Phase 1, Open-Label, Randomized Study of the Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine (mRNA-1273.351) in Naïve and Previously Vaccinated Adults

DMID Protocol Number: 21-0002

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

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STATEMENT OF COMPLIANCE

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

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

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

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

Site Investigator Signature:

Signed: _____ Date: _____

Name, Credentials
Title

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1. PROTOCOL SUMMARY

1.1 Synopsis

Rationale for Proposed Clinical Study

The SARS Coronavirus 2 (SARS-CoV-2) pandemic has continued to intensify and as of January 30, 2021, there are over 102 million cases and over 2 million deaths globally (Center for Systems Science and Engineering (CSSE) at Johns Hopkins University [systems.jhu.edu]).

ModernaTX, Inc has developed a messenger RNA (mRNA)-based vaccine platform 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 used its mRNA-based technology to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine encoding for the spike (S) protein of the original Wuhan-Hu-1 isolate of SARS-CoV-2 (mRNA-1273) and in 2020 initiated Phase 1, Phase 2, and Phase 3 trials of a two-dose schedule of this vaccine, given 28 days apart, in adults, in the United States (Jackson LA et al, 2020; Anderson EJ et al, 2020; Widge AT et al, 2020; Baden LR et al, 2020). The Phase 3 trial demonstrated 94.1% efficacy against symptomatic confirmed Coronavirus Disease 2019 (COVID-19) 14 days or later after the second vaccination and 100% efficacy against severe COVID-19 (Baden LR et al, 2020). On December 18, 2020 the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for administration of the vaccine to adults in the United States.

Recently, SARS-CoV-2 variants with mutations in the S protein have emerged. A variant first identified in South Africa (B.1.351) is associated with increased transmission, higher viral burden, and possibly increased mortality in infected persons (Tegally H et al, 2020). To date, four SARS-CoV-2 vaccines, all based on the Wuhan-sequence of the S protein, have shown reduced activity against the B.1.351 variant (Wang P et al, 2021; Wu K et al, 2021). Sera from individuals vaccinated with mRNA-based vaccines had a 6-to-9-fold reduction in neutralizing activity against a B.1.351-matched pseudovirion relative to a Wuhan-matched pseudovirion. More recently, pivotal vaccine efficacy studies testing both viral vector and adjuvanted protein vaccines had lower efficacy in regions where B.1.351 was known to be circulating (Callaway E & Mallapaty S, 2021; Cohen J, 2021).

There is an urgent need for vaccination strategies that induce broader protection that includes variants such as B.1.351 to decrease morbidity and mortality and reduce SARS-CoV-2 transmission. ModernaTX, Inc, is developing a mRNA vaccine (mRNA-1273.351) that is similar to the mRNA-1273 vaccine available under the EUA, but in which the mRNA encodes for the S protein of the B.1.351 variant.

This phase 1 clinical trial will evaluate the safety and immunogenicity of varying doses of mRNA-1273.351, given in vaccination schedules alone, in sequences with mRNA-1273, or as a combination vaccine that includes mRNA-1273, in adults 18 years of age and older who are either naïve to SARS-CoV-2 (have no history of COVID-19 disease or vaccination) or who have been previously vaccinated with mRNA-1273.

Study Design

This is a phase 1, open-label, randomized clinical trial in males and non-pregnant females, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial is designed to assess the

safety, reactogenicity and immunogenicity of mRNA-1273.351 manufactured by ModernaTX, Inc, given in vaccination schedules alone, sequentially, or coadministered with mRNA-1273. mRNA-1273.351 is a novel LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant. Enrollment will occur at approximately five domestic clinical research sites.

This study includes two cohorts. Cohort 1 will provide rapid information about the immunogenicity of mRNA-1273.351 in a previously vaccinated group. This cohort can inform near term public health decisions if the variant virus becomes more widespread. Cohort 2 will evaluate different strategies for generation of cross protective immune responses in a naïve population. This cohort will take longer to provide information on the immunogenicity of mRNA-1273.351, but is important to inform future public health strategies. As Cohorts 1 and 2 are in different populations, they can be enrolled in parallel as determined by each site.

Cohort 1 will include subjects 18 years of age and older who received two vaccinations of mRNA-1273 at dosages of 50 mcg, 100 mcg, or 250 mcg in the Phase 1 clinical trial (DMID 20-0003). Those subjects will be offered enrollment into this study approximately 9 to 12 months after they received the second vaccination in DMID 20-0003. At enrollment in this study, their long-term follow-up in DMID 20-0003 will be terminated. Subjects will be randomized, within each of the DMID 20-0003 cohorts (age and dosage groups – 50 mcg, 100 mcg, and 250 mcg), 1:1 (as outlined in Table 1) to either:

- Arm 1A, vaccination with a 50-mcg dose of the mRNA-1273.351 variant, or
- Arm 1B, vaccination with a combination vaccination that includes 25 mcg of mRNA-1273 and 25 mcg of mRNA-1273.351.

The anticipated sample size to be drawn from the DMID 20-0003 study population is approximately 45 subjects 18 through 55 years of age and approximately 20 subjects 56 years of age and older.

Subjects in Cohort 1 will receive a single intramuscular (IM) injection of the designated vaccine and will be followed through 12 months after vaccination. Follow-up visits will occur on Days 8, 15, and 29, as well as 3, 6, and 12 months after the vaccination.

Table 1. Cohort 1 Treatment Arms

Arm	Sample Size	Vaccination Product and Dose
1A	~30	50 mcg mRNA-1273.351
1B	~30	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351

Cohort 2 will include approximately 150 participants 18 through 55 years of age who have not received a COVID-19 vaccine, have no known history of COVID-19 or SARS-CoV-2 infection, and do not have underlying conditions that are associated with an increased risk of severe illness from SARS-CoV-2 infection. Enrollment may close before the full 150 participants based on estimates on the timing of immunogenicity results and the need to inform public health decisions. They will be randomly assigned to one of 8 treatment arms and will receive 2 or 3 IM injections of the vaccine (as outlined in Table 2), and followed through 12 months after the last

vaccination. Follow-up visits will occur 7, 14, and 28 days after each vaccination, as well as 3, 6 and 12 months post the last vaccination.

Table 2: Cohort 2 Treatment Arms

Arm	Sample Size	First Vaccination	Second Vaccination		Third Vaccination	
		Product and Dose	Interval	Product and Dose	Interval	Product and Dose
2A	15	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351
2B	15	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351
2C	20	100 mcg mRNA-1273.351	28 days	100 mcg mRNA-1273.351	None	
2D	20	50 mcg mRNA-1273.351	28 days	50 mcg mRNA-1273.351	None	
2E	20	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273.351	None	
2F	20	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351	None	
2G	20	50 mcg mRNA-1273 + 50 mcg mRNA-1273.351	28 days	50 mcg mRNA-1273 + 50 mcg mRNA-1273.351	None	
2H	20	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351	28 days	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351	None	

Summary of Treatment Arms:

- 2A: Evaluates the mRNA1273 EUA vaccination series, plus a variant vaccine as a third dose.
- 2B: Evaluates a 50-mcg vaccination series, plus a variant vaccine as a third dose.
- 2C-2D: Evaluate 2 doses of the homologous variant vaccine at different dose levels.
- 2E-2F: Evaluate heterologous prime-boost strategies at 2 dose levels.
- 2G-2H: Evaluate a 1:1 mix of vaccine (2 doses), with the total dose for both vaccines equal to 100 mcg and 50 mcg, respectively.

For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays.

Objectives

- Primary: To evaluate the safety and reactogenicity of mRNA-1273 and mRNA-1273.351 vaccines, in naïve and previously vaccinated individuals.
- Secondary: To assess humoral immunogenicity of mRNA-1273 and mRNA-1273.351 vaccines, in naïve and previously vaccinated individuals.

Inclusion Criteria

See inclusion criteria in Section 5.1.

Exclusion Criteria

See exclusion criteria in Section 5.2.

Study Phase

- 1

Study Population

- Cohort 1, approximately 60 males and non-pregnant females 18 years of age and older, who are in good health and received two vaccinations of mRNA-1273 at dosages of 50 mcg, 100 mcg or 250 mcg in DMID 20-0003.
- Cohort 2, approximately 150 males and non-pregnant females, 18 through 55 years of age, who are in good health.

Sites

- Approximately five domestic clinical research sites.

Study Intervention:

- mRNA-1273 (0.2 milligrams [mg]/mL)
- mRNA-1273.351 (0.5 mg/mL)
- Each vaccine formulation will be diluted in 0.9% Sodium Chloride (NaCl) for injection, United States Pharmacopeia (USP).
- Each dose will be administered via IM injection into the deltoid muscle.
- For Cohort 2, Arms 2A-H, the second dose of vaccine will be administered preferably in the same arm used for the first dose.
- For Cohort 2, Arms 2A and 2B, the third dose of vaccine will also be administered preferably in the same arm used for the first dose.

Study Duration

- The study duration is anticipated to be approximately 17 months (from start of screening through last subject last visit).

Subject Duration

- The duration for each individual subject in Cohort 1 (from first contact to last visit) is approximately 13 months.
- The duration for each individual subject in Cohort 2 (from first contact to last visit) is approximately:
    - 15 months for Arms 2A and 2B.
    - 14 months for Arms 2C through 2H.

Safety

- The study will use pausing rules for vaccinations in the study overall and for not administering second or third vaccinations to 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.

1.2 Schedule of Activities (SOA)

Table 3: SOA for Cohort 1 (One Vaccination)

Study Day	-42 to -1	1	8*	15	29	91	181	366	Unscheduled Visit	Early Termination Visit
Visit Window (±number of days)		0	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05	06	07		
Informed Consent	X	X[a]								
Review Eligibility Criteria	X	X								
Medical History	X	X[a]								
Vaccination		X								
Concomitant Medications		X	X	X	X					
Interim History		X[b]		X	X	X	X	X	X	X
Symptom-Directed Physical Examination	X	X		X	X	X	X	X	X	X
Vital Signs[c]		X		X	X	X	X	X	X	X
Height and Weight (for BMI)	X	X[a]								
Pregnancy Test[d]		X								
Memory Aid: Solicited AEs		X	X	X[e]						
Unsolicited AEs		X	X	X	X				X	X
SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs		X	X	X	X	X	X	X	X	X
Serum for Serological Immunogenicity Assays		X		X	X	X	X	X		X
Peripheral Blood Mononuclear Cells (PBMCs) for Cellular Immunology Assays (and Plasma)		X		X			X	X		X

* Telephone call.

a) If not performed at Visit 00.

b) If medical history performed at Visit 00, then interim history at Visit 01.

c) Vital signs to be obtained pre and post vaccination. Otherwise, only as clinically indicated.

d) For women of childbearing potential, a negative urine pregnancy test on Day 1 with results confirmed prior to enrollment.

e) Collect Memory Aid and assess for delayed onset local reactions.

Table 4: SOA for Cohort 2: 2A-B (Three Vaccinations)

Study Day	-42 to -1	1	8*	15	29	36*	43	57	64*	71	85	147	237	422	Unsc Visit	Early Term Visit
Visit Window (±number of days)		0	1	2	2	1	2	2	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05[e]	06[e]	07[e]	08[f]	09[f]	10[f]	11[f]	12[f]	13[f]		
Informed Consent	X	X[a]														
Review Eligibility Criteria	X	X														
Medical History	X	X[a]														
Vaccination		X			X			X								
Concomitant Medications		X	X	X	X	X	X	X	X	X	X					
Interim History		X[b]		X	X		X	X		X	X	X	X	X	X	X
Symptom-Directed Physical Examination	X	X		X	X		X	X		X	X	X	X	X	X	X
Vital Signs[c]		X		X	X		X	X		X	X	X	X	X	X	X
Height and Weight (for BMI)	X	X[a]														
Pregnancy Test[d]		X			X			X								
Memory Aid: Solicited AEs		X	X	X[g]	X	X	X[g]	X	X	X[g]						
Unsolicited AEs		X	X	X	X	X	X	X	X	X	X					
SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum for Serological Immunogenicity Assays		X		X	X		X	X		X	X	X	X	X		X
Peripheral Blood Mononuclear Cells (PBMCs) for Cellular Immunology Assays (and Plasma)		X		X	X		X	X		X			X	X		X

* Telephone call.

a) If not performed at Visit 00.

b) If medical history performed at Visit 00, then interim history at Visit 01.

c) Vital signs to be obtained pre and post vaccination. Otherwise, only as clinically indicated.

d) For women of childbearing potential, a negative urine pregnancy test on Day 1 with results confirmed prior to enrollment.

e) Visits 05-07 windows should be based off the actual Visit 04 date.

f) Visits 08-13 windows should be based off the actual Visit 07 date.

g) Collect Memory Aid and assess for delayed onset local reactions.

Table 5: SOA for Cohort 2: 2C-H (Two Vaccinations)

Study Day	-42 to -1	1	8*	15	29	36*	43	57	119	209	394	Unsc Visit	Early Term Visit
Visit Window (±number of days)		0	1	2	2	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05[e]	06[e]	07[e]	08[e]	09[e]	10[e]		
Informed Consent	X	X[a]											
Review Eligibility Criteria	X	X											
Medical History	X	X[a]											
Vaccination		X			X								
Concomitant Medications		X	X	X	X	X	X	X					
Interim History		X[b]		X	X		X	X	X	X	X	X	X
Symptom-Directed Physical Examination	X	X		X	X		X	X	X	X	X	X	X
Vital Signs[c]		X		X	X		X	X	X	X	X	X	X
Height and Weight (for BMI)	X	X[a]											
Pregnancy Test[d]		X			X								
Memory Aid: Solicited AEs		X	X	X[f]	X	X	X[f]						
Unsolicited AEs		X	X	X	X	X	X	X					
SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs		X	X	X	X	X	X	X	X	X	X	X	X
Serum for Serological Immunogenicity Assays		X		X	X		X	X	X	X	X		X
Peripheral Blood Mononuclear Cells (PBMCs) for Cellular Immunology Assays (and Plasma)		X		X	X		X			X	X		X

* Telephone call.

a) If not performed at Visit 00.
b) If medical history performed at Visit 00, then interim history at Visit 01.
c) Vital signs to be obtained pre and post vaccination. Otherwise, only as clinically indicated.
d) For women of childbearing potential, a negative urine pregnancy test on Day 1 with results confirmed prior to enrollment.
e) Visits 05-10 windows should be based off the actual Visit 04 date.
f) Collect Memory Aid and assess for delayed onset local reactions.

2. INTRODUCTION

2.1 Background and Study Rationale

An outbreak of COVID-19 caused by a novel SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease has since spread globally (WHO 2020a). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 Mar 2020; however, widespread community transmission was already occurring in many locations. As of 14 Jan 2021, more than 92 million cases and 1.9 million deaths worldwide have been attributed to the COVID-19 pandemic (JHU 2020; WHO 2020a).

ModernaTX, Inc has developed a vaccine platform based on the principle and observations that cells *in vivo* can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. mRNA is highly precise in its translation into proteins that match viral antigens. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The estimated half-life for mRNA after injection is approximately 8 to 10 hours, before degradation by native RNases in the body, but the duration of effect also depends on the half-life of the expressed protein, which persists in the body for several days. mRNA vaccines have been used to induce immune responses against infectious viral pathogens such as cytomegalovirus, human metapneumovirus, parainfluenza virus type 3, Zika, and influenza.

The mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S-2P) in a prefusion conformation, derived from the Wuhan-Hu-1 strain (Corbett KS et al, 2020). The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study sponsored by DMID (NCT04283461), for safety and immunogenicity in a Moderna-sponsored Phase 2a study (NCT04405076), and for safety, efficacy, and immunogenicity in a Moderna-sponsored Phase 3 study (NCT04470427). All three of these studies are ongoing and conducted in the US.

The primary efficacy objective of the Phase 3 study was met, with the vaccine efficacy of mRNA-1273 to prevent symptomatic COVID-19 disease observed to be 94.1%. The vaccine was also observed to be efficacious in preventing severe COVID-19. In December 2020 the FDA issued Emergency Use Authorization of mRNA-1273 (Moderna COVID-19 Vaccine) for active immunization to prevent COVID-19 in individuals 18 years of age and older.

Recently, SARS-CoV-2 variants with mutations in the S protein have emerged. A variant first identified in South Africa (B.1.351) is associated with increased transmission, higher viral burden, and possibly increased mortality in infected persons (Tegally H et al, 2020). To date, four vaccines, all based on the Wuhan-sequence of the S protein, have shown reduced activity against the B.1.351 variant. Sera from individuals vaccinated with mRNA-based vaccines had a 6-to-9-fold reduction in neutralizing activity against a B.1.351-matched pseudovirion relative to a Wuhan-matched pseudovirion (Wang P et al, 2021; Wu K et al, 2021). More recently, pivotal studies testing both viral vector and adjuvanted protein technologies had lower efficacy in regions where B.1.351 was known to be circulating (Callaway E & Mallapaty S; Cohen J, 2021). Hence, the development and testing of vaccines targeting this SARS-CoV-2 variant is urgently needed.

mRNA-1273.351, like mRNA-1273, encodes the prefusion stabilized S protein of SARS-CoV-2. However, the mRNA of mRNA-1273.351 incorporates the key mutations present in the B.1.351 strain of the virus. This phase 1 clinical trial will evaluate the immunological benefit of boosting subjects previously vaccinated with mRNA-1273 (DMID 20-0003) with the B.1.351 strain-specific S protein, as well as the breadth of response induced by vaccinating with mRNA-1273 and mRNA-1273.351 in naïve persons, who have not previously received a SARS-CoV-2 vaccine and are not known to have been previously infected with SARS-CoV-2.

Results from this study will inform the design of subsequent clinical studies of mRNA-1273.351. Plans for further clinical development are being drafted in consultation with regulatory authorities by Moderna. This will include evaluation in a subsequent Phase 2/3 study that will assess the safety and immunogenicity of both monovalent mRNA-1273.351 and multivalent mRNA-1273/mRNA-1273.351. These studies will assess both single-dose boosting at different dose intervals than the current study and a two-dose primary series at different dose levels in larger numbers of study participants.

2.1.1 Public Readiness and Emergency Preparedness Act

The study vaccines, mRNA-1273 and mRNA-1273.351, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as mRNA-1273 and mRNA-1273.351. The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 10, 2020 and is retroactively effective from February 4, 2020.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at http://www.hrsa.gov/cicp/. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

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

Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

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

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, IM injection, possible reactions to the mRNA-1273 and mRNA-1273.351 vaccines, and breach of confidentiality.

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

Risks of mRNA-1273 and mRNA-1273.351

Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent O et al, 2002).

Anaphylactic reactions have occurred after administration of the Moderna and the Pfizer mRNA COVID-19 vaccines in vaccination campaigns under Emergency Use Authorization (EUA) in the United States. Most of these reactions had onset within 30 minutes of vaccination, most of these events occurred in persons with a prior history of allergy, and nearly all were women. The currently estimated risk of an anaphylactic reaction to the Moderna EUA COVID-19 vaccine is about 3 events per million vaccinations.

As a precaution, all subjects will remain under observation at the study site for at least 30 minutes after injection.

Infrequently, people who have received dermal fillers might experience swelling at or near the site of filler injection (usually face or lips) following administration of a dose of an mRNA COVID-19 vaccine. The swelling appears to be temporary and resolves with medical treatment, including corticosteroid therapy. COVID-19 vaccines can be administered to people who have received injectable dermal fillers who have no contraindications or precautions for vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by ModernaTX, Inc containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection. A small percentage of participants may experience late local inflammatory reactions, with onset seven or more days after, usually the first, vaccination, and characterized by redness in the deltoid area of the upper arm and/or pain or itching (Baden LR et al, 2020). These reactions are self-limited and are not a contraindication to subsequent vaccinations in the vaccination series.

The majority of local and systemic solicited adverse events (AEs) observed after injection with mRNA-1273 at the 100-mcg dose level have been mild to moderate in severity. The most commonly reported systemic AEs were headache, myalgia, fatigue, chills, and fever (Baden LR et al, 2020). In the majority of cases, the reactions resolved spontaneously within several days. Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline, pre-vaccination (Day 1) values over time. The clinical significance of these observations is unknown.

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

Subjects will be informed of the potential risk of myocarditis or pericarditis and be advised to monitor for symptoms of myocarditis or pericarditis, including chest pain, shortness of breath, tachycardia, or palpitations. Subjects will be encouraged to immediately contact research staff and their medical provider if these symptoms occur following a study vaccination.

There is limited experience with administration of a third dose of the mRNA COVID-19 vaccines, and it is possible that the third dose may be associated with more frequent or more severe adverse events.

Further details are provided in the current IB for mRNA-1273. mRNA-1273.351 has not been tested clinically, but based on its similarity to mRNA-1273, the risks are expected to be similar.

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. Data from the Phase 3 placebo-controlled clinical trial of mRNA-1273 demonstrated 94.1% efficacy of the vaccine when 100 mcg is administered as a two-vaccination series versus placebo against SARS-CoV-2 infection. The efficacy of other dosages of mRNA-1273 (e.g., 25, 50, or 250 mcg) is not known. The doses and vaccination strategies used in this trial may or may not alter this protection. It is unknown if the mRNA-1273.351 vaccine will provide protection against infection with the B.1.351 variant.

3. OBJECTIVES AND ENDPOINTS

Table 6: Objectives and Endpoints (Outcome Measures)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To evaluate the safety and reactogenicity of mRNA-1273 and mRNA-1273.351 vaccines, in naïve and previously vaccinated individuals.	• 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, Protocol Specified AESIs, NOCMCs, and MAAEs

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	from the first vaccination through 12 months after the last vaccination.
Secondary	
• To assess humoral immunogenicity of mRNA-1273 and mRNA-1273.351 vaccines, in naïve and previously vaccinated individuals.	• Response rate, and magnitude of SARS-CoV-2-specific antibody binding and neutralization titers in serum samples as assessed via a range of assays at all timepoints.
Exploratory	
• To assess, in at least a subset of samples the innate immune response and B cell response following vaccination.	• Magnitude, phenotype, and percentage of innate immune cells and SARS-CoV-2 specific B cells, as measured by flow cytometry, and targeted B cell repertoire analysis at different timepoints post vaccination relative to baseline.
• 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.

4. STUDY DESIGN

4.1 Overall Design

This is a phase 1, open-label, randomized clinical trial in males and non-pregnant females, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of mRNA-1273.351 manufactured by ModernaTX, Inc, given in vaccination schedules alone, sequentially, or coadministered with mRNA-1273. mRNA-1273.351 is a novel LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant. Enrollment will occur at approximately five domestic clinical research sites.

This study includes two cohorts. Cohort 1 will provide rapid information about the immunogenicity of mRNA-1273.351 in a previously vaccinated group. This cohort can inform near term public health decisions if the variant virus becomes more widespread. Cohort 2 will evaluate different strategies for generation of cross protective immune responses in a naïve population. This cohort will take longer to provide information on the immunogenicity of

mRNA-1273.351, but is important to inform future public health strategies. As Cohorts 1 and 2 are in different populations, they can be enrolled in parallel as determined by each site.

Cohort 1 will include subjects 18 years of age and older who received two vaccinations of mRNA-1273 at dosages of 50 mcg, 100 mcg, or 250 mcg in the Phase 1 clinical trial (DMID 20-0003). Those subjects will be offered enrollment into this study approximately 9 to 12 months after they received the second vaccination in DMID 20-0003. At enrollment in this study, their long-term follow-up in DMID 20-0003 will be terminated. Subjects will be randomized, within each of the DMID 20-0003 cohorts (age and dosage groups – 50 mcg, 100 mcg, and 250 mcg), 1:1 (as outlined in Table 7) to either:

- Arm 1A, vaccination with a 50-mcg dose of the mRNA-1273.351 variant, or
- Arm 1B, vaccination with a combination vaccination that includes 25 mcg of mRNA-1273 and 25 mcg of mRNA-1273.351.

The anticipated sample size to be drawn from the DMID 20-0003 study population is approximately 45 subjects 18 through 55 years of age and approximately 20 subjects 56 years of age and older.

Subjects in Cohort 1 will receive a single intramuscular (IM) injection of the designated vaccine and will be followed through 12 months after vaccination. Follow-up visits will occur on Days 8, 15, and 29, as well as 3, 6, and 12 months after the vaccination.

Table 7. Cohort 1 Treatment Arms

Arm	Sample Size	Vaccination Product and Dose
1A	~30	50 mcg mRNA-1273.351
1B	~30	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351

Cohort 2 will include approximately 150 participants 18 through 55 years of age who have not received a COVID-19 vaccine, have no known history of COVID-19 or SARS-CoV-2 infection, and do not have underlying conditions that are associated with an increased risk of severe illness from SARS-CoV-2 infection. Enrollment may close before the full 150 participants based on estimates on the timing of immunogenicity results and the need to inform public health decisions. They will be randomly assigned to one of 8 treatment arms and will receive 2 or 3 IM injections of the vaccine (as outlined in Table 8), and followed through 12 months after the last vaccination. Follow-up visits will occur 7, 14, and 28 days after each vaccination, as well as 3, 6, and 12 months post the last vaccination.

Table 8: Cohort 2 Treatment Arms

Arm	Sample Size	First Vaccination	Second Vaccination		Third Vaccination	
		Product and Dose	Interval	Product and Dose	Interval	Product and Dose
2A	15	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351
2B	15	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351
2C	20	100 mcg mRNA-1273.351	28 days	100 mcg mRNA-1273.351	None	
2D	20	50 mcg mRNA-1273.351	28 days	50 mcg mRNA-1273.351	None	
2E	20	100 mcg mRNA-1273	28 days	100 mcg mRNA-1273.351	None	
2F	20	50 mcg mRNA-1273	28 days	50 mcg mRNA-1273.351	None	
2G	20	50 mcg mRNA-1273 + 50 mcg mRNA-1273.351	28 days	50 mcg mRNA-1273 + 50 mcg mRNA-1273.351	None	
2H	20	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351	28 days	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351	None	

Summary of Treatment Arms:

- 2A: Evaluates the mRNA1273 EUA vaccination series, plus a variant vaccine as a third dose.
- 2B: Evaluates a 50-mcg vaccination series, plus a variant vaccine as a third dose.
- 2C-2D: Evaluate 2 doses of the homologous variant vaccine at different dose levels.
- 2E-2F: Evaluate heterologous prime-boost strategies at 2 dose levels.
- 2G-2H: Evaluate a 1:1 mix of vaccine (2 doses), with the total dose for both vaccines equal to 100 mcg and 50 mcg, respectively.

For both Cohorts 1 and 2, reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays.

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

Schedule of assessments are found in **Section 1.2, Schedule of Activities.**

4.2 Scientific Rationale for Study Design

This phase 1 clinical trial is designed as an open-label study, without administration of a placebo formulation. An open-label study will facilitate the need for rapid review and dissemination of study data for public health reasons.

4.3 Justification for Doses

In the Phase 1 clinical trial, DMID 20-0003, mRNA-1273, administered as two injections 28 days apart, was investigated at dosages of 25, 50, 100 and 250 mcg in subjects 18 through 55 years of age, and at dosages of 25, 50, and 100 mcg in older cohorts (56-70 years of age and >71 years of age) (Jackson LA et al, 2020; Anderson EJ et al, 2020). The 100-mcg dose induced higher antibody titers than the 25-mcg dose, whereas the 250-mcg dose did not lead to significant increases, which supported evaluation of the 100-mcg dose in Phase 2 and Phase 3 trials. Subsequent to the start of the Phase 3 trial, an interim analysis of immunogenicity data from the Phase 2 demonstrated that the 50 and 100-mcg doses in a two-dose series are similarly immunogenic (Chu L et al, 2021) and warrants further evaluation. The primary efficacy analysis from the Phase 3 trial evaluating a two-dose schedule of a 100-mcg mRNA-1273 vaccine led to the issuance of the EUA and initiation of a vaccination campaign in the United States.

The Phase 2 trial of mRNA-1273 evaluated doses of 50 mcg and 100 mcg, administered as a two-vaccination series, in 600 adults ≥18 years of age. The safety profile of both formulations was acceptable (Chu L et al, 2021). Anti-SARS-CoV-2 S binding and neutralizing antibodies were induced by both dose levels of mRNA-1273 within 28 days after the first vaccination, and rose substantially to peak titers by 14 days after the second vaccination, exceeding levels of convalescent sera from COVID-19 patients. The antibodies remained elevated through the last timepoint assessed at 57 days. Neutralizing responses met criteria for seroconversion within 28 days after the first vaccination in the majority of participants, with rates of 100% observed at 14 and 28 days after the second vaccination. Binding and neutralizing antibody responses were generally comparable in participants who received the 100 mcg mRNA-1273 and the 50 mcg dose at all time points and across the age groups of ≥18 to <55 years and ≥55 years. These findings support the evaluation of mRNA-1273 and mRNA-1273.351 at total dosages of 50 or 100 mcg per vaccination.

Table 1. Cohort 1 Treatment Arms

Arm	Sample Size	Vaccination Product and Dose

1A	~30	50 mcg mRNA-1273.351
1B	~30	25 mcg mRNA-1273 + 25 mcg mRNA-1273.351

Cohort 2 will include approximately 150 participants 18 through 55 years of age who have not received a COVID-19 vaccine, have no known history of COVID-19 or SARS-CoV-2 infection, and do not have underlying conditions that are associated with an increased risk of severe illness from SARS-CoV-2 infection. Enrollment may close before the full 150 participants based on estimates on the timing of immunogenicity results and the need to inform public health decisions. They will be randomly assigned to one of 8 treatment arms and will receive 2 or 3 IM injections of the vaccine (as outlined in Table 2), and followed through 12 months after the last vaccination. Follow-up visits will occur 7, 14, and 28 days after each vaccination, as well as 3, 6 and 12 months post the last vaccination.

5. TABLE 3TABLE 3STUDY POPULATION

Two cohorts will be enrolled. For Cohort 1, approximately 60 males and non-pregnant female subjects 18 years of age and older, who are in good health and received two vaccinations of mRNA-1273 at dosages of 50 mcg, 100 mcg or 250 mcg in DMID 20-0003 will be invited to participate in this study.

For Cohort 2, approximately 150 males and non-pregnant females, 18 through 55 years of age, who have never been vaccinated against SARS-CoV-2 or are not known to have been infected with SARS-CoV-2, and are at low risk for severe disease, in good health, and meet all eligibility criteria will be enrolled. The target population should reflect the community at large.

The estimated time from initiation of enrollment to complete enrollment in this clinical trial is approximately 4 weeks (though could take up to 8 weeks). Information regarding this trial may be provided to potential subjects who have previously participated in other vaccine trials conducted at the participating site. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use. Screening can occur up to 42 days prior to the first vaccination.

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 principal investigator (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. Cohort 1: previously received 2 doses of mRNA-1273 IM as part of DMID 20-0003.
5. Cohort 1: Male or non-pregnant female, ≥18 years of age at time of enrollment.

   Cohort 2: Male or non-pregnant female, 18 through 55 years of age at time of enrollment.
6. Women of childbearing potential[1] must agree to practice abstinence or use at least one acceptable primary form of contraception.[2,3]

   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]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.

[3]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. In good health.[4]

   [4]As determined by medical history and physical examination to evaluate acute or ongoing chronic medical diagnoses/conditions that have been present for at least 90 days, which would affect the assessment of safety of subjects. Chronic medical diagnoses/conditions should be stable for the last 60 days (no hospitalizations, ER, or urgent care for condition or need for supplemental oxygen). This includes no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis/condition in the 60 days before enrollment. Any prescription change that is due to change of health care provider, insurance company, etc., or done for financial reasons, and in the same class of medication, will not be considered a deviation of this inclusion criterion. Any change in prescription medication due to ***improvement*** *of a disease outcome or for dose optimization, as determined by the participating site PI or appropriate sub-investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the participating site PI or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity, and do not indicate a worsening of medical diagnosis/condition. Similarly, medication changes subsequent to enrollment and study vaccination are acceptable provided the change was not precipitated by deterioration in the chronic medical condition, and there is no anticipated additional risk to the subject or interference with the evaluation of responses to study vaccination.*

8. Oral temperature is less than 100.0°F (37.8°C).
9. Must agree to have samples stored for secondary research.
10. Agrees to adhere to Lifestyle Considerations (defined in Section 5.4) throughout study duration.
11. 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 prior to each vaccine administration.
2. BMI >40.0 kg/m^2.
3. Female subject who is breastfeeding.
4. Has any medical disease or condition that, in the opinion of the participating site PI or appropriate sub-investigator, precludes study participation.[5]

[5]*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.*

5. Presence of self-reported or medically documented significant medical or psychiatric condition(s).[6]

   [6]*Significant medical or psychiatric conditions include but are not limited to:*

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

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

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

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

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

   An immunodeficiency of any cause.

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

   Type 2 diabetes mellitus, not including prediabetes.

6. Has an acute illness[7], as determined by the participating 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.

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

7. Has participated in another investigational study involving any investigational product[8] within 5 half-lives before the first vaccine administration.

   [8]*study drug, biologic or device*

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

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

[10]*Up to 15 months after the first vaccination.*

9. Has a history of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticaria, angioedema, other significant reaction) to drugs or any previous licensed or unlicensed vaccines or to polyethylene glycol (PEG) or a PEG-containing product.
10. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness.[11]

    [11]*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.*
11. Anticipating the need for immunosuppressive treatment within the next 6 months.
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. Received or plans to receive a licensed, live vaccine within 4 weeks before or after each vaccination.
15. Received or plans to receive a licensed, inactivated vaccine within 2 weeks before or after each vaccination.
16. Receipt of any other SARS-CoV-2 vaccine or any experimental coronavirus vaccine at any time prior to or during the study, except Cohort 1 subjects who received mRNA-1273 in DMID 20-0003.
17. Close contact of anyone known to have SARS-CoV-2 infection within 14 days prior to vaccine administration.
18. History of COVID-19 diagnosis, positive SARS-CoV-2 PCR test, or, for Cohort 2 only, a known positive SARS-CoV-2 serologic test.
19. On current treatment with investigational agents for prophylaxis of COVID-19.

5.2.1 Exclusion of Specific Populations

The effects on the fetus are not known; therefore, pregnant women will not be eligible for the trial. Children will not be included in this trial as presently there are no safety or efficacy data in adults for the variant strain. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including these populations.

5.3 Inclusion of Vulnerable Subjects

Not Applicable

5.4 Lifestyle Considerations

During this study subjects are asked to:

- 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.

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/baseline 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: There are two clinical presentations of mRNA-1273 — mRNA-1273 and mRNA-1273.351

mRNA-1273 (0.2 mg/mL) is an LNP dispersion containing an mRNA that encodes for the pre fusion stabilized S protein of the Wuhan-Hu-1 strain of SARS-CoV-2. mRNA-1273 consists of an mRNA Drug Substance that is manufactured into LNPs composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and PEG2000 DMG.

mRNA-1273.351 (0.5 mg/mL) is formulated in the same way but contains mRNA that encodes for the prefusion stabilized S protein of the B.1.351 variant SARS-CoV-2 strain.

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 (0.2 mg/mL) will be diluted in 0.9% NaCl for injection, USP to obtain the specified antigen content in 0.5 mL doses.

mRNA-1273.351 (0.5 mg/mL) will be diluted in 0.9% NaCl for injection, USP to obtain the specified antigen content in 0.5 mL doses.

Each dose will be administered via IM injection into the deltoid muscle.

For Cohort 2, Arms 2A-H, the second dose of vaccine will be administered preferably in the same arm used for the first dose.

For Cohort 2, Arms 2A and 2B, the third dose of vaccine will also be administered preferably in the same arm used for the first dose.

The pharmacist will prepare a single dose for each subject based on cohort assignment.

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 and mRNA-1273.351 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 participating site will receive specific instructions on how to return the affected study product(s) to the DMID Clinical Material Services (CMS) or destroy the affected study product(s) on-site. If the study product 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 from the same final mixed vial within 30 minutes of completion of dosing solution preparation. 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 study vaccine is 8 hours at room temperature after the solution is drawn into the dosing syringe.

6.1.3 4.1Dose Modifications

No dose modifications.

6.2 Accountability/Handling/Storage/Preparation

6.2.1 Acquisition and Accountability

Product: mRNA-1273 and mRNA-1273.351

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

Upon request by DMID, study product 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 study product, diluent (0.9% NaCl for injection, USP), and vial admixtures, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the DMID-approved clinical monitoring plan (CMP).

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

- used and unused mRNA-1273 or mRNA-1273.351 vials
- used mixing vials
- mRNA-1273 or mRNA-1273.351 cartons

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

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

6.2.2 Formulation and Appearance

Product: mRNA-1273 and mRNA-1273.351

mRNA-1273 is provided as a sterile liquid for injection, white to off-white dispersion in appearance.

mRNA-1273.351 is provided as a sterile liquid for injection, white to off-white dispersion in appearance.

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 and mRNA-1273.351

mRNA-1273 vials are stored frozen between -25º to -15ºC. Vials can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use. Unpunctured vials may be stored between 8° to 25°C for up to 12 hours. Do not refreeze. Store in the original carton to protect from light.

mRNA-1273.351 vials are stored frozen between -60°C to -90°C. Stability and compatibility with the apparatus intended for administration for up to 8 hours after preparation were assessed. The prepared doses were stable for clinical in-use for up to 8 hours at room temperature. Store in the original carton to protect from light.

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 participating site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on-site. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

mRNA-1273 and mRNA-1273.351 must be stored in a secure area with limited access (pharmacy staff only), and must be stored frozen. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator; or alternate plan in the event of a power failure. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, vaccine accountability study staff (e.g., pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. Only vaccine accountability study staff (e.g., pharmacy staff) should have access to the product used in this study. The participating site is responsible for reporting any mRNA-1273 and mRNA-1273.351 that was not temperature controlled during shipment or during storage to the pharmacy staff. Such mRNA-1273 and mRNA-1273.351 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.

6.3.2 Randomization and Blinding

Subjects in Cohort 1 will be stratified by DMID 20-0003 cohort (age and dosage group) and randomized 1:1 to Arm 1A or 1B. Subjects in Cohort 2 will be randomized in a ratio of 3:3:4:4:4:4:4:4 for Arms 2A-H. Randomization will be done in the SDCC's Advantage eClinical[SM] (Electronic Data Capture System).

6.3.3 Blinding and Masking Procedures

This study is unblinded.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Concomitant medications include only prescription medications and vaccines received outside of the study taken by the subject at the time of enrollment through 28 days after the last vaccination. At each study visit, if there are new SAEs, Protocol Specified AESIs, MAAEs, or NOCMCs, concomitant medications 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 Pausing Criteria and Discontinuation of Study Intervention

7.1.1 Pausing 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) related to vaccine administration, in the same Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding.

7.1.2 Criteria for Continuation of Dosing and Redosing

In the event a pausing rule is met:

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

7.1.3 Discontinuation of Study Intervention

For Cohort 2, Arms 2A-H, prior to receiving the second vaccination, and, for Arms 2A and 2B, prior to receiving the third vaccination, subjects will be reassessed. The following events constitute contraindications to any further administration of study vaccines. If any of these events occur during the study prior to the second vaccination, the subject must not receive the second vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination. For Cohort 2, Arms 2A and 2B, if any of these events occur after the second vaccination and before the third vaccination the subject must not receive the third vaccination but will be encouraged to continue study participation for safety and immunogenicity evaluations through 12 months after their last vaccination.

- Any clinically significant medical condition that, in the opinion of the participating site PI or appropriate sub-investigator, poses an additional risk to the subject if he/she continues to participate in the study.
- Confirmed SARS-CoV-2 infection.
- Anaphylaxis or unexpected systemic hypersensitivity reaction following the administration of a prior study vaccination.
- Any SAE judged to be related to vaccine.
- Pregnancy.
- New information becomes available that makes further participation unsafe or interferes with the evaluation of responses.
- Termination of this trial.

7.1.3.1 Delay of Study Vaccination

If any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date.

- 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.

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

It is preferred that the vaccination still occur within the window specified in the SOA if possible but delays outside the windows are permitted (would still be a protocol deviation).

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.

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.
- Initial 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 or third 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 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, interferes with the subject's successful completion of this study, or interferes with the evaluation of responses.
- If any AE or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- Any SAE judged to be related to vaccine.

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 or Enrollment/Baseline 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 the enrollment/baseline visit. Screening assessments can occur up to 42 days before or at the subject's first vaccination visit (Day 1). At the screening (optional) or enrollment/baseline 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 (optional) or enrollment/baseline visit to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Obtain medical history.
- Review pre-study medications and therapies at screening and record on the appropriate DCF. Review of adult vaccinations, including any other SARS-CoV-2 or other experimental coronavirus vaccines.
- Review any participation in investigational trials in the last 6 months.
- Measure vital signs (HR, BP, and oral temperature), and height and weight for determination of BMI.
- Review of birth control history with female subjects.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Urine pregnancy test (in women of childbearing potential).

- Review inclusion and exclusion criteria.

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 unless the screening and vaccination are scheduled on the same day.

If a physiologic parameter, e.g., vital signs, 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 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.

The screening and first vaccination procedures can be both conducted at the enrollment/baseline visit.

8.1.2 Immunogenicity Evaluations

Serological Immunogenicity Assays:

The following serological immunogenicity assays will be performed:

- IgG ELISA to SARS-CoV-2 proteins.
- Neutralization assays using a SARS-CoV-2 pseudovirus.
- Neutralization assay using live SARS-CoV-2.

Preparation of blood samples and shipping instructions for serological immunogenicity assays are outlined in the protocol-specific MOP. Inability (e.g., failure of venipuncture) 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 B and T cell immune responses using multiparametric flow cytometry.

Refer to the protocol-specific immune monitoring plan for details.

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 TablesTable *9*,Table *10* andTable *11*.

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. Secondary research samples may also be used for other genomic analysis, including, but not limited to, single nucleotide polymorphisms (SNP) arrays, human leukocyte antigen (HLA) typing, transcriptomic analysis, evaluation of the immune response to the vaccine, and/or evaluation of any AE from the vaccine.

8.1.3.2 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 purposes 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 (optional) or enrollment/baseline visit. Subjects will be queried regarding a history of significant medical disorders.
  - 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 to identify intercurrent Protocol Specified AESIs, MAAEs, and NOCMCs.
- Physical examination:
  - A symptom-directed (targeted) physical examination will be performed if indicated at any timepoint at the discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs.

  - Reactogenicity assessments of solicited AEs occurring from the time of vaccination through 7 days post 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 30 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 7 days after vaccination.

- 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 vaccination days, 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.
  - Urine pregnancy test: Urine pregnancy test will be performed locally by the site laboratory within 24 hours prior to each vaccination, 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 as applicable.
- Memory aid:
  - All subjects will complete a Memory Aid from the time of each vaccination through 7 days post each 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 7 days after each vaccination. Based on the information collected, subjects may be asked to return to the clinic for evaluation. Memory Aids will be collected and subjects will be assessed for delayed onset local reactions 14 days after each vaccination.

Table 9: Venipuncture Volumes for Cohort 1 (One Vaccination)

Study Day	-42 to -1	1	8	15	29	91	181	366	Early Termination Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05	06	07		
Vaccination		X								
Serum for Serological Immunogenicity Assays[1]		16		16	16	16	16	16	16[2]	96
PBMCs (and Plasma) for Cellular Immunology Assays		64		64			64	64	16[2]or 40[2]	256
Serum for Secondary Research		16		16	16	16	16	16	16[2]	96
Per Visit Blood Volume Total (mL)		96		96	32	32	96	96		448
Cumulative Blood Volume (mL) (prior 56 days)		112*	112	208	240	32	96	96		
Running Blood Volume Total (mL)		96	96	192	224	256	352	448		

[1] Inability (e.g., failure of venipuncture) 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 blood volume is collected.

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

*16 mL was drawn concurrently as part of the early termination visit from DMID 20-0003.

Table 10: Venipuncture Volumes for Cohort 2: 2A-B (Three Vaccinations)

Study Day	-42 to -1	1	8	15	29	36	43	57	64	71	85	147	237	422	Early Term Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	1	2	2	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05[3]	06[3]	07[3]	08[4]	09[4]	10[4]	11[4]	12[4]	13[4]		
Vaccination		X			X			X								
Serum for Serological Immunogenicity Assays[1]		16		16	16		16	16		16	16	16	16	16	16[2]	160
PBMCs (and Plasma) for Cellular Immunology Assays		64		48	40		64	40		64			64	64	16[2]or 40[2]	448
Serum for Secondary Research		16		16	16		16	16		16	16	16	16	16	16[2]	160
Per Visit Blood Volume Total (mL)		96		80	72		96	72		96	32	32	96	96		768
Cumulative Blood Volume (mL) (prior 56 days)		96	96	176	248	248	344	416	320	416	368	64	96	96		
Running Blood Volume Total (mL)		96	96	176	248	248	344	416	416	512	544	576	672	768		

[1] Inability (e.g., failure of venipuncture) 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 blood volume is collected.
[2] These blood volumes are not included in the blood volume totals. Blood volume depends upon day of early termination visit.
[3] Visits 05-07 windows should be based off the actual Visit 04 date.
[4] Visits 08-13 windows should be based off the actual Visit 07 date.

Table 11: Venipuncture Volumes for Cohort 2: 2C-H (Two Vaccinations)

Study Day	-42 to -1	1	8	15	29	36	43	57	119	209	394	Early Term Visit	Total Volume of Blood Drawn (mL)
Visit Window (±number of days)		0	1	2	2	1	2	2	7	7	14		
Study Visit	Screening (optional) 00	01	02	03	04	05[3]	06[3]	07[3]	08[3]	09[3]	10[3]		
Vaccination		X			X								
Serum for Serological Immunogenicity Assays[1]		16		16	16		16	16	16	16	16	16[2]	128
PBMCs (and Plasma) for Cellular Immunology Assays		64		48	40		64			64	64	16[2]or 40[2]	344
Serum for Secondary Research		16		16	16		16	16	16	16	16	16[2]	128
Per Visit Blood Volume Total (mL)		96		80	72		96	32	32	96	96		600
Cumulative Blood Volume (mL) (prior 56 days)		96	96	176	248	248	344	376	64	96	96		
Running Blood Volume Total (mL)		96	96	176	248	248	344	376	408	504	600		

[1] Inability (e.g., failure of venipuncture) 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 blood volume is collected.

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

[3] Visits 05-10 windows should be based off the actual Visit 04 date.

8.2.1 Procedures to be Followed in the Event of Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, 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 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, 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 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be reported as AEs.

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

AEs will be followed to resolution or stabilization.

8.3.1.1 Solicited Adverse Events

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

Solicited AEs (i.e., reactogenicity) will be collected using a memory aid and recorded on the appropriate DCF from the time of each vaccination through 7 days post each vaccination.

For this study, solicited AEs will be:

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

Subjects will also be assessed for delayed onset local reactions through 14 days post each vaccination.

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 28 days post last vaccination.

After 28 days post last vaccination through the end of study, only SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs (as detailed in Section 8.3.2) will be reported as AEs.

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's Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

8.3.4 Classification of an Adverse Event

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

8.3.4.1 Severity of Adverse Events

All AEs and 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 for 7 days post each vaccination.
- unsolicited AEs will be collected until 28 days post last vaccination
- SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from Day 1 through the end of the study.

8.3.6 Adverse Event Reporting

8.3.6.1 Investigators Reporting of AEs

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

8.3.7 Serious Adverse Event Reporting

8.3.7.1 Investigators Reporting of SAEs

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

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

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

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

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

8.3.7.2 Regulatory Reporting of SAEs

Following notification from the participating site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any SUSAR in an IND safety report to the FDA and will notify all participating site PIs (i.e., all PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

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

8.3.8 Reporting Events to Subjects

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

8.3.9 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) represent any events for which additional data (besides the standard AE data) are desired. An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or

program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is required. Such an event may require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) may also be required. These may be at the request of the regulatory agency, industry partner or DMID, and driven by a regulatory requirement, or known or potential risk from the product or class. Non-structured data similar to SAEs will be collected for AESIs. AESIs encompass the following terms:

- Protocol Specified AESIs: See Section 12, Appendix A.
    - All suspected cases of anaphylaxis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis should be reported as a potential case of anaphylaxis.
    - All suspected cases of myocarditis or pericarditis should be recorded. For reporting purposes, a participant who displays signs/symptoms consistent with myocarditis or pericarditis should be reported as a potential case of myocarditis or pericarditis.
- NOCMCs – defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.
- MAAEs – defined as a hospitalization, emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason; and considered related to study product.

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 the end of the study) should be reported to the sponsor on the appropriate DCF. Pregnancy should be followed to outcome.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

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

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

8.4.2 Unanticipated Problem Reporting

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

- UPs that are SAEs will be reported to the IRB and to the SDCC/study sponsor within 24 hours of the participating site PI or appropriate sub-investigator becoming aware of the event per the above-described SAE reporting process.
- UPs that are SAEs will be collected from Day 1 through the end of the study.
- Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the participating site PI or appropriate sub-investigator becoming aware of the problem.
- UPs that are not SAEs will be collected from Day 1 through 28 days after last vaccination.

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 1, open-label, randomized clinical trial and is not designed to test a specific hypothesis. Rather, it is intended to obtain preliminary estimates in healthy adults of the safety, reactogenicity, and immunogenicity of mRNA-1273.351 alone and in combination with 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 12. 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 approximately 30 subjects in each arm (Arms 1A and 1B), the chance of observing at least one AE of probability 10% or more is approximately 96%. Therefore, if no AEs of a given type occur in a Cohort 1 Arm, we can be relatively confident that they will occur in fewer than 10% of people once the vaccine is implemented. With approximately 60 subjects across these two Arms (1A and 1B), the chance of observing at least one AE of probability 5% or more is at least 95%. Therefore, if no AEs of a given type occur across Cohort 1, we can be very confident that any combination independent event will occur in fewer than 5% of people once the vaccine is implemented as a boost.

With 15 subjects in Arms 2A and 2B, 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 Arms 2A or 2B, we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With 20 subjects in each arm (Arms 2C-2H), the chance of observing at least one AE of probability 20% or more is approximately 99%. Therefore, if no AEs of a given type occur in Arms 2C-2H, we can be relatively confident that they will occur in fewer than 20% of people once the vaccine is implemented. With approximately 150 subjects across these eight Arms (2A-2H), the chance of observing at least one AE of probability 3% or more is at least 99%. Therefore, if no AEs of a given type occur across Cohort 2, we can be very confident that any dosage/combination independent event will occur in fewer than 3% of people once the vaccine is implemented.

Table 12: Probability of Observing an Adverse Event for Various Event Rates

Cohort 1					
N	**"True" Event Rate**	**Probability of Observation (%)**	**N**	**"True" Event Rate**	**Probability of Observation (%)**
30	0.1%	3.0	60	0.1%	5.8
	0.5%	14.0		0.5%	26.0
	1.0%	26.0		1.0%	45.3
	2.0%	45.5		2.0%	70.2
	3.0%	59.9		3.0%	83.9
	4.0%	70.6		4.0%	91.4
	5.0%	78.5		5.0%	95.4
	10.0%	95.8		10.0%	99.8
	15.0%	99.2		15.0%	>99.9
	20.0%	99.9		20.0%	>99.9

Cohort 2								
N	**"True" Event Rate**	**Probability of Observation (%)**	**N**	**"True" Event Rate**	**Probability of Observation (%)**	**N**	**"True" Event Rate**	**Probability of Observation (%)**
15	0.1%	1.5	20	0.1%	2.0	150	0.1%	13.9
	0.5%	7.2		0.5%	9.5		0.5%	52.9
	1.0%	14.0		1.0%	18.2		1.0%	77.9
	2.0%	26.1		2.0%	33.2		2.0%	95.2
	3.0%	36.7		3.0%	45.6		3.0%	99.0
	4.0%	45.8		4.0%	55.8		4.0%	99.8
	5.0%	53.7		5.0%	64.2		5.0%	>99.9
	10.0%	79.4		10.0%	87.8		10.0%	>99.9
	15.0%	91.3		15.0%	96.1		15.0%	>99.9
	20.0%	96.5		20.0%	98.8		20.0%	>99.9

9.3 Populations for Analyses

The Safety Analysis population for the study includes all subjects who received one dose of study vaccine. Analyses for the safety population will include safety reported through the end of the study. The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood sample 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 to the protocol deviations that are considered to affect the science.
- Data from any visit that occurs substantially out of window.

9.4 Statistical Analyses

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

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

9.4.1 General Approach

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

9.4.2 Analysis of the Primary Endpoint(s)

Section 9.4.4 describes the analyses of Safety which is the primary endpoint of this protocol.

9.4.3 Analysis of the Secondary Endpoint(s)

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

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

Seroconversion rates, GMFR and GMT for SARS-CoV-2 as measured by a range of assays measuring total Spike-specific IgG (ELISA-based) and function (neutralization, receptor binding domain (RBD) binding, or similar) will be calculated for all timepoints by arm 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.

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 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). SAEs, Protocol Specified AESIs, MAAEs, and NOCMCs will be collected from the time of first vaccination through the end of the study. The numbers of SAEs, Protocol Specified AESIs 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.

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 arm and cohort.

9.4.6 Planned Interim and Early Analyses

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

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

9.4.6.1 Interim Safety Analyses

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

The SMC will review cumulative AE data after all subjects in Cohort 1 have been dosed and completed Day 8. The SMC will also review cumulative AE data after all subjects in Cohort 2 have been dosed and prior to the second vaccination (preferably after all subjects have completed Day 8). Reports may be combined if projected milestones for reports will occur close enough to each other where, in the opinion of the protocol team, producing one report, as opposed to two separate reports, is more informative regarding the safety of subjects and more beneficial to the overall needs of the protocol team.

9.4.6.2 Interim Immunogenicity Review

Interim data review of immunogenicity may be performed to inform public health decisions.

Statistical analyses of secondary immunogenicity endpoints, by vaccine schedule group, may be performed when subjects have completed key immunogenicity visits. Immunogenicity reviews may be shared with the SMC, as determined by DMID.

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

9.4.6.3 Interim Immunogenicity and Safety Review

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

9.4.7 Sub-Group Analyses

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

9.4.8 Tabulation of Individual Subject Data

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

9.4.9 Exploratory Analyses

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 innate immune cells and SARS-CoV-2 specific B cells will be summarized at each timepoint by arm.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

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

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

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

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

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

10.1.1 Informed Consent Process

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

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

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

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

Subjects will be informed that the monitor(s), 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. This extra/residual blood and corresponding serum, plasma and PBMCs will be used as back-up specimens for PP defined assays or designated for secondary research use and stored indefinitely at a designated storage facility.

Subjects will be asked to consent specifically to genetic testing on primary and secondary research samples, including but not limited to transcriptomics and 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.

If subjects choose not to provide permission for extra blood and secondary research 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.

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 SARS-CoV-2 or other infections. Secondary research using DNA may also be warranted to understand genetic factors involved in vaccination failures.

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

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

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

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

Human Genetic Testing

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

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

10.1.2 Study Termination and Closure

In Section 7, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

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

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

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

The sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the participating site PI, including, but not limited to, medical records (office, clinic, or hospital)

and pharmacy records for the subjects in this study. The participating site will permit access to such records.

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

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

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

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

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

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

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

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

10.1.4 Secondary Use of Stored Specimens and Data

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

10.1.4.1 Samples for Secondary Research

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

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

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

Residual/Repository Research Samples, upon written request and approval from DMID and any approvals required by the site or network, may be shared for secondary research with investigators at the participating site, with researchers at other Infectious Disease Clinical Research Consortium (IDCRC) sites or other institutions, or company-designated research laboratories. The samples will not be sold or used directly for production of any commercial product. DMID will authorize shipment from the DMID CMS.

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

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

10.1.4.2 Data Sharing for Secondary Research

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

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

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

10.1.5 Key Roles and Study Governance

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

10.1.6 Safety Oversight

10.1.6.1 Safety Monitoring Committee (SMC)

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

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

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

The SMC will review cumulative AE data after all subjects in Cohort 1 have been dosed and completed Day 8. The SMC will also review cumulative AE data after all subjects in Cohort 2 have been dosed and prior to the second vaccination (preferably after all subjects have completed Day 8).

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

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

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

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a CMP. The CMP describes in detail who will conduct the monitoring, at what

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

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

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

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

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

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

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

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

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

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

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

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

10.1.9.2 Study Record Retention

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

10.1.9.3 Source Records

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

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

10.1.10 Protocol Deviations

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

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

It is the responsibility of the participating site PI and study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol

deviations must be sent to the local IRB/IEC per their guidelines. The participating site PI and study staff are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

10.1.11 Publication and Data Sharing Policy

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

10.1.12 Human Data Sharing Plan

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

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

10.1.13 Genomic Data Sharing (GDS) Plan

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

10.1.14 Publication

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

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

10.1.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

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

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

For this protocol, the study vaccines, mRNA-1273 and mRNA-1273.351, manufactured by ModernaTX, Inc. are covered under the PREP Act, as described in Section 2.1.1.

10.3 Abbreviations

Table 13: Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
BP	Blood Pressure
°C	Degrees Celsius
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
COC	Certificate of Confidentiality
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
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
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EUA	Emergency Use Authorization
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GWAS	Genome-Wide Association Studies
HEENT	Head, Ears, Eyes, Nose, and Throat
HLA	Human Leukocyte Antigen
HR	Heart Rate
HRSA	Health Resources and Services Administration
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDCRC	Infectious Disease Clinical Research Consortium
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LNP	Lipid Nanoparticle
m	Meter
MAAE	Medically-Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mg	Milligrams
MI	Myocardial Infarction
min	Minute
mITT	Modified Intent-To-Treat

mL	Milliliter
mm Hg	Millimeter of Mercury
MOP	Manual of Procedures
mRNA	Messenger Ribonucleic Acid
N	Number (typically refers to subjects)
NaCl	Sodium Chloride
NDA	New Drug Application
Neut	Neutralizing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Condition
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PEG	Polyethylene Glycol
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act
QA	Quality Assurance
QC	Quality Control
RDB	Receptor Binding Domain
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
Th	T helper
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
VRC	Vaccine Research Center
WBC	White Blood Cell
WHO	World Health Organization
WIV1	Chinese Horseshoe Bat Coronavirus WIV1

10.4 Protocol Amendment History

Table 14: Protocol Amendment History

Version, Date	Section	Description of Change	Brief Rationale
2.0, March 22, 2021	Throughout	Administrative.	Advanced version and date.
	Throughout	Added two treatment arms to Cohort 2, adjusted the sample size of each Cohort 2 treatment arm, revised the summary of Cohort 2 treatment arms, and updated Cohort 1 and 2 probability table.	To address IND non-hold and SMC comments.
	Throughout	Added Protocol Specified AESIs, including Section 12, Appendix A: AESIs Terms	To address Manufacturer surveillance request.
	Throughout	Added assess for delayed onset local reactions through 14 days post each vaccination.	To address SMC comments.
	1.2	Updated SOA for Cohort 1 (One Vaccination) table as follows: • Study Day 85 to 91. • Study Day 169 to 181.	To address PI comment.
	2.2.1	Added dermal filler risk.	To address SMC comments.
	2.2.1	Added "There is limited experience with administration of a third dose of the mRNA COVID-19 vaccines, and it is possible that the third dose may be associated with more frequent or more severe adverse events."	To address PI comment.
	7.1.3	Added confirmed SARS-CoV-2 infection and interferes with the evaluaton of responses.	To address SMC comments.
	8.2	Updated Venipuncture Volumes for Cohort 1 (One Vaccination) table as follows: • Study Day 85 to 91. • Study Day 169 to 181. • Cumulative Blood Volume (mL) (prior 56 days) for Study Days 29 (280 to 240), 91 (64 to	To address PI comment.

Version, Date	Section	Description of Change	Brief Rationale
		32), 181 (80 to 96), and 366 (80 to 96).	
	8.3.9	Expanded AESI definition and added AESI reporting of suspected cases of anaphylaxis.	To address Manufacturer surveillance request.
3.0, July 30, 2021	Throughout	Administrative.	Advanced version and date.
	Protocol Summary, Study Design and Sect. 4.1	Added: Enrollment may close before the full 150 participants based on estimates on the timing of immunogenicity results and the need to inform public health decisions.	Updated enrollment plan.
	Sect. 2.2.1	Myocarditis and pericarditis added to the risks of mRNA-1273 and mRNA-1273.351.	Per updated Moderna COVID-19 EUA Vaccine Fact Sheet.
	Sect. 8.3.9	Myocarditis and pericarditis classified as protocol specified AESIs.	To address Manufacturer surveillance request.

11. REFERENCES

1. Anderson, E. J., Rouphael, N. G., Widge, A. T., Jackson, L. A., Roberts, P. C., Makhene, M., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Corbett, K. S., Swanson, P. A., 2nd, Padilla, M., Neuzil, K. M., … mRNA-1273 Study Group (2020). Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. The New England Journal of Medicine, 383(25), 2427–2438. https://doi.org/10.1056/NEJMoa2028436.

2. Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Kehtan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., … COVE Study Group (2020). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. The New England Journal of Medicine, 10.1056/NEJMoa2035389. Advance online publication. https://doi.org/10.1056/NEJMoa2035389.

3. Callaway, E. & Mallapaty, S. (2021). Novavax offers first evidence that COVID vaccines protect people against variants. Nature, 10.1038/d41586-021-00268-9. Advance online publication. https://doi.org/10.1038/d41586-021-00268-9.

4. Center for Systems Science and Engineering (CCSE) at Johns Hopkins University (JHU). COVID-19 Dashboard. 2020. https://coronavirus.jhu.edu/map.html. Accessed 04 Feb 2021.

5. Chu L., McPhee R., Huang W., Bennett H., Pajon R., Nestorova B., Leav B., … mRNA-1273 Study Group (2021). A Preliminary Report of a Randomized Controlled Phase 2 Trial of the Safety and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine. Vaccine. Advance online publication. https://doi.org/10.1016/j.vaccine.2021.02.007.

6. Cohen, J. (2021). One-dose COVID-19 vaccine offers solid protection against severe disease. Science. 29 Jan 2021. https://www.sciencemag.org/news/2021/01/one-dose-covid-19-vaccine-offers-solid-protection-against-severe-disease. Accessed 02 Feb 2021.

7. Corbett, K. S., Edwards, D. K., Leist, S. R., Abiona, O. M., Boyoglu-Barnum, S., Gillespie, R. A., Himansu, S., Schäfer, A., Ziwawo, C. T., DiPiazza, A. T., Dinnon, K. H., Elbashir, S. M., Shaw, C. A., Woods, A., Fritch, E. J., Martinez, D. R., Bock, K. W., Minai, M., Nagata, B. M., Hutchinson, G. B., … Graham, B. S. (2020). SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature, 586(7830), 567–571. https://doi.org/10.1038/s41586-020-2622-0.

8. Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A., Flach, B., Doria-Rose, N. A., Corbett, K. S., Morabito, K. M., O'Dell, S., Schmidt, S. D., Swanson, P. A., 2nd, Padilla, M., … mRNA-1273 Study Group (2020). An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. The New England Journal of Medicine, 383(20), 1920–1931. https://doi.org/10.1056/NEJMoa2022483.

9. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. MedRxiv 2020.12.21.20248640.

10. Wang P, Liu L, Iketani S, et al. Increased resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7 to antibody neutralization. bioRxiv : the preprint server for biology, 2021.01.428137. https://doi.org/10.1101/2021.01.25.428137.

11. Widge, A. T., Rouphael, N. G., Jackson, L. A., Anderson, E. J., Roberts, P. C., Makhene, M., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Neuzil, K. M., Bennett, H., Leav, B., Makowski, M., … mRNA-1273 Study Group (2021). Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. The New England Journal of Medicine, 384(1), 80–82. https://doi.org/10.1056/NEJMc2032195.

12. World Health Organization (WHO). (Data reported as of 13 Nov 2020). Weekly Operational Update on COVID-19. 2020a. https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---13-november-2020. Accessed 04 Feb 2021.

13. Wu, K., Werner, A. P., Moliva, J. I., Koch, M., Choi, A., Stewart-Jones, G., Bennett, H., Boyoglu-Barnum, S., Shi, W., Graham, B. S., Carfi, A., Corbett, K. S., Seder, R. A., & Edwards, D. K. (2021). mRNA-1273 vaccine induces neutralizing antibodies against spike

mutants from global SARS-CoV-2 variants. bioRxiv : the preprint server for biology, 2021.01.25.427948. https://doi.org/10.1101/2021.01.25.427948.

14. Zent, O., Arras-Reiter, C., Broeker, M., and Hennig, R. (2002). Immediate allergic reactions after accinations – a post-marketing surveillance review. European Journal of Pediatrics, 161, 21-25.

12. APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST (AESIS) TERMS

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in the protocol. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc.) • Include all cases that meet the following criteria: o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours;

Medical Concept	Additional Notes
	○ OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days ○ OR Urine volume ≤0.5 ml/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc.) • Include all cases that meet the following criteria ○ > 3-fold elevation above the upper normal limit for ALT or AST ○ OR • > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (e.g., gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: ○ Guillain-Barre Syndrome ○ Acute disseminated encephalomyelitis (ADEM) ○ Peripheral facial nerve palsy (Bell's palsy) ○ Transverse myelitis ○ Encephalitis/Encephalomyelitis ○ Aseptic meningitis ○ Febrile seizures ○ Generalized seizures/convulsions ○ Stroke (Hemorrhagic and non-hemorrhagic) ○ Narcolepsy

Medical Concept	Additional Notes
Anaphylaxis	• Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by: o sudden onset AND o rapid progression of signs and symptoms AND o involving two or more organ systems, as follows: o Skin/ mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes o Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation o Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea o Gastrointestinal: diarrhea, abdominal pain, nausea, vomiting • Follow reporting procedures in protocol.
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome)