treatment Compliance

All subjects are to receive 2 doses of study product administered in the clinic.

5. SAMPLE SIZE CONSIDERATIONS

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 the table below. 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, 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 cohort, we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With 45 subjects across the three dosing cohorts, the chance of observing at least one AE of probability 5% or more is at least 90%. 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.

N	"True" Event Rate	Probability of Observation (%)	N	"True" Event Rate	Probability of Observation (%)
15	0.1%	1.5	45	0.1%	4.4
	0.5%	7.2		0.5%	20.2
	1.0%	14.0		1.0%	36.4
	2.0%	26.1		2.0%	59.7
	3.0%	36.7		3.0%	74.6
	4.0%	45.8		4.0%	84.1
	5.0%	53.7		5.0%	90.1
	10.0%	79.4		10.0%	99.1
	15.0%	91.3		15.0%	99.9
	20.0%	96.5		20.0%	>99.9

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All 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. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment and will be annotated with the total population size relevant to that table/cohort, including any missing observations.

6.2. Analysis Populations

6.2.1. Modified Intention-to-Treat (mITT) Population

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.

6.2.2. Per Protocol Population

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.

6.2.3. Safety Population

The Safety Analysis population includes all subjects who received one dose of vaccine.

6.3. Covariates and Subgroups

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

6.4. Missing Data

There are no imputations planned for missing data.

For neutralization assays, any percent neutralization below zero will be imputed as zero for modeling purposes.

6.5. Interim Analyses and Data Monitoring

Cumulative safety information, study status, and primary endpoint results may be presented at a public forum in a blinded manner or presented as summaries aggregated by study arm at the discretion of the sponsor while the primary study is ongoing. Any ad-hoc analyses, jointly developed by the SDCC and/or the VRC 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.

The SMC will review cumulative AE data after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Given the 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 will be solicited electronically.

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

- For sentinel subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For all subjects in cohorts 1 and 2, the ELISA IgG data through Day 29;
- For sentinel subjects in cohort 3, the ELISA IgG data through Day 29;
- For all subjects in cohort 3, the ELISA IgG data through Day 29;
- Sentinels in cohorts 1 and 2, ELISA IgG data through Day 57;
- All subjects in cohorts 1 and 2, ELISA IgG data through Day 57;
- Sentinels in cohort 3, ELISA IgG data through Day 57;
- All subjects in cohort 3, ELISA IgG data through Day 57.
- 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.

6.6. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for vaccination and assessment of solicited and unsolicited adverse events, and the study relies on central laboratories for the assessment of immunogenicity and clinical efficacy endpoints.

6.7. Multiple Comparisons/Multiplicity

There are no adjustments planned for multiple comparisons.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A flowchart showing the disposition of study subjects, adapted from the Consort Statement will be included. This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by treatment arm.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and vaccination group for all subjects.

8. EFFICACY EVALUATION

8.1. Primary Efficacy Analysis

See Section 9 for safety analyses which are the primary endpoints of this study.

8.2. Secondary Efficacy 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 per-protocol (PP) analysis may also be performed.

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

Seroconversion rates, GMFR, GMT and geometric mean of the AUC for SARS-CoV-2 (S-2P and RBD) 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, GMT, and geometric mean of the AUC will be presented with their corresponding 95% confidence interval (CI) estimates (using Student's t-distribution) at each timepoint and overall peak GMT/AUC, and the pair-wise differences between seroconversion rates by cohort will be summarized by study day along with 95% Cis (exact methods). AUC is calculated using the trapezoidal method applied to a serial dilution curve. Pseudovirus neutralization ID_{50} and ID_{80} are calculated using a 5-parameter nonlinear function.

8.3. Exploratory Efficacy 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, GMT and geometric mean of AUC for SARS-CoV-2 (S-2P and RBD) as measured by IgG, IgA and IgM ELISA, calculated for specified timepoints by cohort and will be summarized graphically (log_{10} scale). Seroconversion rates, GMFR, GMT, and geometric mean of AUC will be presented with their corresponding 95% CI estimates (using Student's t-distribution) at each timepoint and overall peak GMT/AUC, and the pair-wise differences between seroconversion rates by cohort will be summarized by study day along with 95% CI (exact methods). AUC is calculated using the trapezoidal method applied to a serial dilution curve.

Neutralization assays using SARS-CoV-2 pseudovirus and neutralization assay (PsVNA) using a wild-type SARS-CoV-2 (PRNT) will be run using serial dilutions. ID_{50} and ID_{80} will be calculated for PsVNA data using a 5-parameter logistic regression model. ID_{50} and ID_{80} will be summarized by group using the geometric mean and 95% CI (using Student's t-distribution). Similarly, for PRNT data, $PRNT_{80}$ will be calculated using a 5-parameter logistic model. $PRNT_{80}$ will be summarized using a geometric mean and 95% CI. The minimum, median and maximum will also be reported. Neutralizing endpoints will also be displayed graphically on a log_2 scale.

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.

The magnitude and phenotype of S protein-specific B cells will be summarized at each timepoint by vaccination group.

B-cell receptor sequence analysis to identify representative B cell clones and associated major antigenic sites and amino acid residues will be described.

9. SAFETY EVALUATION

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 last vaccination. Unsolicited AEs will be coded by MedDRA® for preferred term and system organ class (SOC). All SAEs, 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 and relationship for each visit, and as the maximum over all post-vaccination visits. Graphical presentations will include bar plots.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by vaccination group. Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as “No” to each racial option.

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 23.0r higher.

Summaries of subjects’ pre-existing medical conditions will be presented by vaccination group.

Individual subject listings will be presented for all medical conditions.

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and vaccination group.

Individual subject listings will be presented for all concomitant medications.

9.2. Measurements of Treatment Compliance

The number of doses of study product administered to subjects will be presented by vaccination group as part of the subject disposition table.

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total population size. All adverse events reported will be included in the summaries and analyses.

9.3.1. Solicited Events and Symptoms

Systemic solicited adverse events were collected pre-vaccination, and systemic and local solicited adverse events were collected 30 minutes post-vaccination and then daily for 7 days after each vaccination and graded on a scale of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). Systemic events include: fatigue, headache, myalgia, arthralgia, nausea, chills and fever. Local events include: pain at injection site, erythema, and induration.

The proportion of subjects reporting at least one solicited adverse event will be summarized for each solicited adverse event, any systemic symptom, any local symptom, and any symptoms. The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) will be presented.

For each systemic and local event, any systemic event, any local event, and any solicited event, the maximum severity over 7 days after each vaccination will be summarized for the Safety population. The number and percentage of subjects reporting each event will be summarized by the maximum severity and treatment group, separately for each vaccination and over all vaccinations. For each event the denominator is the number of subjects with non-missing data for the specific event.

The number of subjects reporting a solicited adverse event will be summarized for each day post vaccination for each vaccination and for all vaccinations combined both in a summary table and graphically in a bar chart.

Solicited adverse events by subject will be presented in a listing.

9.3.2. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each vaccination and over all vaccinations. Denominators for percentages are the number of subjects who received the vaccination being summarized.

Adverse events by subject will be presented in a listing.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, vaccination and vaccination group:

- Subject incidence and total frequency of adverse events over time by dose with 95% CI (Days 1-8, Days > 8);

- Summary of severity and relationship to study product;
- Subject incidence and total frequency of related adverse events over time (Days 1-8, Days > 8) (Table 28);
- Subject listing of non-serious adverse events of moderate or greater severity;
- Listing of other significant adverse events;
- Bar chart of non-serious related adverse events by severity and MedDRA system organ class;
- Bar chart of non-serious related adverse events by severity.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

The following listings will be presented including Subject ID, Age (years) Adverse Event Description, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events;
- Adverse Events of Special Interest;
- New Onset Chronic Medical Conditions and Medically Attended Adverse Events.

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A table summarizing the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births by treatment will be presented. In addition, a listing of pregnancies and outcomes will be presented.

9.6. Clinical Laboratory Evaluations

The safety laboratories presented will be white blood cells, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, creatinine and serum lipase. The distribution of laboratory results by severity, time point, and vaccination group will be presented. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point, for each laboratory parameter, will be summarized. Subject visits with abnormal laboratory results, Grade 1 severity or higher, will be presented. A complete listing of individual clinical laboratory results with applicable reference ranges will be presented.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements included systolic blood pressure, diastolic blood pressure, pulse and oral temperature. Vital signs were assessed at Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 119, Day 209 and Day 394. Vital signs will be tabulated by visit and vaccination group.

Physical Examinations performed at Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 119, Day 209 and Day 394. The change in physical examination data from Day 1 will be summarized for each

visit by vaccination group for subjects in the Safety population. The following body systems will be assessed: Abdomen, Cardiovascular/heart, Extremities, General Appearance, Hepatobiliary/spleen, HEENT, Lymph nodes, Musculoskeletal, Neck, Neurological, Pulmonary/Chest, and Skin.

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and vaccination group for the Safety population.

9.9. Other Safety Measures

Not applicable.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

See Section 8.

12. OTHER ANALYSES

Not Applicable.

13. REPORTING CONVENTIONS

The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4, R 3.6.2 and PRISM v8.2.0 or above will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Not Applicable.

16. REFERENCES

1. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.