16.1.1 Protocol and Protocol Amendments

This section includes the following documents:

Protocol, dated 22 April 2020

Protocol Amendment 1, dated 18 May 2020

Protocol Amendment 2, dated 01 July 2020

Protocol Amendment 3, dated 02 September 2020

CLINICAL STUDY PROTOCOL

A PHASE 2a, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF MRNA-1273 SARS-COV-2 VACCINE IN ADULTS AGED 18 YEARS AND OLDER

IND NUMBER: 19745
PROTOCOL NUMBER: mRNA-1273-P201

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Date of Protocol: 22 Apr 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice.

Signature Page

PROTOCOL TITLE: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

PROTOCOL NUMBER: mRNA-1273-P201

See esignature and date signed on last page of document.

Tal Zaks, MD, PhD
Chief Medical Officer
ModernaTX, Inc.

Date

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Investigator	Date
Printed Name of Investigator	

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number: **mRNA-1273-P201**

Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Study Phase: 2

Study Sites: Approximately 10 study sites in the United States or its territories.

Objectives:

Primary:

- To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart
- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of specific binding antibody (bAb)

Secondary:

- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

Exploratory:

- To profile the relative proportion of S protein-specific serum immunoglobulin G (IgG)
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29).
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2

Study Design and Methodology:

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age.

Two dose levels (50 µg and 250 µg), will be evaluated in this study, based in part on initial safety data from the Phase 1 Division of Microbiology and Infectious Diseases (DMID) study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 250 µg, and 100 participants will receive saline placebo.

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment. Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data though Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 197 (Month 7), and Day 365 (Month 13). There are also scheduled biweekly safety phone calls to collect medically attended adverse events (MAAEs), adverse events (AEs) leading to withdrawal, serious AEs (SAEs), concomitant medications associated with these events, and receipt of non-study vaccinations. These phone calls are scheduled biweekly from Day 71 through Day 183 and from Day 211 through Day 351. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 365 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasal swab samples will be collected at the Screening Visit (Day 0) and also at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-

specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment.

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml intramuscular (IM) injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment.

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned interim analyses.

The end of study (EOS) is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the Schedule of Events for the last participant in this study. Participants are considered to have completed the study if they complete the final visit on Day 365 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited adverse reactions (ARs) within a provided electronic diary (eDiary). Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at 9 scheduled study site visits during the study, for safety and immunogenicity assessments or other medical concerns according to the investigator's judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Study Population:

Participants (males and females 18 years of age or older at time of consent), will be included in the study if they are in good health according to the assessment of the investigator and can comply with study procedures. Negative pregnancy tests will be required at Screening and before vaccine administration for female participants of childbearing potential. The full lists of inclusion and exclusion criteria are provided in the body of the protocol.

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 365 or withdrawal from the study.
- MAAEs from Day 1 through Day 365 or withdrawal from the study.
- SAEs from Day 1 through Day 365 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.

Immunogenicity Assessments:

Immunogenicity assessments will include the following:

- Serum bAb titer against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 spike protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Investigational Product, Dosage, and Route of Administration:

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available). mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with at least a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273

250 µg, or saline. Preferably, vaccine should be administered into the nondominant arm. The second dose of vaccine should be administered in the same arm as the first dose.

Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform vaccine accountability, dose preparation, and vaccine administration.

Sample Size:

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 250 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. A sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Statistical Methods:

General Considerations: All analyses will be performed by treatment group and for the 2 cohorts separately, unless specified otherwise. Data from participants who received placebo will be pooled across cohorts for all dosing. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

Safety: Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials is used in this study with modification for rash, solicited ARs, unsolicited AE, and vital signs.

Rash will be graded in the following manner:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms

- Grade 2 = maculopapular rash covering <50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR and with any solicited AR during the 7-day follow-up period after each injection will be provided with a 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, injection group and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the statistical analysis plan (SAP).

Demographic variables (eg, age, height, weight, and body mass index (BMI)) and baseline characteristics will be summarized by injection group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

Immunogenicity: The analyses of immunogenicity will be based on the Per-Protocol (PP) Set. For each age cohort, if the number of participants in the Full Analysis Set (FAS) and PP Set differ (defined as the difference divided by the total number of participants in the PP

Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint, geometric mean titer (GMT) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint, GMT of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the limit of detection (LOD) or lower limit of quantification (LLOQ) will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with GMFR ≥ 2, GMFR ≥ 3, and GMFR ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher log-transformed titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb titers may be performed.

Date of Protocol: 22 Apr 2020

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
bAb	binding antibody
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics and Evaluation Research
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CoV	coronavirus
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunoabsorbent assay
EOS	end of study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold-rise
GMP	Good Manufacturing Practice

Abbreviation	Definition
GMT	geometric mean titer
HCP	healthcare practitioner
hDPP4	dipeptidyl peptidase 4
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LOD	limit of detection
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger RNA
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no adverse effect level
nAb	neutralizing antibody
PCR	polymerase chain reaction
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PIV3	parainfluenza virus type 3
PP	per-protocol
PT	prothrombin time
PTT	partial thromboplastin time
S	spike
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate
SMC	Safety Monitoring Committee
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
USP	United States Pharmacopoeia
VRC	Vaccine Research Center
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are zoonotic, meaning they are transmitted between animals and people.

An outbreak of the CoV disease (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 200 other countries and territories, including the United States (WHO 2020). A CoV ribonucleic acid was quickly identified in some of these patients.

As of 20 Apr 2020, the World Health Organization (WHO) reported more than 2,314,621 confirmed cases and 157,847 deaths globally and have therefore made the assessment that COVID-19 can be characterized as a pandemic (WHO 2020). As of 20 Apr 2020, the US Centers for Disease Control and Prevention (CDC) reported 746,625 confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with 39,083 attributed and probable deaths (CDC 2020a). The CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease (CDC 2020b).

There is currently no vaccine against SARS-CoV-2. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapeutic currently exists. Therefore, there is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease.

ModernaTX, Inc. has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is 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. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). 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) into a prefusion conformation. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P expresses well and is in the prefusion conformation (Wrapp et al 2020).

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). Two dose levels will be chosen for evaluation in this Phase 2 study, based on the data from the Phase 1 DMID study (Section 3.1.1). The development of this vaccine is being accelerated as, if it is demonstrated safe and immunogenic, it may be used to address the current COVID-19 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273.

1.2 Nonclinical Studies in Development of mRNA-1273

Nonclinical studies in mice, at National Institute of Health's Vaccine Research Center (VRC), part of the NIAID, have demonstrated that CoV S proteins are immunogenic and that vaccines encoding S proteins, including DNA and mRNA delivery platforms, are protective in animals. The S proteins of closely related beta-CoVs stabilized by the 2P mutation, including HKU1, MERS, SARS, and WIV1, are potent immunogens in mice (Pallesen et al 2017).

The VRC and the Sponsor produced mRNA expressing the MERS S-2P protein sequence and compared to it to mRNA expressing wild-type S protein in dipeptidyl peptidase 4 (hDPP4) mice. The mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 µg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in hDPP4 mice and protected mice from MERS challenge.

Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and the Sponsor designed mRNA expressing a membrane-anchored SARS-CoV-2 S protein

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

In support of development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

To estimate the generalized tissue distribution and tissue half-life of mRNA-1273, the biodistribution of mRNA-1647, a novel mRNA-based CMV vaccine formulated in a mixture of the same 4 lipids as mRNA-1273, was evaluated. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1273 and mRNA-1647) are expected to distribute similarly. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen.

The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102-containing LNP matrix encapsulating mRNA constructs encoding for various antigens have been evaluated in multiple Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies in Sprague Dawley rats followed by a 2-week recovery period. The Sponsor considers that the toxicity associated with mRNA vaccines formulated in LNP formulations are driven primarily by the LNP composition and to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the similar and consistent toxicity profile observed in these GLP studies at intramuscular (IM) doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix, differing only by the encapsulated mRNA sequence(s). Thus, the aggregate toxicity results from these studies supports the development of mRNA-1273. All doses administered in these GLP-compliant repeat dose toxicity studies in rats were tolerated. Test article related in-life observations observed at ≥ 9 µg/dose included reversible or reversing erythema and edema at the injection site and transient increases in body temperature at 6 hours post dose returning to baseline 24 hours post dose. The lowest no adverse effect level (NOAEL) determined across the aggregate of the completed studies was 89 µg/dose.

In GLP-compliant studies, SM-102 was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in

SM-102-containing LNPs (mRNA-1706, which encodes the Zika virus pre-membrane and envelope polypeptide), induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

A detailed review of non-clinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.3 Clinical Studies With Lipid Nanoparticle mRNA Vaccines

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in the dose-ranging Phase 1 DMID study of healthy adults at least 18 years of age (Section 3.1.1).

As of March 2020, there have been 8 clinical studies initiated across the Sponsor's infectious disease vaccine platform with over 1,000 participants receiving at least one dose of an mRNA vaccine. mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV (NCT03382405), HMPV/PIV3 (NCT03392389), and Zika virus (NCT04064905). As of January 6, 2020, approximately 365 participants were dosed with either an SM-102-containing lipid vaccine or placebo (doses ranging from 10 to 300 µg) across 3 Phase 1 studies. Of the 365 participants dosed, 264 participants experienced at least 1 solicited adverse reaction (AR). The most common solicited events were pain (28% of total events reported), headache (15%), fatigue (15%), myalgia, (13%), arthralgia (9%), nausea (7%), chills (6%), fever (4%), erythema (2%), and swelling (2%). The majority of the events were of Grade 1 to 2 with approximately 9% being reported as Grade 3. The most common Grade 3 events were pain, myalgia, fatigue, headache, and chills. Grade 3 events were typically recorded on Day 1 or Day 2 following vaccination, with most occurring on Day 2 and resolving by Day 6. In the hMPV/PIV3 Phase 1 study, which is unblinded, unsolicited related adverse events (AEs) included mild to moderate chills, hot flush, diarrhea, pyrexia, temperature intolerance, white blood cell increased, headache, and rash erythematous, as well as severe injection site pain, prothrombin time prolonged and myalgia. All of the severe events occurred at the 300 µg × 2 dose level. In the blinded Phase 1 CMV study, unsolicited related AEs in more than 2 participants included chills (19 participants, 10.5%), fatigue (10 participants, 5.5%), lymphadenopathy, injection site pain, and pyrexia (9 participants each, 5.0%), arthralgia, (8 participants, 4.4%), myalgia, (7 participants, 3.9%), headache, (5 participants, 2.8%), diarrhea, (4 participants, 2.2%), and injection site bruising, (3 participants, 1.7%). Of these AEs, severe events were reported in

3 of 19 participants with chills, 5 of 10 participants with fatigue, 4 of 9 participants with pyrexia, 4 of the 8 participants with arthralgia, and 4 of the 7 participants with myalgia. There were no related serious AEs (SAEs) reported in the Phase 1 CMV, HMPV/PIV3, or Zika vaccine studies.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart.

2.1.2 Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of specific binding antibody (bAb).

2.2 Secondary Objective

The secondary objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

2.3 Exploratory Objectives

The exploratory objectives are the following:

- To profile the relative proportion of S protein-specific serum immunoglobulin G (IgG)
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29).
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age. The study schematic is presented in Figure 1 and the Schedule of Events is presented in Table 7.

Two dose levels, 50 µg and 250 µg, will be evaluated in this study, based in part on initial safety data from the Phase 1 DMID study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 250 µg, and 100 participants will receive saline placebo (Figure 1).

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment (Figure 2). Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC; Section 6.1.1).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data through Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

Figure 1: Study Flow Schema

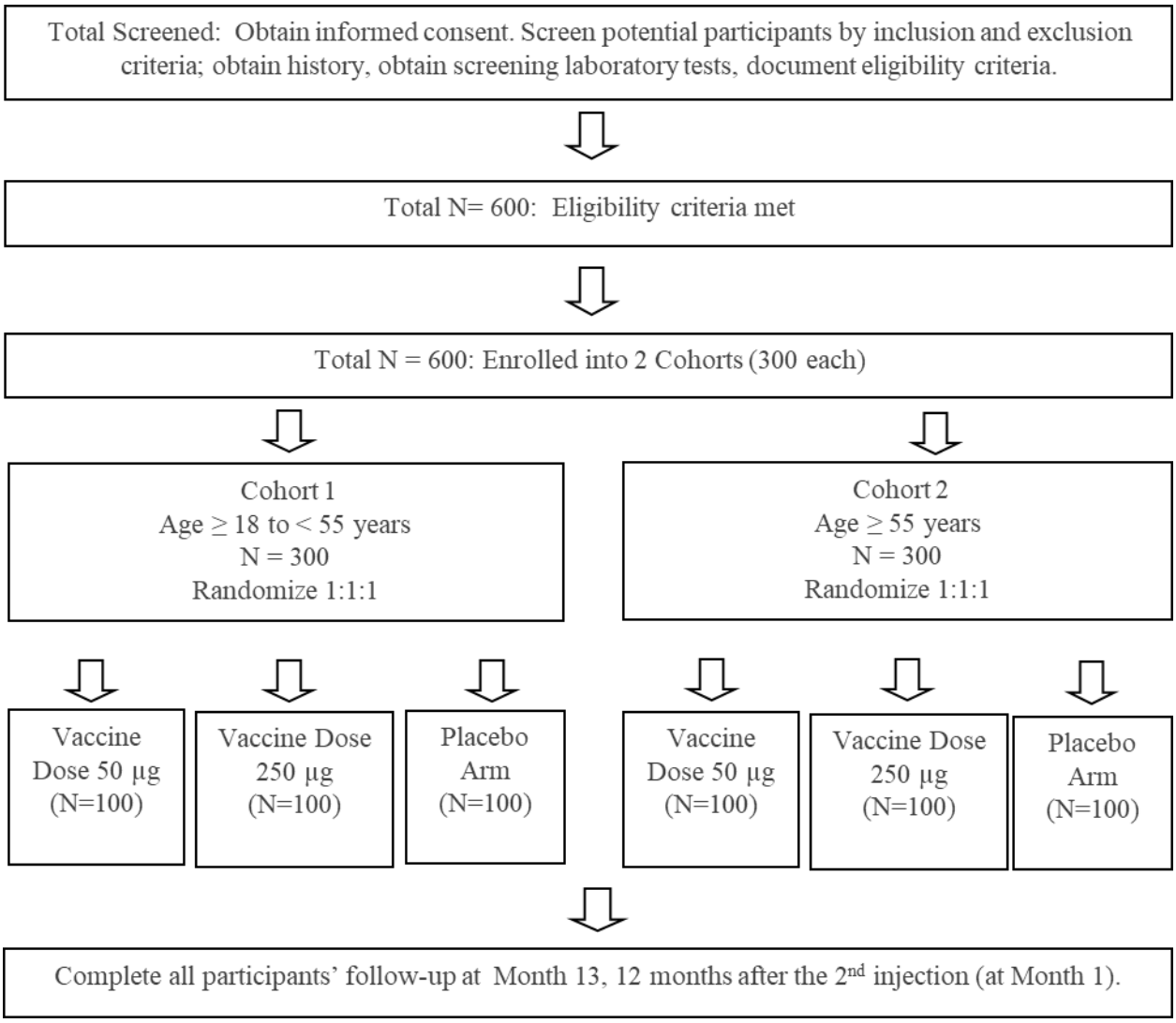
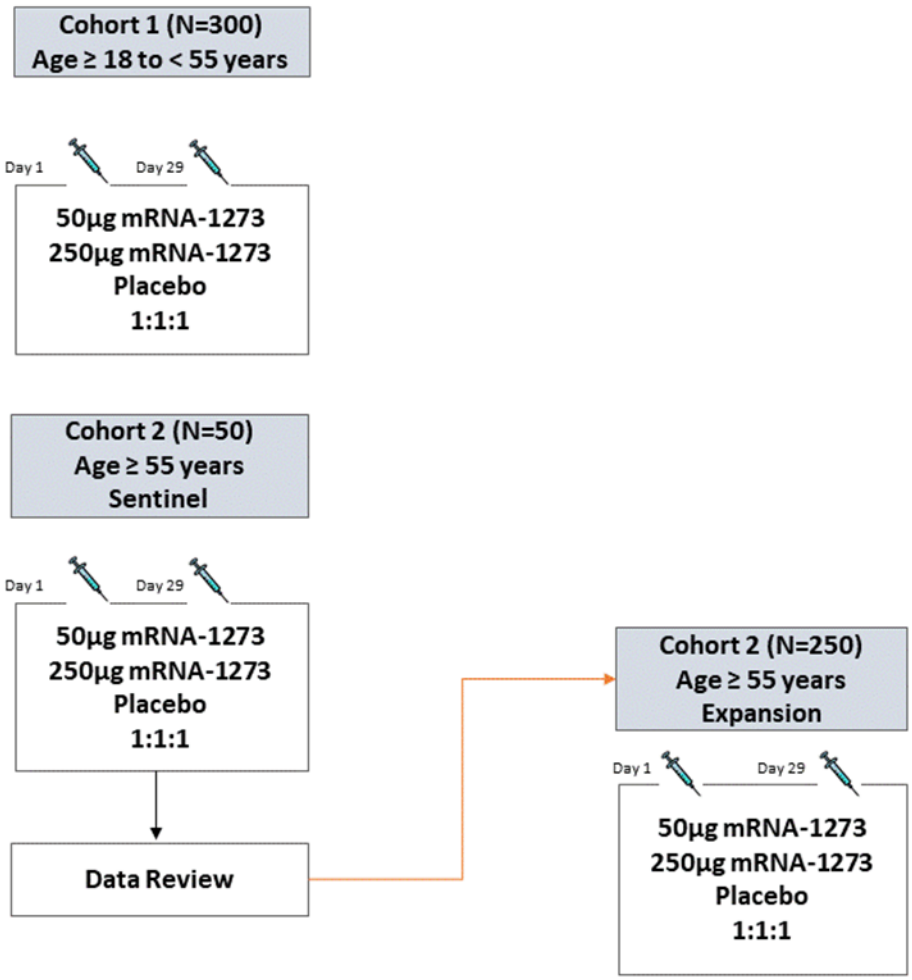


Figure 2: Sentinel and Expansion Cohort Schema



The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 197 (Month 7), and Day 365 (Month 13). There are also scheduled biweekly safety phone calls to collect medically attended adverse events (MAAEs), AEs leading to withdrawal, SAEs, concomitant medications associated with these events, and receipt of non-study vaccinations (Table 7). These phone calls are scheduled biweekly from Day 71 through Day 183 and from Day 211 through Day 351. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 365 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasal swab samples will be collected at the Screening Visit (Day 0) and also at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment (Section 3.5.1).

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml IM injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment (Section 3.4.5).

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned interim analyses (Section 4.7).

The end of study (EOS) is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the Schedule of Events (Table 7) for the last participant in this study. Participants are considered to have completed the study if they complete the final visit on Day 365 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within a provided electronic diary (eDiary). Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at 9 scheduled study visits during the study for safety and immunogenicity assessments or other medical concerns, according to the investigator's judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Detailed information on all statistical analysis of data is presented in Section 4.6.2.

3.1.1 Rationale for Dose Selection

In this study, the 2 dose levels of mRNA-1273 tested in participants will be 50 µg, and 250 µg, based on assessment of available safety and immunogenicity data from the Phase 1 DMID study (Section 1.1) and Phase 1 studies of mRNA-1647 and mRNA-1443.

The Phase 1 DMID study is an open-label dose ranging study of mRNA-1273 in healthy adult male and non-pregnant female participants in 3 age groups: age 18 to 55 years, inclusive (45 participants); age 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants). Participants in each cohort will be randomly assigned to 1 of 3 dose levels of mRNA-1273: 25 µg, 100 µg, and 250 µg. Each participant will receive an IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed for 12 months after the second injection.

As of 17 Apr 2020, 15 participants in each of the 3 dose levels of the 18 to 55-year cohort had received at least 1 dose of mRNA-1273. Recruitment of participants in the 2 older cohorts was ongoing.

The 50 µg and 250 µg doses proposed for this Phase 2a study fall within the doses being evaluated in the Phase 1 DMID Study.

3.1.2 Rationale for Study Design

The 2 age cohorts in this Phase 2a study, ≥ 18 to < 55 years old and ≥ 55 years old, were established to better understand the relationships among dose, tolerability, and immunogenicity in different age groups, one being healthy older adults. The older cohort in this Phase 2a study corresponds to the 2 older age cohorts in the Phase 1 DMID study.

Because there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 3.4.5).

The Phase 1 DMID study is small (105 participants at 3 dose levels) and does not incorporate a placebo. Having a sample size of 600 participants in this Phase 2a study and including a placebo will help to improve understanding of AEs.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and post-injection blood samples for antibody analysis through 12 months after the last dose of investigational product. In addition, participants will have nasal swab samples collected at Screening (Day 0), before the injections on Day 1 and Day 29, and at Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and polymerase chain reaction (PCR). Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Since it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the nasal swab samples collected before study injection may help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

3.2 Selection of Study Population

Healthy male or female participants will be enrolled at study sites in the US or its territories.

3.2.1 Inclusion Criteria

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 18 years of age or older at the time of consent (Screening Visit, Day 0).

2. Understands and agrees to comply with the study procedures and provides written informed consent.

3. According to the assessment of the investigator, is in good general health and can comply with study procedures.

4. Body mass index (BMI) of 18 kg/m^2 to 30 kg/m^2 (inclusive) at the Screening Visit (Day 0).

5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening (Day 0) without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

    - Has a negative pregnancy test at Screening (Day 0) and on the day of the first injection (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).

- Is not currently breastfeeding.

Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception from the time of the first injection and through 3 months after the last injection.

   Adequate contraception for male participants is defined as:

   - Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
   - Use of barrier methods and spermicide
   - History of surgical sterilization

   Male participants with partners who have become pregnant prior to Screening are eligible to participate in the study.

3.2.2 Exclusion Criteria

Participants meeting any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known exposure to someone with SARS-CoV-2 infection or COVID-19.

2. Travel outside of the US in the 28 days prior to the Screening Visit (Day 0).

3. Pregnant or breastfeeding.

4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled

within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

5. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.

6. Current treatment with investigational agents for prophylaxis against COVID-19.

7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.

8. Is a healthcare worker or a member of an emergency response team.

9. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).

10. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).

11. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of Screening.

12. Known history of hypertension, or systolic blood pressure > 150 mm Hg in participants in Cohort 1 (≥ 18 to < 55 years old) or systolic blood pressure > 160 mm Hg in participants in Cohort 2 (≥ 55 years old) at the Screening Visit (Day 0).

13. Known history of hypotension or systolic blood pressure < 85 mm Hg at the Screening Visit (Day 0).

14. Diabetes mellitus

15. Diagnosis of chronic pulmonary disease (eg, chronic obstructive pulmonary disease, asthma)

16. Chronic cardiovascular disease

17. Resides in a nursing home

18. Grade 1 or higher toxicity on clinical safety laboratory testing at the Screening Visit (Day 0)

19. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.

20. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to the Screening Visit (Day 0) (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the Screening Visit (Day 0).

21. Anticipating the need for immunosuppressive treatment at any time during participation in the study.

22. Positive serology for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies identified at the Screening Visit (Day 0).

23. History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine.

24. Bleeding disorder considered a contraindication to IM injection or phlebotomy.

25. Diagnosis of malignancy within previous 10 years (excluding non-melanoma skin cancer).

26. Has received or plans to receive a licensed vaccine ≤ 28 days prior to the first injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after any study injection. Licensed influenza vaccines may be received more than 14 days before or after any study injection.

27. Receipt of systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (Day 0) or plans for receipt during the study.

28. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.

29. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.

30. Is an immediate family member or household member of study personnel

3.2.3 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated

Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In the event an eligible participant was not enrolled as a result of a cohort being full and the participant having surpassed their 28-day (+7 days) screening period, the investigator may rescreen the participant for enrollment by assigning the participant a new identification number and repeating all screening procedures (Section 3.3.4).

3.2.4 Participant Restrictions During the Study

3.2.4.1 General and Dietary

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

3.3 Withdrawal of Participants From the Study or Study Dosing

3.3.1 Participant Withdrawal From the Study

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS electronic case report form (eCRF).

Potential reasons for withdrawing a participant from the study include the following:

- SAE
- AE (non-SAE)
- Protocol violation (specify)
- Consent withdrawal (document reason)
- Lost to follow-up
- Other (specify)

3.3.2 Handling Withdrawal From the Study

When a participant withdraws or is withdrawn from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These participants will be requested to complete the EOS assessments scheduled for Day 365 (Month 13).

3.3.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's study source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (eg, study site visit, phone call).

3.3.4 Replacements

Any participant who is withdrawn, who is significantly outside the allowed injection window, or who is lost to follow-up from the study may be replaced at the Sponsor's discretion.

3.3.5 Participant Withdrawal From Study Dosing

Every reasonable attempt will be made to follow up with participants for safety throughout the entire study period, even if further injection is withheld or the participant misses one or more visits. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all scheduled visits and assessments. (Table 7).

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to investigational product (Section 3.5.8.9) and is of Grade 3 (severe) or greater severity (Appendix 2)
- Experiences an AE or SAE that, in the judgment of the investigator, requires study vaccine withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly attributed to study vaccine
- Experiences generalized urticaria related to the study vaccine

The reason(s) for withdrawal from further injection will be recorded.

3.4 Study Dosing Groups

3.4.1 Method of Assigning Participants to Dosing Groups

There are 2 age cohorts in this study: participants ≥ 18 to < 55 years old in Cohort 1 and participants ≥ 55 years old in Cohort 2. Within each age cohort, approximately 300 participants will be randomly assigned in 1:1:1 ratio to receive mRNA-1273 50 µg, mRNA-1273 250 µg, or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules. Only the unblinded pharmacy personnel (Section 3.4.5) will have controlled access to which arm the participant is randomly assigned.

Dose group assignment in each cohort and stratification within each cohort is summarized in Table 1.

Table 1: Dose Group Assignment

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 250 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 250 µg	100
	Placebo Arm	Placebo	100
Total			**600**

3.4.2 Investigational Product Administration

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with at least a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 250 µg, or saline placebo. Preferably, vaccine should be administered into the nondominant arm. The second dose of investigational product should be administered in the same arm as the first dose.

The investigational product will be prepared for injection as a single 0.5 mL dose for each participant based on the cohort and randomization assignment, as detailed in the mRNA-1273-P201 Pharmacy Manual. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform investigational product accountability, dose preparation, and investigational product administration. The investigator will designate an unblinded clinical team member to provide oversight to the administration of investigational product so that it proceeds according to the procedures stipulated in this study protocol and the mRNA-1273-P201 Pharmacy Manual. Study-specific training will be provided.

At each visit when investigational product is administered, participants will be monitored for a minimum of 60 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (Schedule of Events, Table 7).

Eligibility for subsequent investigational product injection is determined by following the criteria outlined in Section 3.4.2.2.

The study site will be appropriately staffed, staff will be trained on emergency resuscitation, and will have stocked rescue medications (such as epinephrine, steroids, antihistamines, and intravenous fluids) should any severe reaction (eg, anaphylaxis or urticaria) occur that requires immediate intervention.

The rules for pausing dosing are provided in Section 3.4.2.1.

3.4.2.1 Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause (Table 2).

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than injection	≥ 3
3	ICU admissions in Cohort 1 due to SARS-CoV-2 infection	≥ 3
4	ICU admissions in Cohort 2 due to SARS-CoV-2 infection	≥ 6

Abbreviations: AE = adverse event; ICU = intensive care unit; SAE = serious adverse event.

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold event is adjudicated by the Safety Monitoring Committee (SMC; Section 6.1.1).

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event potentially meeting any pause rule criterion. The Sponsor will inform the SMC (Section 6.1.2) of any event potentially meeting any pause rule criterion. The SMC will review all available study data to adjudicate such events in accordance with the SMC charter.

The Sponsor will also actively monitor the following and provide them to the SMC for review as they become available:

- Instances of study halting rules triggered in the Phase 1 DMID study (NCT04283461)
- Histopathological data suggestive of vaccine-enhanced disease in ongoing nonclinical studies

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

3.4.2.2 Contraindications to Subsequent Injection

Prior to receiving a second injection, participants will be reassessed to ensure that they continue to meet eligibility requirements as outlined below.

The following events in a participant constitute absolute contraindications to any further administration of the investigational product to that participant. If any of these events occur during the study, the participant must not receive additional doses of vaccine but will be encouraged to continue study participation for safety through 12 months following last injection (Section 3.3.5).

- Diagnosed COVID-19. If COVID-19 is suspected, further administration of investigational product must be withheld until COVID-19 test results are available.
- Anaphylaxis or systemic hypersensitivity reaction following the administration of vaccine.
- Any SAE judged by investigator or Sponsor to be related to study vaccine.
- Pregnancy
- Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the participant if he/she continues to participate in the study.

The following events constitute contraindications to administration of study vaccine at certain points in time, and if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the Schedule of Events (Table 7), or the participant may be withdrawn from dosing at the discretion of the investigator (Section 3.3.5):

- Acute moderate or severe infection with or without fever at the time of injection
- Fever, defined as body temperature ≥ 38.0°C (100.4°F) at the time of injection

Participants with a minor illness without fever, as assessed by the investigator, can be administered investigational product. Participants with a fever of 38.0°C (100.4°F) or higher will be contacted within the time window acceptable for participation and reevaluated for eligibility.

3.4.3 Identity of Investigational Product

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol;

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 Injection is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

3.4.4 Management of Investigational Product

3.4.4.1 Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the investigational product
- Confirming the appropriate labeling of mRNA-1273 Injection, so that it complies with the legal requirements of the US

The investigator is responsible for acknowledging the receipt of the investigational product by a designated staff member at the site, including the following:

- Confirming that the investigational product was received in good condition
- Confirmation that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming whether the Sponsor has authorized the investigational product for use
- Ensuring the appropriate dose level of mRNA-1273 Injection is properly prepared using aseptic technique

Further description of the investigational product and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the investigational product are described in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.2 Packaging and Labeling

The Sponsor will provide the investigator and study site with adequate quantities of mRNA-1273. The sterile vaccine product is packaged in a 2-mL glass vial with a 0.6-mL fill

volume. mRNA-1273 vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future participant identification purposes.

mRNA-1273 Injection will be packaged and labeled in accordance with the standard operating procedures (SOPs) of the Sponsor or of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, guidelines for Quality System Regulations, and applicable regulations.

The Sponsor or Sponsor's designee will supply the 0.9% sodium chloride injection for use as both a placebo and a diluent to mRNA-1273. The 0.9% sodium chloride bears a commercial label and does not contain study-specific identification.

3.4.4.3 Storage

mRNA-1273 vaccine must be stored at -60°C to -90°C (-76°F to -130°F) in a secure area with limited access (unblinded pharmacy staff only) and protected from moisture and light until it is prepared for administration (Section 3.4.2). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There must be an available back-up freezer. The freezers must be connected to a back-up generator. In addition, vaccine accountability study staff (eg, the unblinded pharmacy personnel) are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1273 vaccine that was not temperature controlled during shipment or during storage to the unblinded site monitor. Such mRNA-1273 will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

The 0.9% sodium chloride injection (USP) should be stored at 20ºC to 25ºC (68ºF to 77ºF) in a restricted access area.

3.4.4.4 Investigational Product Accountability

It is the investigator's responsibility that the unblinded pharmacy personnel maintain accurate records in an investigational product accountability log of receipt of all investigational product, inventory at the site, dispensing of mRNA-1273 and placebo, study injections, and return to the Sponsor or alternative disposition of used/unused products.

An unblinded site monitor will review the inventory and accountability log during site visits and at the completion of the study. Additional details are found in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.5 Handling and Disposal

An unblinded site monitor will reconcile the investigational product during the conduct and at the end of the study for compliance. Once fully reconciled at the site at the end of the study, the investigational product can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Investigational product may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be completed and sent to the Sponsor or designee.

3.4.5 Blinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of investigational product to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the investigational product accountability monitors. They will have responsibilities to ensure that sites are following all proper investigational product accountability, preparation, and administration procedures.
- An unblinded statistical and programming team will perform the pre-planned interim analyses (Section 4.7). Sponsor team members will be pre-specified to be unblinded to the interim analysis results and will not communicate the results of interim analyses to the blinded investigators, study site staff, clinical monitors, or participants.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the investigational product in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different than placebo. Only delegated unblinded site staff will conduct the injection procedure. Once the injection is

completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

3.4.6 Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 4.7.

3.4.7 Dosing Compliance

All doses of investigational product will be administered at the study site under direct observation of unblinded pharmacy personnel and appropriately recorded (date and time) in the eCRF. Unblinded pharmacy personnel will confirm that the participant has received the entire dose of vaccine. If a participant does not receive vaccine or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Participants who miss the second injection due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all safety and immunogenicity assessments required through the scheduled EOS.

The study site is responsible for ensuring participants comply with the study windows allowed. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Table 7). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (eg, clinical laboratory testing, eDiary review for reactogenicity, immunologic testing, as applicable).

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

3.4.8.2 Concomitant Medications and Therapies

At each study visit, study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the first study injection.
- All concomitant medications and non-study vaccinations taken through 28 days after each injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each study injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the postinjection study visits or via other participant interactions (eg, phone calls).

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis (analysis sets are described in Section 4.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean

that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.

- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- A licensed vaccine administered during the period from 28 days before through 28 days after each study injection, except for any licensed influenza vaccine that was administered more than 14 days before or after any study injection.
- Immunoglobulins and/or any blood products administered during the study period.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

3.5 Study Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 5.3). Participants will undergo study procedures at the time points specified in the Schedule of Events (Table 7).

A participant also can be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

3.5.1 Assessment for SARS-CoV-2 Infection

Study participants will have nasal swab samples collected for SARS-CoV-2 testing at time points specified in the Schedule of Events (Table 7).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect a nasal swab sample to ascertain the presence of SARS-CoV-2 via PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020c)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case. All findings will be recorded in the eCRF.

If scheduled, a study site illness visit may include assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasal swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. Blood samples will be collected for potential future serologic diagnosis of SARS-CoV-2 infection.

Any confirmed SARS-CoV-2 infection or COVID-19 occurring in participants will be captured as an MAAE.

3.5.2 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, as well as about occurrence of any non-study vaccinations (Section 3.5.8.6).

The timing of the safety telephone calls is provided in Table 7.

All safety information described by the participant must be documented in source documents and not documented on the script used for the safety telephone contact.

3.5.3 Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 3.5.8.4) on Day 1.

At each injection visit, participants will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants will record data into the eDiary starting approximately 1 hour after injection under supervision of the study site staff to ensure successful entry of assessments. The site staff will perform any retraining as necessary. Study participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 3.5.8.4, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in the eDiary until resolution. Adverse reactions recorded in diaries beyond Day 7 should be reviewed by study site staff either during the next scheduled phone call or at the next study site visit (Table 7).
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on a day of injection or for the 6 subsequent days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. If assessments are not recorded for a given day, the participant will have a limited time window on the following day to complete qualitative assessments for the previous day, excluding measurements of body temperature and of any injection site erythema, swelling, or induration. Any new safety information reported during safety phone calls or at site visits (including a solicited reaction) not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF.

Study site staff will review eDiary data with participants at the Day 8 and Day 36 visits.

3.5.4 Safety Laboratory Assessments

Laboratory tests will be performed by the central laboratory, unless otherwise specified. Screening safety laboratory tests will include complete blood count with differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (ALP), blood urea nitrogen/creatinine, prothrombin time (PT), and partial thromboplastin time (PTT). These safety laboratory tests are to be repeated at Day 29 and Day 57 only for Cohort 2 (≥ 55 years of age).

Additional tests include the following:

- A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine administration (Day 1 and Day 29). At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.
- If not documented in a female participant's medical records, an FSH test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.
- Hepatitis B surface antigen, hepatitis C virus antibody, and HIV virus (types 1 and 2) antibody at the Screening Visit (Day 0).

3.5.5 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, blood samples for immunogenicity assessment will be collected before administration of vaccine. The following analytes will be measured:

- Serum bAb titer against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 S protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow further testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

The ELISA and measurement of nAb titers will be performed in a laboratory designated by the Sponsor.

For participants who provide consent (Section 5.3), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to with SARS-CoV-2, additional assay development, and the immune response across CoV.

3.5.6 Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant are 66 mL for 1 day, 182 mL for 28 days, and 398 mL for the complete study (Table 3).

Table 3: Maximum Blood Sampling Volumes per Participant by Visit

Study Visit Day	D0	D1	D15	D29	D43	D57	D197	D365	Total
Safety laboratory tests	16 mL			16[1] mL		16[1] mL			48 mL
Immunogenicity assays		50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	350 mL
Total	**16 mL**	**50 mL**	**50 mL**	**66 mL**	**50 mL**	**66 mL**	**50 mL**	**50 mL**	**398 mL**

Abbreviation: D = Day.

[1] Only participants in Cohort 2 will have blood sampled for safety laboratory tests at Day 29 and Day 57.

3.5.7 Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 3.5.8.4) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 3.5.3).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs (Section 3.5.8.4).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 365 or withdrawal from the study.
- MAAEs from Day 1 through Day 365 or withdrawal from the study.
- SAEs from Day 1 through Day 365 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 3.5.1).

3.5.8 Safety Definitions

3.5.8.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to vaccine or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test result (hematology, clinical chemistry, or PT/PTT) or other safety assessment (eg, electrocardiogram, radiological scan, vital sign measurement), including one that worsens from baseline and is considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after mRNA-1273 vaccine administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the investigational product caused the AE (Section 3.5.8.4). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the investigational product and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol; is specified as a solicited AR in the protocol; or is specified as a solicited AR in the protocol, but starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.2 Medically Attended Adverse Event

An MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner (HCP). This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, SARS-CoV-2 infection or COVID-19 [Section 3.5.1]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review

unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be fully reported on the MAAE page of the eCRF.

3.5.8.3 Serious Adverse Event

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study vaccine.
- Is life-threatening
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission.
  Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Congenital anomaly or birth defect
- Medically important event
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize

the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. 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.

3.5.8.4 Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after vaccine administration. The eDiary (Section 3.5.3) will solicit participant reporting of ARs using a structured checklist. Participants will record such occurrences in an eDiary on the day of each vaccine administration and for the 6 days after a day of injection.

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, body temperature (potentially fever), and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following occurs within 7 days after study injection:

- Severe (Grade 3) local or systemic ARs (Table 4),
- Presence of any rash, or
- Presence of any underarm swelling or tenderness on the same side as the injection arm

The purpose of the contact is to assess the nature of AR, including assessment of potential pause rules. In the event that rash or underarm swelling or tenderness on the same side as the injection arm is reported, the participant will be asked to return to the study site for assessment by the investigator.

The investigator will review, confirm, and Grade reactogenicity according to the grading scales presented in Table 4, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. All solicited ARs (local and systemic) will be considered causally related to injection.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F
Rash*	No rash	Localized rash, without associated symptoms	Maculopapular rash, covering < 50% body surface area	Generalized urticarial, covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis, eg, Stevens-Johnson syndrome or erythema multiforme

* Grading for rash and Grade 4 events per Investigator assessment (with exception of fever)

In case of any rash episode observed within 7 days after study injection, the participants will be instructed to contact the study site within 24 hours. During participant evaluation, the investigator should categorize the rash as one of the following:

- Rash no longer present and history not consistent with urticaria.
- Rash no longer present but history is consistent with urticaria.
- Rash present but clinical findings are not consistent with urticaria. Alternative diagnosis should be specified as an AE.
- Rash present and clinical findings consistent with urticaria.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded as an AE in the participant's Adverse Event eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)

- Solicited local or systemic AR lasting beyond 7 days post-injection
- Solicited local or systemic AR that leads to participant withdrawal from vaccine
- Solicited local or systemic AR that otherwise meets the definition of an SAE
- Solicited AR sign measurement with a toxicity score of Grade 3 or greater

An unsolicited AE is any AE reported by the participant that is either not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but it starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.5 Pregnancy

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 3.5.8.7).

3.5.8.6 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor. Unsolicited AEs will be captured from Day 1 through 28 days after each dose up to Day 57 (±5 days), Both MAAEs and SAEs will be captured from Day 1 throughout entire study duration (Day 365 for all participants), as specified in the Schedule of Events (Table 7). Any AEs occurring before receipt of the vaccine will be analyzed separately from TEAEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically-related changes in their well-being according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, data from clinical laboratory test results, physical examination findings, or other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

3.5.8.7 Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to vaccine or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes cohort, type of event, time of onset, investigator-specified assessment of severity and relationship to vaccine, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.8.3) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the vaccine caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341
- SAE Fax line (USA and Canada): +1-866-599-1342

3.5.8.8 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities and will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life-threatening (Grade 4) using the following criteria:

- Mild (Grade 1): These events do not interfere with the participant's daily activities.
- Moderate (Grade 2): These events cause some interference with the participant's daily activities but do not require medical intervention.
- Severe (Grade 3): These events prevent the participant's daily activity and require medical intervention.
- Life-threatening (Grade 4): These events require an emergency room visit or hospitalization.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Table 4. Specific criteria for clinical and laboratory abnormalities are presented in Appendix 2 (Table 8 and Table 9, respectively) and will be graded if outside of the reference range for the laboratory utilized.

3.5.8.9 Assessment of Causality

The investigator's assessment of an AE's relationship to vaccine is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the vaccine caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: There is not a reasonable possibility of a relationship to the investigational product. Participant did not receive the investigational product OR temporal sequence of the AE onset relative to administration of the investigational product is not reasonable OR the AE is more likely explained by another cause than the investigational product.

- Related: There is a reasonable possibility of a relationship to the investigational product. There is evidence of exposure to the investigational product. The temporal sequence of the AE onset relative to the administration of the investigational product is reasonable. The AE is more likely explained by the investigational product than by another cause.

3.5.8.10 Follow-up of Adverse Events

All AEs, SAEs, and MAAEs must be reported in detail on the appropriate page of the eCRF and followed until the event is resolved or stable or judged by the investigator to be not clinically significant.

3.5.9 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, vital sign measurements will be collected once before vaccine administration and at least 1 hour after vaccine administration (before participants are discharged from the study site).

Febrile participants at Day 1 and Day 29 visits (fever is defined as a body temperature ≥ 38.0°C/100.4°F) may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities (Table 8) of Grade 3 or greater, the abnormal value and Grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.5.10 Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Schedule of Events (Table 7). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular,

abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as a MAAE.

Symptom-directed physical examinations may be performed at other timepoints at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

Body mass index will be calculated at the Screening Visit (Day 0) only.

4 STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or Clinical Study Report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

4.1 Blinding and Responsibility for Analyses

Blinding during the study will be conducted as described in Section 3.4.5. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Planned interim analyses and data presentation for unblinded SMC review are described in Section 4.7 and Section 6.1, respectively. At each interim analysis, pre-identified Sponsor members will be unblinded to review treatment level results as defined in the study Data Blinding Plan. The unblinded interim analysis and any data presentation or analysis for SMC review will be handled by the unblinded team of statisticians and programmers. A strict firewall between the blinded and unblinded teams will be maintained during study conduct. Sponsor personnel who have access to review unblinded results will be documented. Study sites will remain blinded. The results of interim analyses will not be shared with the investigators before completion of the study.

4.2 Hypothesis Testing

There is no hypothesis testing in this study.

4.3 Analysis Endpoints

4.3.1 Primary Endpoints

4.3.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.

- Unsolicited AEs through 28 days after each injection.
- MAAEs through the entire study period.
- SAEs throughout the entire study period.
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only).
- Vital sign measurements and physical examination findings.

4.3.1.2 Primary Immunogenicity Endpoint

- Titer of SARS-CoV-2-specific binding antibody (bAb) measured by ELISA on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 197 (M7), and Day 365 (M13).

4.3.2 Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

- Titer of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 197 (M7), and Day 365 (M13).
- Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 197 (M7), and Day 365 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) to equal to or above LOD or LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers.

4.3.3 Exploratory Endpoints

The exploratory endpoints are the following:

- Titers of S protein-specific bAb (IgM and IgG) and nAb in serum collected on Day 15.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels in serum
- Clinical severity and immune response of participants infected by SARS-CoV-2

4.4 Analysis Populations

4.4.1 Randomized Set

The Randomized Set consists of all participants who are randomly assigned in the study, regardless of the participants' treatment status in the study.

4.4.2 Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomly assigned and received any study injection, and contribute any solicited AR data; ie, have at least one post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the injection group corresponding to the study injection they actually received.

4.4.3 Safety Set

The Safety Set consists of all randomly assigned participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the injection group corresponding to the study injection they actually received for the analysis of safety data using the Safety Set.

4.4.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who a) receive any study injection, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-injection assessment for the analysis endpoint. Participants will be included in the injection group to which they were randomly assigned.

4.4.5 Per-Protocol Set

The Per-Protocol (PP) Set consists of all FAS participants who meet all of the following criteria:

- Complied with the injection schedule
- Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective
- Did not have SARS-CoV-2 infection
- Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the injection group to which they were randomly assigned.

4.5 Sample Size Determination

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 250 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. Table 5 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. The 2-sided 95% CI is estimated (0.01%, 1.4%) at sample size of 400 with 1 participant reporting an AE. Furthermore, a sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Table 5: 95% Confidence Interval for One Participant with AE and the Lowest Detectable Incidence Rate at 95% Probability in Selected Sample Size

Sample Size Receiving mRNA-1273	Rate and 95% CI (%) at One Participant with AE			Lowest Detectible Rate (%) with ≥95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75

Abbreviations: AE = adverse event; CI = confidence interval.

4.6 Statistical Methods

There are 2 age cohorts in this study: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). All analyses will be performed by treatment group and for the 2 cohorts separately, unless specified otherwise. Data from participants who received placebo will be pooled across cohorts for all dosing.

4.6.1 Summary of Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by injection group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

4.6.2 Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the MedDRA for adverse reaction terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash, solicited ARs, unsolicited AEs, and vital signs (Table 4).

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR and with any solicited AR during the 7-day follow-up period after each injection will be provided with a 2-sided 95% exact CI using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided and Table 6 summarizes analysis strategy for safety parameters.

Table 6: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by preferred term coded by MedDRA.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, injection group, and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the SAP.

4.6.3 Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set. For each age cohort, if the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint (Section 4.3.1.2), geometric mean titer (GMT) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint (Section 4.3.2), GMT of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the LOD or LLOQ will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with GMFR ≥ 2, GMFR ≥ 3, and GMFR ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher log-transformed titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb titers may be performed.

4.6.4 Exploratory Analyses

Exploratory analyses may include the following:

- Descriptive summaries of the relative proportions of S protein-specific serum IgG, IgM, and nAb during the study. Subclass analysis of specific IgG may be performed.
- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study

- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study

4.7 Interim Analyses

Interim analyses (IAs) will be conducted on cleaned data and may be combined depending on study timelines.

1. An interim analysis of safety and immunogenicity will be triggered after the first 100 participants in each cohort have completed Day 29 visits. Pre-identified Sponsor team members will be unblinded to group treatment level results.
2. An interim analysis of safety and immunogenicity will be triggered after the first 100 participants in each cohort have completed Day 57 visits. Pre-identified Sponsor team members will be unblinded to participant level results.
3. An interim analysis of safety and immunogenicity will be triggered after all participants in each cohort have completed the Day 197 visits (Month 7). Pre-identified Sponsor team members will be unblinded to participant level results.

An independent, unblinded statistics team will carry out the IAs. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded throughout the study.

The final analysis of safety and immunogenicity will be performed after all participants have completed the study and after the database is cleaned and locked. Results of this analysis will be presented in a CSR, including individual listings.

Additional information can be found in the SAP.

4.8 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonized tripartite guideline E6(R2): GCP and current SOPs. The eCRFs will be utilized and accessed through iMedidata® via the internet. This EDC system is validated and compliant with US Title 21 of CFR Part 11. Each person involved with the study will have an individual identification code and password that allow for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Due to safety review requirements, study sites must follow the data entry and availability instructions provided by Sponsor in the study readiness trainings. As a quality measure,

timeliness of data entry and data query resolution will be followed closely. Other issues of data quality that may hinder safety review or pose a concern with patient safety will be brought to the attention of the Sponsor or CRO, with appropriate awareness to the SMC if needed.

5 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study and may be pursuant to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

5.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

5.2 Institutional Review

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

5.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to

study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study, be allowed to read the approved ICF, and be given answers to any questions. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF. Separate counseling and consent will be provided for HIV testing.

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to with SARS-CoV-2, additional assay development, and the immune response across CoV.

The investigator or designee will provide a copy of the ICF to the participant. The original form shall be maintained in the participant's medical records at the site.

5.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to Sponsor according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

5.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor, the CRO, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, the CRO, nor the study site is financially responsible for further treatment of the disease under study.

5.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

5.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

5.8 Data Collection

5.8.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic case report forms are accessed through iMedidata® via the internet. This EDC system is validated and compliant with 21 CFR 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

5.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

5.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

5.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

5.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the vaccine. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

5.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

6 STUDY MANAGEMENT

6.1 Monitoring

Ongoing safety monitoring will be performed in a blinded manner by the CRO's medical monitor, the Sponsor's medical monitor, and the individual site investigators throughout the study.

6.1.1 Safety Monitoring Committee

Safety oversight will be under the direction of an SMC composed of external independent consultants with relevant expertise. Members of the SMC will be independent from the study conduct and free of conflict of interest. The SMC will meet on a regular basis to assess safety throughout the study conduct. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SMC. Details regarding the SMC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The SMC will convene on an ad hoc basis if any of the pause rules, described in Section 3.4.2.1, are met. The SMC will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

6.1.2 Monitoring of the Study

The study monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The monitor will be blinded to dose assignment. A separate unblinded study monitor will be responsible for vaccine accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

6.2 Management of Protocol Amendments and Deviations

6.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

6.2.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Major protocol deviations are defined as exclusionary from the analysis according to the protocol objectives and endpoints. Protocol deviations will be documented by the study monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of such deviations.

6.3 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last participant completes the last visit (includes the EOS Visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the CSR.

6.4 Clinical Study Reports

Whether the study is completed or prematurely terminated, the Sponsor will ensure that CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory

requirement(s). The Sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSRs. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

A final CSR will contain all data collected through Day 365 (Month 13).

Upon completion of the CSR, the Sponsor will provide the investigator(s) with the final approved CSR.

7 APPENDICES

7.1 Appendix 1: Schedule of Events

The Schedule of Events is presented in Table 7.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening, Day 1, and Day 29 visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Screening, Day 1, and Day 29 visits), a safety phone call should be performed that includes the assessments scheduled for the biweekly safety phone calls (Table 7).

Table 7: Schedule of Events

Visit Number	0	1	2	3	4	5	6	7		8		9
Type of Visit	C	C	C	C	C	C	C	C	SC	C	SC	C
Month Timepoint		M0			M1			M2	BW SC	M7	BW SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[10]	D15[10]	D29[11]	D36[10, 11]	D43[10, 11]	D57[10, 11]	Q 2 weeks D71 – D183[11]	D197[10, 11]	Q 2 weeks D211 – D351[11]	D365[10, 11]
Window Allowance (Days)	-28		+3	±3	-3/+7	+3	±3	-3/+7	±3	±14	±3	±14
ICF, demographics, concomitant medications, medical history	X											
Confirm participant meets inclusion and exclusion criteria	X	X										
Blood for safety laboratory tests[2]	X				X[2]			X[2]				
Blood for viral serology (hepatitis B, hepatitis C, HIV [1 and 2])	X											
Physical examination including vital signs[3]	X	X	X	X	X	X	X	X		X		X
Pregnancy testing[4]	X	X			X							
Randomization		X										
Study injection (including 60-minute post-dosing observation period)		X			X							
Blood for vaccine immunogenicity[6]		X		X	X		X	X		X		X
Nasal swab sample for SARS-CoV-2[9]		X			X			X				
eDiary activation for recording solicited adverse reactions (7 days)[5]		X			X							
Review of eDiary			X			X						
Follow-up safety calls[7]									X		X	
Recording of Unsolicited AEs		X	X	X	X	X	X	X				

Visit Number	0	1	2	3	4	5	6	7		8		9
Type of Visit	C	C	C	C	C	C	C	C	SC	C	SC	C
Month Timepoint		M0			M1			M2	BW SC	M7	BW SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8 [10]	D15 [10]	D29 [11]	D36 [10, 11]	D43 [10, 11]	D57 [10, 11]	Q 2 weeks D71 – D183 [11]	D197 [10, 11]	Q 2 weeks D211 – D351 [11]	D365 [10, 11]
Window Allowance (Days)	-28		+3	±3	-3/+7	+3	±3	-3/+7	±3	±14	±3	±14
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[8]		X	X	X	X	X	X	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[8]	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations[8]		X	X	X	X	X	X	X				
Study completion												X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; BW SC = biweekly safety (phone) call; C = clinic visit; CBC = complete blood count; D = day; HIV = human immunodeficiency virus; ICF = informed consent form; M = month; MAAE = medically attended AE; PCR = PT = prothrombin time; PTT = partial thromboplastin time; Q = every; SAE = serious adverse event.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (FDA March 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined the same day. Additionally, the Day 0 visit may be performed over multiple visits if within the 28-day screening window.
2. Safety laboratory tests include the following: CBC with differential, AST, ALT, total and direct bilirubin, alkaline phosphates, BUN/creatinine, PT/PTT. Safety laboratory tests are to be repeated at Day 29 and Day 57 **only for Cohort 2 (≥ 55 years old).**
3. Physical examination: a full physical examination, including height and weight, will be performed at Day 1, Day 29 and Day 57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as a MAAE. Vital signs are to be collected pre and post-dosing on days of injection (Day 1 and Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator a pregnancy test either via blood or point-of-care urine test can be performed. Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the investigator.
5. Diary entries will be recorded by the participant at approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.

6. Sample must be collected prior to dosing on days of injection (Day 1 and Day 29).
7. Trained study personnel will call all participants to collect information relating to any AEs, MAAEs, AEs leading to study discontinuation, SAEs, information on concomitant medications associated with those events, and any non-study vaccinations.
8. All concomitant medications and non-study vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Screening through the final visit (Day 365).
9. The nasal swab sample will be used to ascertain the presence of SARS-CoV-2 via PCR.
10. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a safety call to the subject should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for adverse events and concomitant medications (e.g. as defined in scheduled biweekly safety phone calls). Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the subject via informed consent and have prior approval from the Sponsor (or its designee).
11. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 -3/+7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. When the extended window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.

7.2 Appendix 2: Toxicity Grading Scale Tables

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 8 and Table 9, respectively. Note that for laboratory abnormalities, grading only occurs if the values are outside of the normal values established by the clinical laboratory. For study-specific laboratory normal ranges and associated toxicity grades, refer to the laboratory manual.

Table 8: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Abbreviation: ER = emergency room.

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)**	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER = emergency room.

Note that fever is classified under systemic reactions for grading purposes.

* Participant should be at rest for all vital sign measurements.

** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise (unusual tiredness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized myalgia (muscle ache or pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized arthralgia (joint ache or pain)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviations: ER = emergency room; IV = intravenous.

* Oral temperature; no recent hot or cold beverages or smoking.

Sources: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

Table 9: Tables for Laboratory Abnormalities

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)**
Blood urea nitrogen (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (female) (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease (cell/mm^3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease (cell/mm^3)	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm^3)	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils (cell/mm^3)	650 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT; increase by factor	> 1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	> 1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Laboratory abnormality grading occurs only when the values fall beyond the normal ranges established by the local laboratory.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007). Note that the criteria for Grade 1 PT and PTT have been adjusted from the source table: instead of >= 1.0 x ULN, both criteria are > 1.0 x ULN. Grade 1 will not be used for hematology values due to the large overlap with normal values at the central laboratory.

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Signature Page for VV-CLIN-000748 v1.0

Approval	Conor Knightly Clinical 22-Apr-2020 20:59:01 GMT+0000

Approval	Wellington Sun Regulatory 22-Apr-2020 23:28:46 GMT+0000

Approval	Tal Zaks Clinical 23-Apr-2020 00:32:43 GMT+0000

Signature Page for VV-CLIN-000748 v1.0

CLINICAL STUDY PROTOCOL

A PHASE 2a, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, DOSE-CONFIRMATION STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF MRNA-1273 SARS-COV-2 VACCINE IN ADULTS AGED 18 YEARS AND OLDER

IND NUMBER: 19745
PROTOCOL NUMBER: mRNA-1273-P201

Sponsor: ModernaTX, Inc.
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Amendment Number: 1

Date of Amendment 1: 18 May 2020

Date of Original Protocol: 22 Apr 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice.

Signature Page

PROTOCOL TITLE:	A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
PROTOCOL NUMBER:	mRNA-1273-P201
AMENDMENT NUMBER:	1
AMENDMENT 1 DATE:	18 May 2020

See esignature and date signed on last page of document.

Tal Zaks, MD, PhD
Chief Medical Officer
ModernaTX, Inc.

Date

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Investigator	Date
Printed Name of Investigator	

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	18 May 2020
Original Protocol	22 April 2020

Amendment 1, 18 May 2020: Current Amendment

Main Rationale for the Amendment:

The main purpose of this amendment is to incorporate the following modifications requested by the FDA Center for Biologics Evaluation and Research:

- Enhance monitoring of participants who are confirmed to have SARS-CoV-2 infection.
- Include a convalescent visit for participants with confirmed SARS-CoV-2 infection.
- Explore the mRNA-1273 vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection.
- Updated the Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to extend the follow-up to a full 12-month period after the second injection on Day 29 (Month 1).
- Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.

The summary of changes table provided here describes the major changes made in this amendment, including the sections modified and the corresponding rationale. Minor editorial or formatting changes are not included in this summary table.

Summary of Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated protocol version and date	Revised version and date of protocol
Title page, Signature page, and header	Updated the protocol title	Revised to reflect the current purpose of the study
Synopsis and Section 2.3 Exploratory Objectives	Added an exploratory objective to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection	Request from the Health Authority
Synopsis, Section 2.3 Exploratory Objectives, Section 4.3.3 Exploratory Endpoints, Section 4.6.4 Exploratory Analyses	Revised wording for the exploratory objective/endpoint regarding spike protein-specific serum immunoglobulin class and subclass and neutralizing antibody in serum	Editorial change
Synopsis, Section 3.1 Study Design, Study Flow Schema (Figure 1), Sentinel and Expansion Cohort Schema (Figure 2), Section 3.1.1 Rationale for Dose Selection, 3.4.1 Method of Assigning Participants to Dosing Groups. Dose Group Assignment (Table 1), 3.4.2 Investigational Product Administration, 4.5 Sample Size Determination	Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg	Decreased based on the preliminary findings of the Phase 1 DMID study
Synopsis and Section 3.1 Study Design	Deleted collection of nasopharyngeal swab samples at the Screening Visit (Day 0)	Editorial update for consistency with Schedule of Events (Table 7)
Synopsis and Section 3.1 Study Design	Deleted the number of visits at which participants will have blood samples collected	Editorial update to avoid confusion as blood samples will be collected at different visits for safety and vaccine immunogenicity assessments
Synopsis; Section 3.1 Study Design, Section 3.5.6 Blood Sampling Volumes (Table 3), Section 3.5.7 Safety Assessments, Section 3.5.8.6 Eliciting and Documenting Adverse Events, Section 4.3.1.2 Primary Immunogenicity Endpoint, Section 4.3.2 Secondary Endpoints, Section 4.7 Interim Analyses, Section 6.4 Clinical Study Reports, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to allow for 6-month and 12-month intervals, respectively, after the second injection on Day 29 (Month 1)	Request from the Health Authority

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 3.1 Study Design, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated the biweekly safety phone calls from Day 211 through Day 351 to Day 223 through Day 377	Consequent to the change made to the Day 209 Visit (Request from the Health Authority)
Synopsis, Section 3.1 Study Design, Section 3.1.2 Rationale for Study Design, Section 3.5.1 Assessment for SARS-CoV-2 Infection, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated nasal swab to nasopharyngeal swab	Clarified the type of swab to be performed
Section 3.1.1 Rationale for Dose Selection	Updated enrollment and preliminary safety data from the ongoing Phase 1 DMID study	Updated based on the preliminary findings of the Phase 1 DMID study
Section 3.2.1 Inclusion Criteria	Updated inclusion criterion #7 to exclude sperm donations through 3 months after the last injection	Update to align with the informed consent form on refraining male participants from sperm donation through 3 months after the last injection based on IRB feedback to the ICF
Section 3.3.2 Handling Withdrawal From the Study	Updated the scheduled end-of study assessments at Day 394 (Month 13) to allow for a 12-month interval after the second vaccination on Day 29 (Month 1)	Request from the Health Authority
Section 3.4.5 Blinding	Updated the method to maintain the blind of the dosing assignment from opaque sleeve to blinding label	Operational change in cases for which opaque sleeves are not used
Section 3.5.1 Assessment for SARS-CoV-2 Infection	• Added more intense monitoring of participants who are confirmed to have SARS-CoV-2 infection (ie, notification of the participant's primary care physician by the investigator and recording of confirmed SARS-CoV-2 infection as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome) • Added a convalescent visit with blood collection after diagnosis of SARS-CoV-2 infection	Request from the Health Authority
Section 3.5.1 Assessment for SARS-CoV-2 Infection and Section 3.5.8.2 Medically Attended Adverse Event	Deleted "or COVID-19"	Editorial update for internal consistency
Section 4.3.3 Exploratory Endpoints	Included a new exploratory endpoint to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection	Request from the Health Authority

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Deleted that Day 0 and Day 1 visits may be combined the same day	Editorial update of template text, which did not apply to this protocol
	Corrected sequential footnote numbering in the schedule of events (Table 7)	Editorial update
	Included a header row titled "Days Since Most Recent Vaccination"	Update to clarify that the visits are relative to the most recent injection

Abbreviation: ICF = informed consent form; IRB = Institutional Review Board; MAAE = medically attended adverse event

IRB and Regulatory Authority Approval

A copy of this amended protocol will be sent to the institutional review board (IRB) and regulatory authority.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number: **mRNA-1273-P201**

Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Study Phase: 2

Study Sites: Approximately 10 study sites in the United States or its territories.

Objectives: Primary:

- To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart
- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of specific binding antibody (bAb)

Secondary:

- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb)

Exploratory:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29)
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

Study Design and Methodology:

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age.

Two dose levels (50 µg and 100 µg), will be evaluated in this study, based in part on initial safety data from the Phase 1 Division of Microbiology and Infectious Diseases (DMID) study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo.

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment. Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data through Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled biweekly safety phone calls to collect medically attended adverse events (MAAEs), adverse events (AEs) leading to withdrawal, serious AEs (SAEs), concomitant medications associated with these events, and receipt of non-study vaccinations. These phone calls are scheduled biweekly from Day 71 through Day 183 and from Day 223 through Day 377. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria

	that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment. Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml intramuscular (IM) injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment. All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned interim analyses. The end of study (EOS) is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the Schedule of Events for the last participant in this study. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1). At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited adverse reactions (ARs) within a provided electronic diary (eDiary). Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study. Participants will have blood sampled at scheduled study site visits during the study, for safety and immunogenicity assessments or other medical concerns according to the investigator's judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.
Study Population:	Participants (males and females 18 years of age or older at time of consent), will be included in the study if they are in good health according to the assessment of the investigator and can comply with study procedures. Negative pregnancy tests will be required at Screening and before vaccine administration for female participants of childbearing potential. The full lists of inclusion and exclusion criteria are provided in the body of the protocol.
Safety Assessments:	Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study.
- MAAEs from Day 1 through Day 394 or withdrawal from the study.
- SAEs from Day 1 through Day 394 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.

Immunogenicity Assessments:

Immunogenicity assessments will include the following:

- Serum bAb titer against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 spike protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Investigational Product, Dosage, and Route of Administration:

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available). mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with at least a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273

100 µg, or saline. Preferably, vaccine should be administered into the nondominant arm. The second dose of vaccine should be administered in the same arm as the first dose.

Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform vaccine accountability, dose preparation, and vaccine administration.

Sample Size:

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. A sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Statistical Methods:

General Considerations: All analyses will be performed by treatment group and for the 2 cohorts separately, unless specified otherwise. Data from participants who received placebo will be pooled across cohorts for all dosing. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

Safety: Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials is used in this study with modification for rash, solicited ARs, unsolicited AE, and vital signs.

Rash will be graded in the following manner:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms

- Grade 2 = maculopapular rash covering <50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR and with any solicited AR during the 7-day follow-up period after each injection will be provided with a 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, injection group and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the statistical analysis plan (SAP).

Demographic variables (eg, age, height, weight, and body mass index (BMI)) and baseline characteristics will be summarized by injection group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

Immunogenicity: The analyses of immunogenicity will be based on the Per-Protocol (PP) Set. For each age cohort, if the number of participants in the Full Analysis Set (FAS) and PP Set differ (defined as the difference divided by the total number of participants in the PP

Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint, geometric mean titer (GMT) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint, GMT of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the limit of detection (LOD) or lower limit of quantification (LLOQ) will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with GMFR ≥ 2, GMFR ≥ 3, and GMFR ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher log-transformed titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb titers may be performed.

Date of Protocol Amendment 1: 18 May 2020

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
bAb	binding antibody
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics and Evaluation Research
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CoV	coronavirus
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunoabsorbent assay
EOS	end of study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold-rise
GMP	Good Manufacturing Practice

Abbreviation	Definition
GMT	geometric mean titer
HCP	healthcare practitioner
hDPP4	dipeptidyl peptidase 4
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LOD	limit of detection
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger RNA
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no adverse effect level
nAb	neutralizing antibody
PCR	polymerase chain reaction
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PIV3	parainfluenza virus type 3
PP	per-protocol
PT	prothrombin time
PTT	partial thromboplastin time
S	spike
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
SMC	Safety Monitoring Committee
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
USP	United States Pharmacopoeia
VRC	Vaccine Research Center
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are zoonotic, meaning they are transmitted between animals and people.

An outbreak of the CoV disease (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 200 other countries and territories, including the United States (WHO 2020). A CoV ribonucleic acid was quickly identified in some of these patients.

As of 20 Apr 2020, the World Health Organization (WHO) reported more than 2,314,621 confirmed cases and 157,847 deaths globally and have therefore made the assessment that COVID-19 can be characterized as a pandemic (WHO 2020). As of 20 Apr 2020, the US Centers for Disease Control and Prevention (CDC) reported 746,625 confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with 39,083 attributed and probable deaths (CDC 2020a). The CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease (CDC 2020b).

There is currently no vaccine against SARS-CoV-2. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapeutic currently exists. Therefore, there is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease.

ModernaTX, Inc. has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is 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. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). 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) into a prefusion conformation. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P expresses well and is in the prefusion conformation (Wrapp et al 2020).

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). Two dose levels will be chosen for evaluation in this Phase 2 study, based on the data from the Phase 1 DMID study (Section 3.1.1). The development of this vaccine is being accelerated as, if it is demonstrated safe and immunogenic, it may be used to address the current COVID-19 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273.

1.2 Nonclinical Studies in Development of mRNA-1273

Nonclinical studies in mice, at National Institute of Health's Vaccine Research Center (VRC), part of the NIAID, have demonstrated that CoV S proteins are immunogenic and that vaccines encoding S proteins, including DNA and mRNA delivery platforms, are protective in animals. The S proteins of closely related beta-CoVs stabilized by the 2P mutation, including HKU1, MERS, SARS, and WIV1, are potent immunogens in mice (Pallesen et al 2017).

The VRC and the Sponsor produced mRNA expressing the MERS S-2P protein sequence and compared to it to mRNA expressing wild-type S protein in dipeptidyl peptidase 4 (hDPP4) mice. The mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 µg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in hDPP4 mice and protected mice from MERS challenge.

Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and the Sponsor designed mRNA expressing a membrane-anchored SARS-CoV-2 S protein

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

In support of development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

To estimate the generalized tissue distribution and tissue half-life of mRNA-1273, the biodistribution of mRNA-1647, a novel mRNA-based CMV vaccine formulated in a mixture of the same 4 lipids as mRNA-1273, was evaluated. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1273 and mRNA-1647) are expected to distribute similarly. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen.

The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102-containing LNP matrix encapsulating mRNA constructs encoding for various antigens have been evaluated in multiple Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies in Sprague Dawley rats followed by a 2-week recovery period. The Sponsor considers that the toxicity associated with mRNA vaccines formulated in LNP formulations are driven primarily by the LNP composition and to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the similar and consistent toxicity profile observed in these GLP studies at intramuscular (IM) doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix, differing only by the encapsulated mRNA sequence(s). Thus, the aggregate toxicity results from these studies supports the development of mRNA-1273. All doses administered in these GLP-compliant repeat dose toxicity studies in rats were tolerated. Test article related in-life observations observed at ≥ 9 µg/dose included reversible or reversing erythema and edema at the injection site and transient increases in body temperature at 6 hours post dose returning to baseline 24 hours post dose. The lowest no adverse effect level (NOAEL) determined across the aggregate of the completed studies was 89 µg/dose.

In GLP-compliant studies, SM-102 was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in

SM-102-containing LNPs (mRNA-1706, which encodes the Zika virus pre-membrane and envelope polypeptide), induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

A detailed review of non-clinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.3 Clinical Studies With Lipid Nanoparticle mRNA Vaccines

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in the dose-ranging Phase 1 DMID study of healthy adults at least 18 years of age (Section 3.1.1).

As of March 2020, there have been 8 clinical studies initiated across the Sponsor's infectious disease vaccine platform with over 1,000 participants receiving at least one dose of an mRNA vaccine. mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV (NCT03382405), HMPV/PIV3 (NCT03392389), and Zika virus (NCT04064905). As of January 6, 2020, approximately 365 participants were dosed with either an SM-102-containing lipid vaccine or placebo (doses ranging from 10 to 300 µg) across 3 Phase 1 studies. Of the 365 participants dosed, 264 participants experienced at least 1 solicited adverse reaction (AR). The most common solicited events were pain (28% of total events reported), headache (15%), fatigue (15%), myalgia, (13%), arthralgia (9%), nausea (7%), chills (6%), fever (4%), erythema (2%), and swelling (2%). The majority of the events were of Grade 1 to 2 with approximately 9% being reported as Grade 3. The most common Grade 3 events were pain, myalgia, fatigue, headache, and chills. Grade 3 events were typically recorded on Day 1 or Day 2 following vaccination, with most occurring on Day 2 and resolving by Day 6. In the hMPV/PIV3 Phase 1 study, which is unblinded, unsolicited related adverse events (AEs) included mild to moderate chills, hot flush, diarrhea, pyrexia, temperature intolerance, white blood cell increased, headache, and rash erythematous, as well as severe injection site pain, prothrombin time prolonged and myalgia. All of the severe events occurred at the 300 µg × 2 dose level. In the blinded Phase 1 CMV study, unsolicited related AEs in more than 2 participants included chills (19 participants, 10.5%), fatigue (10 participants, 5.5%), lymphadenopathy, injection site pain, and pyrexia (9 participants each, 5.0%), arthralgia, (8 participants, 4.4%), myalgia, (7 participants, 3.9%), headache, (5 participants, 2.8%), diarrhea, (4 participants, 2.2%), and injection site bruising, (3 participants, 1.7%). Of these AEs, severe events were reported in

3 of 19 participants with chills, 5 of 10 participants with fatigue, 4 of 9 participants with pyrexia, 4 of the 8 participants with arthralgia, and 4 of the 7 participants with myalgia. There were no related serious AEs (SAEs) reported in the Phase 1 CMV, HMPV/PIV3, or Zika vaccine studies.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart.

2.1.2 Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of specific binding antibody (bAb).

2.2 Secondary Objective

The secondary objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

2.3 Exploratory Objectives

The exploratory objectives are the following:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29)
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age. The study schematic is presented in Figure 1 and the Schedule of Events is presented in Table 7.

Two dose levels, 50 µg and 100 µg, will be evaluated in this study, based in part on initial safety data from the Phase 1 DMID study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo (Figure 1).

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment (Figure 2). Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC; Section 6.1.1).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data through Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

Figure 1: Study Flow Schema

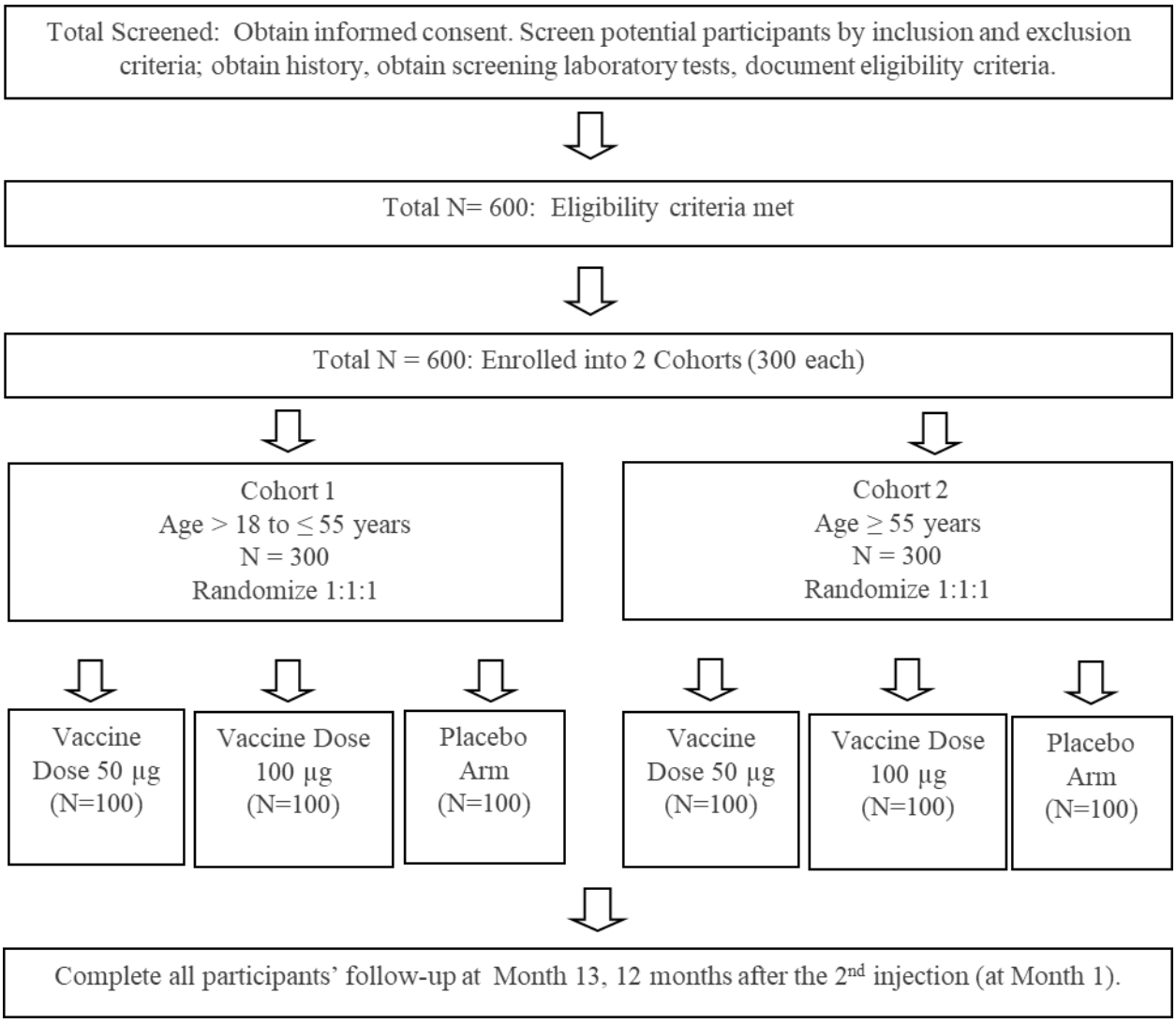
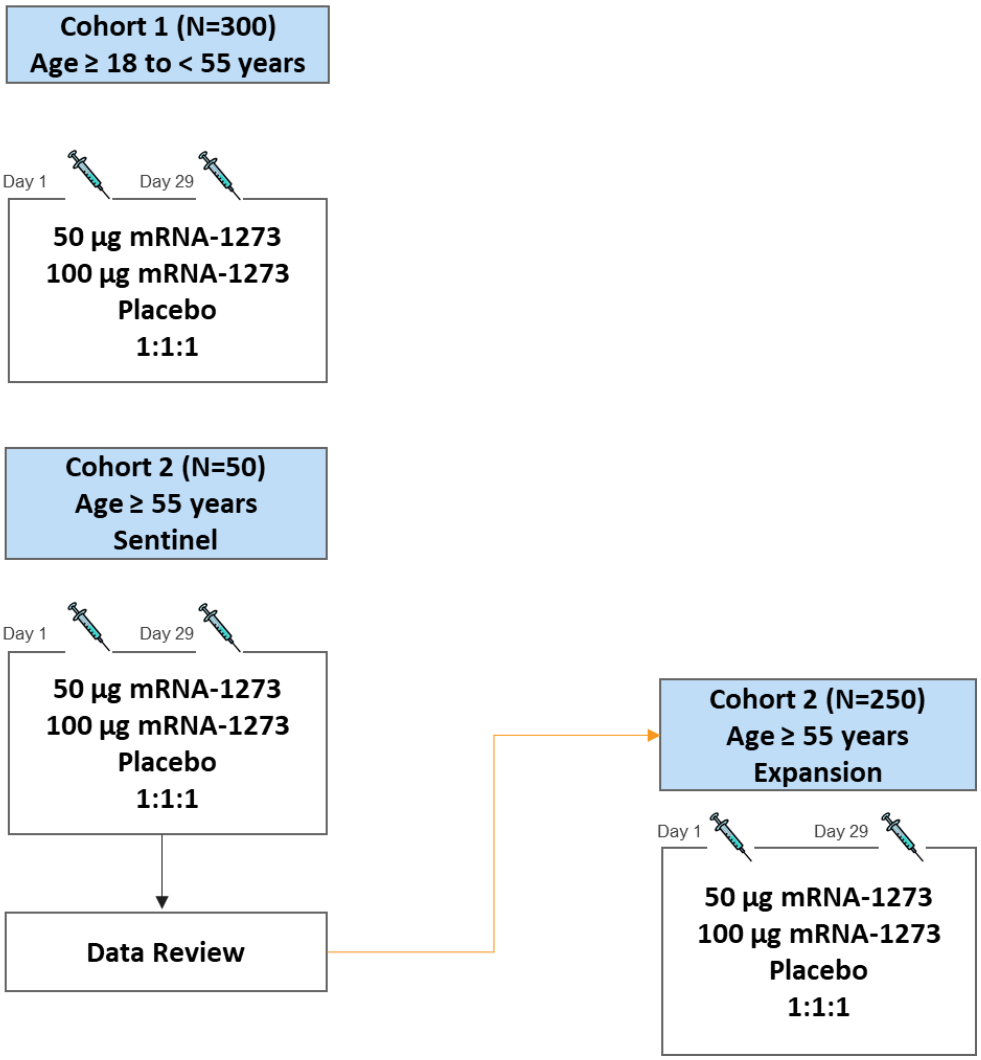


Figure 2: Sentinel and Expansion Cohort Schema



The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled biweekly safety phone calls to collect medically attended adverse events (MAAEs), AEs leading to withdrawal, SAEs, concomitant medications associated with these events, and receipt of non-study vaccinations (Table 7). These phone calls are scheduled biweekly from Day 71 through Day 183 and from Day 223 through Day 377. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment (Section 3.5.1).

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml IM injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment (Section 3.4.5).

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned interim analyses (Section 4.7).

The end of study (EOS) is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the Schedule of Events (Table 7) for the last participant in this study. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within a provided electronic diary (eDiary). Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at scheduled study visits during the study for safety and immunogenicity assessments or other medical concerns, according to the investigator's judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Detailed information on all statistical analysis of data is presented in Section 4.6.2.

3.1.1 Rationale for Dose Selection

In this study, the 2 dose levels of mRNA-1273 tested in participants will be 50 µg, and 100 µg, based on assessment of available safety and immunogenicity data from the Phase 1 DMID study and Phase 1 studies of mRNA-1647 and mRNA-1443 (Section 1.1).

The Phase 1 DMID study, an open-label dose ranging study of mRNA-1273 in healthy adult male and non-pregnant female participants in 3 age groups: age 18 to 55 years, inclusive (45 participants); age 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants) is currently ongoing. Participants in each age cohort will be randomly assigned to 1 of 3 dose levels of mRNA-1273: 25 µg, 100 µg, and 250 µg. Each participant will receive an IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed for 12 months after the second injection.

As of 14 May 2020, 15 participants in each of the 3 dose levels of the 18 to 55-year age cohort had received at least 1 dose of mRNA-1273. Recruitment of participants in the 2 older-age cohorts is ongoing. There have been no SAEs and no triggering of study pause rules. A review of preliminary solicited local and systemic adverse reactions in participants in the 18 to 55-year age cohort after the second injection showed 3 participants in the 100 µg dose group who reported severe local adverse reactions (grade 3 erythema and induration) and 3 participants in the 250 µg dose group who reported severe systemic adverse reactions (fever, fatigue, feverishness, myalgia, and nausea). These adverse reactions resolved within 24 hours and were not assessed as serious.

The 50 µg and 100 µg doses proposed for this Phase 2a study fall within the doses being evaluated in the Phase 1 DMID study.

3.1.2 Rationale for Study Design

The 2 age cohorts in this Phase 2a study, ≥ 18 to < 55 years old and ≥ 55 years old, were established to better understand the relationships among dose, tolerability, and immunogenicity in different age groups, one being healthy older adults. The older cohort in this Phase 2a study corresponds to the 2 older age cohorts in the Phase 1 DMID study.

Because there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 3.4.5).

The Phase 1 DMID study is small (105 participants at 3 dose levels) and does not incorporate a placebo. Having a sample size of 600 participants in this Phase 2a study and including a placebo will help to improve understanding of AEs.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and post-injection blood samples for antibody analysis through 12 months after the last dose of investigational product. In addition, participants will have nasopharyngeal swab samples collected at Day 1 and Day 29 before the

injections, and at Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasopharyngeal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and polymerase chain reaction (PCR). Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Since it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the nasopharyngeal swab samples collected before study injection may help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

3.2 Selection of Study Population

Healthy male or female participants will be enrolled at study sites in the US or its territories.

3.2.1 Inclusion Criteria

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 18 years of age or older at the time of consent (Screening Visit, Day 0).
2. Understands and agrees to comply with the study procedures and provides written informed consent.
3. According to the assessment of the investigator, is in good general health and can comply with study procedures.
4. Body mass index (BMI) of 18 kg/m^2 to 30 kg/m^2 (inclusive) at the Screening Visit (Day 0).
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening (Day 0) without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.
6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

- Has a negative pregnancy test at Screening (Day 0) and on the day of the first injection (Day 1).
- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
- Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).
- Is not currently breastfeeding.

Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception and refrain from sperm donation from the time of the first injection and through 3 months after the last injection.

   Adequate contraception for male participants is defined as:

   - Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
   - Use of barrier methods and spermicide
   - History of surgical sterilization

   Male participants with partners who have become pregnant prior to Screening are eligible to participate in the study.

3.2.2 Exclusion Criteria

Participants meeting any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known exposure to someone with SARS-CoV-2 infection or COVID-19.

2. Travel outside of the US in the 28 days prior to the Screening Visit (Day 0).

3. Pregnant or breastfeeding.

4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

5. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.

6. Current treatment with investigational agents for prophylaxis against COVID-19.

7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.

8. Is a healthcare worker or a member of an emergency response team.

9. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).

10. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).

11. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of Screening.

12. Known history of hypertension, or systolic blood pressure > 150 mm Hg in participants in Cohort 1 (≥ 18 to < 55 years old) or systolic blood pressure > 160 mm Hg in participants in Cohort 2 (≥ 55 years old) at the Screening Visit (Day 0).

13. Known history of hypotension or systolic blood pressure < 85 mm Hg at the Screening Visit (Day 0).

14. Diabetes mellitus

15. Diagnosis of chronic pulmonary disease (eg, chronic obstructive pulmonary disease, asthma)

16. Chronic cardiovascular disease

17. Resides in a nursing home

18. Grade 1 or higher toxicity on clinical safety laboratory testing at the Screening Visit (Day 0)

19. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.

20. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to the Screening Visit (Day 0) (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the Screening Visit (Day 0).

21. Anticipating the need for immunosuppressive treatment at any time during participation in the study.

22. Positive serology for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies identified at the Screening Visit (Day 0).

23. History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine.

24. Bleeding disorder considered a contraindication to IM injection or phlebotomy.

25. Diagnosis of malignancy within previous 10 years (excluding non-melanoma skin cancer).

26. Has received or plans to receive a licensed vaccine ≤ 28 days prior to the first injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after any study injection. Licensed influenza vaccines may be received more than 14 days before or after any study injection.

27. Receipt of systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (Day 0) or plans for receipt during the study.

28. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.

29. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.

30. Is an immediate family member or household member of study personnel

3.2.3 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In the event an eligible participant was not enrolled as a result of a cohort being full and the participant having surpassed their 28-day (+7 days) screening period, the investigator may rescreen the participant for enrollment by assigning the participant a new identification number and repeating all screening procedures (Section 3.3.4).

3.2.4 Participant Restrictions During the Study

3.2.4.1 General and Dietary

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

3.3 Withdrawal of Participants From the Study or Study Dosing

3.3.1 Participant Withdrawal From the Study

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS electronic case report form (eCRF).

Potential reasons for withdrawing a participant from the study include the following:

- SAE
- AE (non-SAE)
- Protocol violation (specify)
- Consent withdrawal (document reason)

- Lost to follow-up
- Other (specify)

3.3.2 Handling Withdrawal From the Study

When a participant withdraws or is withdrawn from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These participants will be requested to complete the EOS assessments scheduled for Day 394 (Month 13).

3.3.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's study source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (eg, study site visit, phone call).

3.3.4 Replacements

Any participant who is withdrawn, who is significantly outside the allowed injection window, or who is lost to follow-up from the study may be replaced at the Sponsor's discretion.

3.3.5 Participant Withdrawal From Study Dosing

Every reasonable attempt will be made to follow up with participants for safety throughout the entire study period, even if further injection is withheld or the participant misses one or more visits. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all scheduled visits and assessments. (Table 7).

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to investigational product (Section 3.5.8.9) and is of Grade 3 (severe) or greater severity (Appendix 3)
- Experiences an AE or SAE that, in the judgment of the investigator, requires study vaccine withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly attributed to study vaccine
- Experiences generalized urticaria related to the study vaccine

The reason(s) for withdrawal from further injection will be recorded.

3.4 Study Dosing Groups

3.4.1 Method of Assigning Participants to Dosing Groups

There are 2 age cohorts in this study: participants ≥ 18 to < 55 years old in Cohort 1 and participants ≥ 55 years old in Cohort 2. Within each age cohort, approximately 300 participants will be randomly assigned in 1:1:1 ratio to receive mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules. Only

the unblinded pharmacy personnel (Section 3.4.5) will have controlled access to which arm the participant is randomly assigned.

Dose group assignment in each cohort and stratification within each cohort is summarized in Table 1.

Table 1: Dose Group Assignment

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Total			**600**

3.4.2 Investigational Product Administration

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with at least a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 100 µg, or saline placebo. Preferably, vaccine should be administered into the nondominant arm. The second dose of investigational product should be administered in the same arm as the first dose.

The investigational product will be prepared for injection as a single 0.5 mL dose for each participant based on the cohort and randomization assignment, as detailed in the mRNA-1273-P201 Pharmacy Manual. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform investigational product accountability, dose preparation, and investigational product administration. The investigator will designate an unblinded clinical team member to provide oversight to the administration of investigational product so that it proceeds according to the procedures stipulated in this study protocol and the mRNA-1273-P201 Pharmacy Manual. Study-specific training will be provided.

At each visit when investigational product is administered, participants will be monitored for a minimum of 60 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (Schedule of Events, Table 7).

Eligibility for subsequent investigational product injection is determined by following the criteria outlined in Section 3.4.2.2.

The study site will be appropriately staffed, staff will be trained on emergency resuscitation, and will have stocked rescue medications (such as epinephrine, steroids, antihistamines, and intravenous fluids) should any severe reaction (eg, anaphylaxis or urticaria) occur that requires immediate intervention.

The rules for pausing dosing are provided in Section 3.4.2.1.

3.4.2.1 Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause (Table 2).

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than injection	≥ 3
3	ICU admissions in Cohort 1 due to SARS-CoV-2 infection	≥ 3
4	ICU admissions in Cohort 2 due to SARS-CoV-2 infection	≥ 6

Abbreviations: AE = adverse event; ICU = intensive care unit; SAE = serious adverse event.

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold event is adjudicated by the Safety Monitoring Committee (SMC; Section 6.1.1).

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event potentially meeting any pause rule criterion. The Sponsor will inform the SMC (Section 6.1.1) of any event potentially meeting any pause rule criterion. The SMC will review all available study data to adjudicate such events in accordance with the SMC charter.

The Sponsor will also actively monitor the following and provide them to the SMC for review as they become available:

- Instances of study halting rules triggered in the Phase 1 DMID study (NCT04283461)

- Histopathological data suggestive of vaccine-enhanced disease in ongoing nonclinical studies

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

3.4.2.2 Contraindications to Subsequent Injection

Prior to receiving a second injection, participants will be reassessed to ensure that they continue to meet eligibility requirements as outlined below.

The following events in a participant constitute absolute contraindications to any further administration of the investigational product to that participant. If any of these events occur during the study, the participant must not receive additional doses of vaccine but will be encouraged to continue study participation for safety through 12 months following last injection (Section 3.3.5).

- Diagnosed COVID-19. If COVID-19 is suspected, further administration of investigational product must be withheld until COVID-19 test results are available.
- Anaphylaxis or systemic hypersensitivity reaction following the administration of vaccine.
- Any SAE judged by investigator or Sponsor to be related to study vaccine.
- Pregnancy
- Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the participant if he/she continues to participate in the study.

The following events constitute contraindications to administration of study vaccine at certain points in time, and if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the Schedule of Events (Table 7), or the participant may be withdrawn from dosing at the discretion of the investigator (Section 3.3.5):

- Acute moderate or severe infection with or without fever at the time of injection
- Fever, defined as body temperature ≥ 38.0°C (100.4°F) at the time of injection

Participants with a minor illness without fever, as assessed by the investigator, can be administered investigational product. Participants with a fever of 38.0°C (100.4°F) or higher

will be contacted within the time window acceptable for participation and reevaluated for eligibility.

3.4.3 Identity of Investigational Product

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 Injection is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

3.4.4 Management of Investigational Product

3.4.4.1 Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the investigational product
- Confirming the appropriate labeling of mRNA-1273 Injection, so that it complies with the legal requirements of the US

The investigator is responsible for acknowledging the receipt of the investigational product by a designated staff member at the site, including the following:

- Confirming that the investigational product was received in good condition
- Confirmation that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming whether the Sponsor has authorized the investigational product for use
- Ensuring the appropriate dose level of mRNA-1273 Injection is properly prepared using aseptic technique

Further description of the investigational product and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the investigational product are described in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.2 Packaging and Labeling

The Sponsor will provide the investigator and study site with adequate quantities of mRNA-1273. The sterile vaccine product is packaged in a 2-mL glass vial with a 0.6-mL fill volume. mRNA-1273 vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future participant identification purposes.

mRNA-1273 Injection will be packaged and labeled in accordance with the standard operating procedures (SOPs) of the Sponsor or of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, guidelines for Quality System Regulations, and applicable regulations.

The Sponsor or Sponsor's designee will supply the 0.9% sodium chloride injection for use as both a placebo and a diluent to mRNA-1273. The 0.9% sodium chloride bears a commercial label and does not contain study-specific identification.

3.4.4.3 Storage

mRNA-1273 vaccine must be stored at -60°C to -90°C (-76°F to -130°F) in a secure area with limited access (unblinded pharmacy staff only) and protected from moisture and light until it is prepared for administration (Section 3.4.2). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There must be an available back-up freezer. The freezers must be connected to a back-up generator. In addition, vaccine accountability study staff (eg, the unblinded pharmacy personnel) are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1273 vaccine that was not temperature controlled during shipment or during storage to the unblinded site monitor. Such mRNA-1273 will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

The 0.9% sodium chloride injection (USP) should be stored at 20ºC to 25ºC (68ºF to 77ºF) in a restricted access area.

3.4.4.4 Investigational Product Accountability

It is the investigator's responsibility that the unblinded pharmacy personnel maintain accurate records in an investigational product accountability log of receipt of all investigational product, inventory at the site, dispensing of mRNA-1273 and placebo, study injections, and return to the Sponsor or alternative disposition of used/unused products.

An unblinded site monitor will review the inventory and accountability log during site visits and at the completion of the study. Additional details are found in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.5 Handling and Disposal

An unblinded site monitor will reconcile the investigational product during the conduct and at the end of the study for compliance. Once fully reconciled at the site at the end of the study, the investigational product can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Investigational product may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be completed and sent to the Sponsor or designee.

3.4.5 Blinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of investigational product to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the investigational product accountability monitors. They will have responsibilities to ensure that sites are following all proper investigational product accountability, preparation, and administration procedures.

- An unblinded statistical and programming team will perform the pre-planned interim analyses (Section 4.7). Sponsor team members will be pre-specified to be unblinded to the interim analysis results and will not communicate the results of interim analyses to the blinded investigators, study site staff, clinical monitors, or participants.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the investigational product in a secure location that is not accessible or visible to other study staff. A blinding label over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different than placebo. Only delegated unblinded site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

3.4.6 Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 4.7.

3.4.7 Dosing Compliance

All doses of investigational product will be administered at the study site under direct observation of unblinded pharmacy personnel and appropriately recorded (date and time) in the eCRF. Unblinded pharmacy personnel will confirm that the participant has received the entire dose of vaccine. If a participant does not receive vaccine or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Participants who miss the second injection due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol. Unless consent is withdrawn, a participant who withdraws or is

withheld from receiving the second dose of study vaccine will remain in the study and complete all safety and immunogenicity assessments required through the scheduled EOS.

The study site is responsible for ensuring participants comply with the study windows allowed. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Table 7). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (eg, clinical laboratory testing, eDiary review for reactogenicity, immunologic testing, as applicable).

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

3.4.8.2 Concomitant Medications and Therapies

At each study visit, study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the first study injection.
- All concomitant medications and non-study vaccinations taken through 28 days after each injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each study injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the postinjection study visits or via other participant interactions (eg, phone calls).

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis (analysis sets are described in Section 4.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- A licensed vaccine administered during the period from 28 days before through 28 days after each study injection, except for any licensed influenza vaccine that was administered more than 14 days before or after any study injection.
- Immunoglobulins and/or any blood products administered during the study period.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

3.5 Study Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 5.3). Participants will undergo study procedures at the time points specified in the Schedule of Events (Table 7).

A participant also can be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the

participant about visits, review eDiary requirements, or follow up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

3.5.1 Assessment for SARS-CoV-2 Infection

Study participants will have nasopharyngeal swab samples collected for SARS-CoV-2 testing at time points specified in the Schedule of Events (Table 7).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect a nasopharyngeal swab sample to ascertain the presence of SARS-CoV-2 via PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020c)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case. All findings will be recorded in the eCRF.

If scheduled, a study site illness visit may include assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasopharyngeal swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. Blood samples will be collected for potential future serologic diagnosis of SARS-CoV-2 infection.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant's primary care physician of the diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a blood sample will be collected for potential future serologic diagnosis of SARS-CoV-2 infection.

Any confirmed SARS-CoV-2 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

3.5.2 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, or AEs leading to study withdrawal and concomitant medications associated with those events, as well as about occurrence of any non-study vaccinations (Section 3.5.8.6).

The timing of the safety telephone calls is provided in Table 7.

All safety information described by the participant must be documented in source documents and not documented on the script used for the safety telephone contact.

3.5.3 Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 3.5.8.4) on Day 1.

At each injection visit, participants will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants will record data into the eDiary starting approximately 1 hour after injection under supervision of the study site staff to ensure successful entry of assessments. The site staff will perform any retraining as necessary. Study participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 3.5.8.4, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in the eDiary until resolution. Adverse reactions recorded in diaries beyond Day 7 should be reviewed by study site staff either during the next scheduled phone call or at the next study site visit (Table 7).

- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on a day of injection or for the 6 subsequent days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. If assessments are not recorded for a given day, the participant will have a limited time window on the following day to complete qualitative assessments for the previous day, excluding measurements of body temperature and of any injection site erythema, swelling, or induration. Any new safety information reported during safety phone calls or at site visits (including a solicited reaction) not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF.

Study site staff will review eDiary data with participants at the Day 8 and Day 36 visits.

3.5.4 Safety Laboratory Assessments

Laboratory tests will be performed by the central laboratory, unless otherwise specified. Screening safety laboratory tests will include complete blood count with differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (ALP), blood urea nitrogen/creatinine, prothrombin time (PT), and partial thromboplastin time (PTT). These safety laboratory tests are to be repeated at Day 29 and Day 57 only for Cohort 2 (≥ 55 years of age).

Additional tests include the following:

- A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine administration (Day 1 and Day 29). At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

- If not documented in a female participant's medical records, an FSH test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.
- Hepatitis B surface antigen, hepatitis C virus antibody, and HIV virus (types 1 and 2) antibody at the Screening Visit (Day 0).

3.5.5 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, blood samples for immunogenicity assessment will be collected before administration of vaccine. The following analytes will be measured:

- Serum bAb titer against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 S protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow further testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

The ELISA and measurement of nAb titers will be performed in a laboratory designated by the Sponsor.

For participants who provide consent (Section 5.3), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoV.

3.5.6 Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant are 66 mL for 1 day, 182 mL for 28 days, and 398 mL for the complete study (Table 3).

Table 3: Maximum Blood Sampling Volumes per Participant by Visit

Study Visit Day	D0	D1	D15	D29	D43	D57	D209	D394	Total
Safety laboratory tests	16 mL			16[1] mL		16[1] mL			48 mL
Immunogenicity assays		50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	350 mL
Total	**16 mL**	**50 mL**	**50 mL**	**66 mL**	**50 mL**	**66 mL**	**50 mL**	**50 mL**	**398 mL**

Abbreviation: D = Day.

[1] Only participants in Cohort 2 will have blood sampled for safety laboratory tests at Day 29 and Day 57.

3.5.7 Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 3.5.8.4) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 3.5.3).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs (Section 3.5.8.4).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study.
- MAAEs from Day 1 through Day 394 or withdrawal from the study.
- SAEs from Day 1 through Day 394 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 3.5.1).

3.5.8 Safety Definitions

3.5.8.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to vaccine or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test result (hematology, clinical chemistry, or PT/PTT) or other safety assessment (eg, electrocardiogram, radiological scan, vital sign measurement), including one that worsens from baseline and is considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after mRNA-1273 vaccine administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the investigational product caused the AE (Section 3.5.8.4). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the investigational product and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.2 Medically Attended Adverse Event

An MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner (HCP). This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, SARS-CoV-2 infection [Section 3.5.1]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be fully reported on the MAAE page of the eCRF.

3.5.8.3 Serious Adverse Event

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study vaccine.
- Is life-threatening
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission.
  Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Congenital anomaly or birth defect
- Medically important event
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered

serious. 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.

3.5.8.4 Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after vaccine administration. The eDiary (Section 3.5.3) will solicit participant reporting of ARs using a structured checklist. Participants will record such occurrences in an eDiary on the day of each vaccine administration and for the 6 days after a day of injection.

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, body temperature (potentially fever), and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following occurs within 7 days after study injection:

- Severe (Grade 3) local or systemic ARs (Table 4),
- Presence of any rash, or
- Presence of any underarm swelling or tenderness on the same side as the injection arm

The purpose of the contact is to assess the nature of AR, including assessment of potential pause rules. In the event that rash or underarm swelling or tenderness on the same side as the injection arm is reported, the participant will be asked to return to the study site for assessment by the investigator.

The investigator will review, confirm, and Grade reactogenicity according to the grading scales presented in Table 4, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution. Adverse reactions

recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit. All solicited ARs (local and systemic) will be considered causally related to injection.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous	Requires emergency room visit or hospitalization for hypotensive shock

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
		24 hours		hydration	
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F
Rash*	No rash	Localized rash, without associated symptoms	Maculopapular rash, covering < 50% body surface area	Generalized urticarial, covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis, eg, Stevens-Johnson syndrome or erythema multiforme

* Grading for rash and Grade 4 events per Investigator assessment (with exception of fever)

In case of any rash episode observed within 7 days after study injection, the participants will be instructed to contact the study site within 24 hours. During participant evaluation, the investigator should categorize the rash as one of the following:

- Rash no longer present and history not consistent with urticaria.
- Rash no longer present but history is consistent with urticaria.
- Rash present but clinical findings are not consistent with urticaria. Alternative diagnosis should be specified as an AE.
- Rash present and clinical findings consistent with urticaria.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded as an AE in the participant's Adverse Event eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days post-injection
- Solicited local or systemic AR that leads to participant withdrawal from vaccine

- Solicited local or systemic AR that otherwise meets the definition of an SAE
- Solicited AR sign measurement with a toxicity score of Grade 3 or greater

An unsolicited AE is any AE reported by the participant that is either not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but it starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.5 Pregnancy

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 3.5.8.7).

3.5.8.6 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor. Unsolicited AEs will be captured from Day 1 through 28 days after each dose up to Day 57 (±5 days), Both MAAEs and SAEs will be captured from Day 1 throughout entire study duration (Day 394 for all participants), as specified in the Schedule of Events (Table 7). Any AEs occurring before receipt of the vaccine will be analyzed separately from TEAEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically-related changes in their well-being according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, data from clinical laboratory test results, physical examination findings, or other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

3.5.8.7 Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to vaccine or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes cohort, type of event, time of onset, investigator-specified assessment of severity and relationship to vaccine, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.8.3) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the vaccine caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341
- SAE Fax line (USA and Canada): +1-866-599-1342

3.5.8.8 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities and will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life-threatening (Grade 4) using the following criteria:

- Mild (Grade 1): These events do not interfere with the participant's daily activities.

- Moderate (Grade 2): These events cause some interference with the participant's daily activities but do not require medical intervention.
- Severe (Grade 3): These events prevent the participant's daily activity and require medical intervention.
- Life-threatening (Grade 4): These events require an emergency room visit or hospitalization.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Table 4. Specific criteria for clinical and laboratory abnormalities are presented in Appendix 2 (Table 8 and Table 9, respectively) and will be graded if outside of the reference range for the laboratory utilized.

3.5.8.9 Assessment of Causality

The investigator's assessment of an AE's relationship to vaccine is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the vaccine caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: There is not a reasonable possibility of a relationship to the investigational product. Participant did not receive the investigational product OR temporal sequence of the AE onset relative to administration of the investigational product is not reasonable OR the AE is more likely explained by another cause than the investigational product.
- Related: There is a reasonable possibility of a relationship to the investigational product. There is evidence of exposure to the investigational product. The temporal sequence of the AE onset relative to the administration of the investigational product is reasonable. The AE is more likely explained by the investigational product than by another cause.

3.5.8.10 Follow-up of Adverse Events

All AEs, SAEs, and MAAEs must be reported in detail on the appropriate page of the eCRF and followed until the event is resolved or stable or judged by the investigator to be not clinically significant.

3.5.9 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, vital sign measurements will be collected once before vaccine administration and at least 1 hour after vaccine administration (before participants are discharged from the study site).

Febrile participants at Day 1 and Day 29 visits (fever is defined as a body temperature ≥ 38.0°C/100.4°F) may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities (Table 8) of Grade 3 or greater, the abnormal value and Grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.5.10 Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Schedule of Events (Table 7). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as a MAAE.

Symptom-directed physical examinations may be performed at other timepoints at the discretion of the investigator. On each injection day before injection and again 7 days after

injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

Body mass index will be calculated at the Screening Visit (Day 0) only.

4 STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or Clinical Study Report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

4.1 Blinding and Responsibility for Analyses

Blinding during the study will be conducted as described in Section 3.4.5. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Planned interim analyses and data presentation for unblinded SMC review are described in Section 4.7 and Section 6.1, respectively. At each interim analysis, pre-identified Sponsor members will be unblinded to review treatment level results as defined in the study Data Blinding Plan. The unblinded interim analysis and any data presentation or analysis for SMC review will be handled by the unblinded team of statisticians and programmers. A strict firewall between the blinded and unblinded teams will be maintained during study conduct. Sponsor personnel who have access to review unblinded results will be documented. Study sites will remain blinded. The results of interim analyses will not be shared with the investigators before completion of the study.

4.2 Hypothesis Testing

There is no hypothesis testing in this study.

4.3 Analysis Endpoints

4.3.1 Primary Endpoints

4.3.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.

- Unsolicited AEs through 28 days after each injection.
- MAAEs through the entire study period.
- SAEs throughout the entire study period.
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only).
- Vital sign measurements and physical examination findings.

4.3.1.2 Primary Immunogenicity Endpoint

- Titer of SARS-CoV-2-specific binding antibody (bAb) measured by ELISA on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13).

4.3.2 Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

- Titer of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13).
- Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) to equal to or above LOD or LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers.

4.3.3 Exploratory Endpoints

The exploratory endpoints are the following:

- Serum titers of S protein-specific binding Ig assessed byclass and subclass and nAb in serum.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels in serum
- Clinical severity and immune response of participants infected by SARS-CoV-2
- Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect non-vaccine antigens of SARS-CoV-2.

4.4 Analysis Populations

4.4.1 Randomized Set

The Randomized Set consists of all participants who are randomly assigned in the study, regardless of the participants' treatment status in the study.

4.4.2 Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomly assigned and received any study injection, and contribute any solicited AR data; ie, have at least one post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the injection group corresponding to the study injection they actually received.

4.4.3 Safety Set

The Safety Set consists of all randomly assigned participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the injection group corresponding to the study injection they actually received for the analysis of safety data using the Safety Set.

4.4.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who a) receive any study injection, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-injection assessment for the analysis endpoint. Participants will be included in the injection group to which they were randomly assigned.

4.4.5 Per-Protocol Set

The Per-Protocol (PP) Set consists of all FAS participants who meet all of the following criteria:

- Complied with the injection schedule
- Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective
- Did not have SARS-CoV-2 infection
- Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the injection group to which they were randomly assigned.

4.5 Sample Size Determination

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. Table 5 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. The 2-sided 95% CI is estimated (0.01%, 1.4%) at sample size of 400 with 1 participant reporting an AE. Furthermore, a sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Table 5: 95% Confidence Interval for One Participant with AE and the Lowest Detectable Incidence Rate at 95% Probability in Selected Sample Size

Sample Size Receiving mRNA-1273	Rate and 95% CI (%) at One Participant with AE			Lowest Detectible Rate (%) with ≥95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75

Abbreviations: AE = adverse event; CI = confidence interval.

4.6 Statistical Methods

There are 2 age cohorts in this study: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). All analyses will be performed by treatment group and for the 2 cohorts separately, unless specified otherwise. Data from participants who received placebo will be pooled across cohorts for all dosing.

4.6.1 Summary of Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by injection group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

4.6.2 Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the MedDRA for adverse reaction terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash, solicited ARs, unsolicited AEs, and vital signs (Table 4).

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR and with any solicited AR during the 7-day follow-up period after each injection will be provided with a 2-sided 95% exact CI using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided and Table 6 summarizes analysis strategy for safety parameters.

Table 6: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by preferred term coded by MedDRA.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, injection group, and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the SAP.

4.6.3 Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set. For each age cohort, if the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint (Section 4.3.1.2), geometric mean titer (GMT) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint (Section 4.3.2), GMT of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by injection group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the LOD or LLOQ will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with GMFR ≥ 2, GMFR ≥ 3, and GMFR ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher log-transformed titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb titers may be performed.

4.6.4 Exploratory Analyses

Exploratory analyses may include the following:

- Descriptive summaries of the relative proportions of S protein-specific serum Igs and nAb during the study. Subclass analysis of specific IgG may be performed.
- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study

- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study

4.7 Interim Analyses

Interim analyses (IAs) will be conducted on cleaned data and may be combined depending on study timelines.

1. An interim analysis of safety and immunogenicity will be triggered after the first 100 participants in each cohort have completed Day 29 visits. Pre-identified Sponsor team members will be unblinded to group treatment level results.
2. An interim analysis of safety and immunogenicity will be triggered after the first 100 participants in each cohort have completed Day 57 visits. Pre-identified Sponsor team members will be unblinded to participant level results.
3. An interim analysis of safety and immunogenicity will be triggered after all participants in each cohort have completed the Day 209 visits (Month 7). Pre-identified Sponsor team members will be unblinded to participant level results.

An independent, unblinded statistics team will carry out the IAs. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded throughout the study.

The final analysis of safety and immunogenicity will be performed after all participants have completed the study and after the database is cleaned and locked. Results of this analysis will be presented in a CSR, including individual listings.

Additional information can be found in the SAP.

4.8 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonized tripartite guideline E6(R2): GCP and current SOPs. The eCRFs will be utilized and accessed through iMedidata® via the internet. This EDC system is validated and compliant with US Title 21 of CFR Part 11. Each person involved with the study will have an individual identification code and password that allow for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Due to safety review requirements, study sites must follow the data entry and availability instructions provided by Sponsor in the study readiness trainings. As a quality measure,

timeliness of data entry and data query resolution will be followed closely. Other issues of data quality that may hinder safety review or pose a concern with patient safety will be brought to the attention of the Sponsor or CRO, with appropriate awareness to the SMC if needed.

5 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study and may be pursuant to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

5.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

5.2 Institutional Review

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

5.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to

study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study, be allowed to read the approved ICF, and be given answers to any questions. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF. Separate counseling and consent may be provided for HIV testing as applicable per local laws or regulations.

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoV.

The investigator or designee will provide a copy of the ICF to the participant. The original form shall be maintained in the participant's medical records at the site.

5.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to Sponsor according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

5.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor, the CRO, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, the CRO, nor the study site is financially responsible for further treatment of the disease under study.

5.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

5.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

5.8 Data Collection

5.8.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic case report forms are accessed through iMedidata® via the internet. This EDC system is validated and compliant with 21 CFR 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

5.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

5.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

5.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

5.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the vaccine. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

5.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

6 STUDY MANAGEMENT

6.1 Monitoring

Ongoing safety monitoring will be performed in a blinded manner by the CRO's medical monitor, the Sponsor's medical monitor, and the individual site investigators throughout the study.

6.1.1 Safety Monitoring Committee

Safety oversight will be under the direction of an SMC composed of external independent consultants with relevant expertise. Members of the SMC will be independent from the study conduct and free of conflict of interest. The SMC will meet on a regular basis to assess safety throughout the study conduct. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SMC. Details regarding the SMC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The SMC will convene on an ad hoc basis if any of the pause rules, described in Section 3.4.2.1, are met. The SMC will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

6.1.2 Monitoring of the Study

The study monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The monitor will be blinded to dose assignment. A separate unblinded study monitor will be responsible for vaccine accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

6.2 Management of Protocol Amendments and Deviations

6.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

6.2.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Major protocol deviations are defined as exclusionary from the analysis according to the protocol objectives and endpoints. Protocol deviations will be documented by the study monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of such deviations.

6.3 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last participant completes the last visit (includes the EOS Visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the CSR.

6.4 Clinical Study Reports

Whether the study is completed or prematurely terminated, the Sponsor will ensure that CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory

requirement(s). The Sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSRs. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

A final CSR will contain all data collected through Day 394 (Month 13).

Upon completion of the CSR, the Sponsor will provide the investigator(s) with the final approved CSR.

7 APPENDICES

7.1 Appendix 1: Schedule of Events

The Schedule of Events is presented in Table 7.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening, Day 1, and Day 29 visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Screening, Day 1, and Day 29 visits), a safety phone call should be performed that includes the assessments scheduled for the biweekly safety phone calls (Table 7).

Table 7: Schedule of Events

Visit Number	0	1	2	3	4	5	6	7		8		9
Type of Visit	C	C	C	C	C	C	C	C	SC	C	SC	C
Month Timepoint		M0			M1			M2	BW SC	M7	BW SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Q 2 weeks D71 – D183[3]	D209[2, 3]	Q 2 weeks D223 – D377[3]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	-3/+7	+3	±3	-3/+7	±3	±14	±3	±14
Days Since Most Recent Vaccination	-	0	7	14	28/0	7	14	28	42 – 154	180	194 – 348	365
ICF, demographics, concomitant medications, medical history	X											
Confirm participant meets inclusion and exclusion criteria	X	X										
Blood for safety laboratory tests[4]	X				X[4]			X[4]				
Blood for viral serology (hepatitis B, hepatitis C, HIV [1 and 2])	X											
Physical examination including vital signs[5]	X	X	X	X	X	X	X	X		X		X
Pregnancy testing[6]	X	X			X							
Randomization		X										
Study injection (including 60-minute post-dosing observation period)		X			X							
Blood for vaccine immunogenicity[7]		X		X	X		X	X		X		X
Nasopharyngeal swab sample for SARS-CoV-2[8]		X			X			X				
eDiary activation for recording solicited adverse reactions (7 days)[9]		X			X							
Review of eDiary			X			X						

Visit Number	0	1	2	3	4	5	6	7		8		9
Type of Visit	C	C	C	C	C	C	C	C	SC	C	SC	C
Month Timepoint		M0			M1			M2	BW SC	M7	BW SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Q 2 weeks D71 – D183[3]	D209[2, 3]	Q 2 weeks D223– D377[3]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	-3/+7	+3	±3	-3/+7	±3	±14	±3	±14
Days Since Most Recent Vaccination	-	0	7	14	28/0	7	14	28	42 – 154	180	194 – 348	365
Follow-up safety calls[10]									X		X	
Recording of Unsolicited AEs		X	X	X	X	X	X	X				
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[11]		X	X	X	X	X	X	X	X	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[11]	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations[11]		X	X	X	X	X	X	X				
Study completion												X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; BW SC = biweekly safety (phone) call; C = clinic visit; CBC = complete blood count; D = day; HIV = human immunodeficiency virus; ICF = informed consent form; M = month; MAAE = medically attended AE; PCR = PT = prothrombin time; PTT = partial thromboplastin time; Q = every; SAE = serious adverse event.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (FDA March 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. The Day 0 visit may be performed over multiple visits if within the 28-day screening window.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for adverse events and concomitant medications (e.g. as defined in scheduled biweekly safety phone calls). Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).
3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 -3/+7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), the window may be extended to Day 29 + 21 days. When the extended window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.

4. Safety laboratory tests include the following: CBC with differential, AST, ALT, total and direct bilirubin, alkaline phosphates, BUN/creatinine, PT/PTT. Safety laboratory tests are to be repeated at Day 29 and Day 57 **only for Cohort 2 (≥ 55 years old).**
5. Physical examination: a full physical examination, including height and weight, will be performed at Day 1, Day 29 and Day 57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as a MAAE. Vital signs are to be collected pre and post-dosing on days of injection (Day 1 and Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
6. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator a pregnancy test either via blood or point-of-care urine test can be performed. Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the investigator.
7. Sample must be collected prior to dosing on days of injection (Day 1 and Day 29).
8. The nasopharyngeal swab sample will be used to ascertain the presence of SARS-CoV-2 via PCR.
9. Diary entries will be recorded by the participant at approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via phone call or at the following study visit.
10. Trained study personnel will call all participants to collect information relating to any AEs, MAAEs, AEs leading to study discontinuation, SAEs, information on concomitant medications associated with those events, and any non-study vaccinations.
11. All concomitant medications and non-study vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Screening through the final visit (Day 394).

7.2 Appendix 2: Toxicity Grading Scale Tables

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 8 and Table 9, respectively. Note that for laboratory abnormalities, grading only occurs if the values are outside of the normal values established by the clinical laboratory. For study-specific laboratory normal ranges and associated toxicity grades, refer to the laboratory manual.

Table 8: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Abbreviation: ER = emergency room.

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)**	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER = emergency room.

Note that fever is classified under systemic reactions for grading purposes.

* Participant should be at rest for all vital sign measurements.

** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise (unusual tiredness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized myalgia (muscle ache or pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized arthralgia (joint ache or pain)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviations: ER = emergency room; IV = intravenous.

* Oral temperature; no recent hot or cold beverages or smoking.

Sources: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

Table 9: Tables for Laboratory Abnormalities

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)**
Blood urea nitrogen (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (female) (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease (cell/mm^3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease (cell/mm^3)	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm^3)	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils (cell/mm^3)	650 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT; increase by factor	> 1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	> 1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Laboratory abnormality grading occurs only when the values fall beyond the normal ranges established by the local laboratory.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007). Note that the criteria for Grade 1 PT and PTT have been adjusted from the source table: instead of >= 1.0 x ULN, both criteria are > 1.0 x ULN. Grade 1 will not be used for hematology values due to the large overlap with normal values at the central laboratory.

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Signature Page for VV-CLIN-000784 v2.0

Approval	Brett Leav Clinical 20-May-2020 12:35:58 GMT+0000

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Signature Page for VV-CLIN-000784 v2.0

CLINICAL STUDY PROTOCOL

A PHASE 2a, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, DOSE-CONFIRMATION STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF MRNA-1273 SARS-COV-2 VACCINE IN ADULTS AGED 18 YEARS AND OLDER

IND NUMBER: 19745
PROTOCOL NUMBER: mRNA-1273-P201

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Amendment Number:	2
Date of Amendment 2	01 Jul 2020
Date of Amendment 1:	18 May 2020
Date of Original Protocol:	22 Apr 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice.

Signature Page

PROTOCOL TITLE:	A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
PROTOCOL NUMBER:	mRNA-1273-P201
AMENDMENT NUMBER:	2
AMENDMENT 2 DATE:	01 Jul 2020

See esignature and date signed on last page of document.

Tal Zaks, MD, PhD
Chief Medical Officer
ModernaTX, Inc.

Date

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Investigator	Date

Printed Name of Investigator

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	01 Jul 2020
Amendment 1	18 May 2020
Original Protocol	22 April 2020

Amendment 2, 01 Jul 2020: Current Amendment

Main Rationale for the Amendment:

The main purpose of this amendment is to change the statistical analysis plan by removing interim analyses and defining the Primary Study Analysis and End of Study Analysis. The summary of changes table provided here describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated the protocol version and date	Reflect the new version and date of the protocol
Synopsis, Section 3.1 Study Design, Section 3.5.2 Use of Electronic Diaries, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (including text, Table 7, and footnotes to Table 7)	Added eDiary questionnaires to the procedure for safety follow-up after the Day 57 visit, with completion of eDiary questionnaires alternating with safety telephone calls approximately every 2 weeks after the Day 57 visit.	Reduce the burden on study site personnel of completing safety follow-up by telephone.
Synopsis, Section 3.1 Study Design, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (footnote 12)	Added exposure to someone with known COVID-19 or SARS-CoV-2 infection and participant experience of COVID-19 symptoms to the list of events queried during scheduled safety telephone calls.	Improve surveillance for incidence of COVID-19 during the study.
Synopsis, Section 3.1 Study Design	End of Study definition was amended.	Minor clarification to define the End of Study

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7 Study Analyses, Section 4.7.1 Primary Study Analysis, Section 4.7.2 End of Study Analysis, Section 6.4 Clinical Study Reports	Added descriptions of the Primary Study Analysis and End of Study Analysis and respective clinical study reports, replacing descriptions of interim analyses and reports. The synopsis contains a new section.	Eliminate interim analyses in favor of a focus on the primary analysis
Synopsis, Section 4.6 Statistical Methods	State that all analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise.	Previous versions of the protocol had not included the overall analysis in statement of the standard scope of analysis.
Synopsis, Section 4.6.3 Immunogenicity Analyses	For the primary immunogenicity endpoint, geometric mean titer was changed to geometric mean.	Assays for bAb are under development. The reported values may or may not be titers, hence the protocol wording has been modified.
Section 3.5.1 Assessment for SARS CoV-2 Infection	Added instructions for asymptomatic patients who have a confirmed SARS-CoV-2 infection.	To clarify the steps for the investigator to follow when a participant is confirmed to have SARS-CoV-2 infection but is asymptomatic.
Section 3.5.8.8 Assessment of Severity	Decoupled life-threatening and Grade 4 in the severity assessment.	To adhere to CDISC guidance and align with case report form page.
Section 3.5.8.8 Assessment of Severity	Added clarification on when an AE is defined as serious.	To clarify when an AE is defined as serious.

Abbreviations: AE = adverse event; bAb = binding antibody; CDISC = Clinical Data Interchange Standards Consortium; eDiary = electronic diary.

IRB and Regulatory Authority Approval

A copy of this amended protocol will be sent to the institutional review board (IRB) and regulatory authority.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number: **mRNA-1273-P201**

Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Study Phase: 2

Study Sites: Approximately 10 study sites in the United States or its territories.

Objectives: Primary:

- To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart
- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific binding antibody (bAb)

Secondary:

- To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb)

Exploratory:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29)
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

Study Design and Methodology:

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age.

Two dose levels (50 µg and 100 µg), will be evaluated in this study, based in part on initial safety data from the Phase 1 Division of Microbiology and Infectious Diseases (DMID) study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo.

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment. Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data through Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled participant contacts approximately every 2 weeks after Day 57 to collect medically attended adverse events (MAAEs), AEs leading to withdrawal, SAEs, concomitant medications associated with these events, receipt of non-study vaccinations, exposure to someone with known COVID-19 or SARS-CoV-2 infection, and participant experience of COVID-19 symptoms. Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363, each participant will complete a questionnaire in an electronic diary (eDiary) that will be reviewed by study site personnel. Safety telephone calls will occur every 4 weeks from Day 85 through Day 165 and from Day 237 through Day 377. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The

participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment.

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml intramuscular (IM) injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment.

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned analyses.

The end of study (EOS) is defined as the release of the last testing result of samples collected at Visit 9 or the completion of the last participant’s last visit, whichever occurs later. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited adverse reactions (ARs) within a provided eDiary. Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at scheduled study site visits during the study, for safety and immunogenicity assessments or other medical concerns according to the investigator’s judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Study Population:	Participants (males and females 18 years of age or older at time of consent), will be included in the study if they are in good health according to the assessment of the investigator and can comply with study procedures. Negative pregnancy tests will be required at Screening and before vaccine administration for female participants of childbearing potential. The full lists of inclusion and exclusion criteria are provided in the body of the protocol.
Safety Assessments:	Safety assessments will include monitoring and recording of the following for each participant: • Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries. • Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs. • AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study. • MAAEs from Day 1 through Day 394 or withdrawal from the study. • SAEs from Day 1 through Day 394 or withdrawal from the study. • Results of safety laboratory tests. • Vital sign measurements. • Physical examination findings. • Assessments for SARS-CoV-2 infection from Day 1 through study completion.

Immunogenicity Assessments:

Immunogenicity assessments will include the following:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 spike protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Investigational Product, Dosage, and Route of Administration:

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available). mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 100 µg, or saline. Preferably, vaccine should be administered into the nondominant arm. The second dose of vaccine should be administered in the same arm as the first dose.

Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform vaccine accountability, dose preparation, and vaccine administration.

Sample Size:

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. A sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Statistical Methods:

General Considerations: All analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of

participants, mean, median, standard deviation, minimum, and maximum).

Safety: Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials is used in this study with modification for rash, solicited ARs, and vital signs.

Rash will be graded in the following manner:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering <50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized. A 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, treatment group and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the statistical analysis plan (SAP).

Demographic variables (eg, age, height, weight, and body mass index (BMI)) and baseline characteristics will be summarized by treatment group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

Immunogenicity: The analyses of immunogenicity will be based on the Per-Protocol (PP) Set. For each age cohort, if the number of participants in the Full Analysis Set (FAS) and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint, geometric mean (GM) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint, geometric mean titer (GMT) of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the limit of detection (LOD) or lower limit of quantification (LLOQ) will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to

	equal to or above LOD or LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers. Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb levels/titers may be performed.
Study Analyses	A primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. A limited number of Sponsor and clinical research organization personnel will be unblinded to perform the primary study analysis and prepare a final Clinical Study Report (CSR), including individual listings. The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study. The EOS analysis of all endpoints will be performed after all participants have completed Month 13 study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an EOS CSR, including individual listings.
Date of Protocol Amendment 2:	01 Jul 2020

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
bAb	binding antibody
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics and Evaluation Research
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CoV	coronavirus
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunoabsorbent assay
EOS	end of study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold-rise
GMP	Good Manufacturing Practice

Abbreviation	Definition
GM	geometric mean
GMT	geometric mean titer
HCP	healthcare practitioner
hDPP4	dipeptidyl peptidase 4
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LOD	limit of detection
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger RNA
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no adverse effect level
nAb	neutralizing antibody
PCR	polymerase chain reaction
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PIV3	parainfluenza virus type 3
PP	per-protocol
PT	prothrombin time
PTT	partial thromboplastin time
S	spike
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
SMC	Safety Monitoring Committee
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
USP	United States Pharmacopoeia
VRC	Vaccine Research Center
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are zoonotic, meaning they are transmitted between animals and people.

An outbreak of the CoV disease (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 200 other countries and territories, including the United States (WHO 2020). A CoV ribonucleic acid was quickly identified in some of these patients.

As of 20 Apr 2020, the World Health Organization (WHO) reported more than 2,314,621 confirmed cases and 157,847 deaths globally and have therefore made the assessment that COVID-19 can be characterized as a pandemic (WHO 2020). As of 20 Apr 2020, the US Centers for Disease Control and Prevention (CDC) reported 746,625 confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with 39,083 attributed and probable deaths (CDC 2020a). The CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease (CDC 2020b).

There is currently no vaccine against SARS-CoV-2. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapeutic currently exists. Therefore, there is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease.

ModernaTX, Inc. has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is 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. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). 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) into a prefusion conformation. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P expresses well and is in the prefusion conformation (Wrapp et al 2020).

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). Two dose levels will be chosen for evaluation in this Phase 2 study, based on the data from the Phase 1 DMID study (Section 3.1.1). The development of this vaccine is being accelerated as, if it is demonstrated safe and immunogenic, it may be used to address the current COVID-19 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273.

1.2 Nonclinical Studies in Development of mRNA-1273

Nonclinical studies in mice, at National Institute of Health's Vaccine Research Center (VRC), part of the NIAID, have demonstrated that CoV S proteins are immunogenic and that vaccines encoding S proteins, including DNA and mRNA delivery platforms, are protective in animals. The S proteins of closely related beta-CoVs stabilized by the 2P mutation, including HKU1, MERS, SARS, and WIV1, are potent immunogens in mice (Pallesen et al 2017).

The VRC and the Sponsor produced mRNA expressing the MERS S-2P protein sequence and compared to it to mRNA expressing wild-type S protein in dipeptidyl peptidase 4 (hDPP4) mice. The mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 µg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in hDPP4 mice and protected mice from MERS challenge.

Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and the Sponsor designed mRNA expressing a membrane-anchored SARS-CoV-2 S protein

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

In support of development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

To estimate the generalized tissue distribution and tissue half-life of mRNA-1273, the biodistribution of mRNA-1647, a novel mRNA-based CMV vaccine formulated in a mixture of the same 4 lipids as mRNA-1273, was evaluated. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1273 and mRNA-1647) are expected to distribute similarly. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen.

The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102-containing LNP matrix encapsulating mRNA constructs encoding for various antigens have been evaluated in multiple Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies in Sprague Dawley rats followed by a 2-week recovery period. The Sponsor considers that the toxicity associated with mRNA vaccines formulated in LNP formulations are driven primarily by the LNP composition and to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the similar and consistent toxicity profile observed in these GLP studies at intramuscular (IM) doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix, differing only by the encapsulated mRNA sequence(s). Thus, the aggregate toxicity results from these studies supports the development of mRNA-1273. All doses administered in these GLP-compliant repeat dose toxicity studies in rats were tolerated. Test article related in-life observations observed at ≥ 9 µg/dose included reversible or reversing erythema and edema at the injection site and transient increases in body temperature at 6 hours post dose returning to baseline 24 hours post dose. The lowest no adverse effect level (NOAEL) determined across the aggregate of the completed studies was 89 µg/dose.

In GLP-compliant studies, SM-102 was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in

SM-102-containing LNPs (mRNA-1706, which encodes the Zika virus pre-membrane and envelope polypeptide), induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

A detailed review of non-clinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.3 Clinical Studies With Lipid Nanoparticle mRNA Vaccines

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in the dose-ranging Phase 1 DMID study of healthy adults at least 18 years of age (Section 3.1.1).

As of March 2020, there have been 8 clinical studies initiated across the Sponsor's infectious disease vaccine platform with over 1,000 participants receiving at least one dose of an mRNA vaccine. mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV (NCT03382405), HMPV/PIV3 (NCT03392389), and Zika virus (NCT04064905). As of January 6, 2020, approximately 365 participants were dosed with either an SM-102-containing lipid vaccine or placebo (doses ranging from 10 to 300 µg) across 3 Phase 1 studies. Of the 365 participants dosed, 264 participants experienced at least 1 solicited adverse reaction (AR). The most common solicited events were pain (28% of total events reported), headache (15%), fatigue (15%), myalgia, (13%), arthralgia (9%), nausea (7%), chills (6%), fever (4%), erythema (2%), and swelling (2%). The majority of the events were of Grade 1 to 2 with approximately 9% being reported as Grade 3. The most common Grade 3 events were pain, myalgia, fatigue, headache, and chills. Grade 3 events were typically recorded on Day 1 or Day 2 following vaccination, with most occurring on Day 2 and resolving by Day 6. In the hMPV/PIV3 Phase 1 study, which is unblinded, unsolicited related adverse events (AEs) included mild to moderate chills, hot flush, diarrhea, pyrexia, temperature intolerance, white blood cell increased, headache, and rash erythematous, as well as severe injection site pain, prothrombin time prolonged and myalgia. All of the severe events occurred at the 300 µg × 2 dose level. In the blinded Phase 1 CMV study, unsolicited related AEs in more than 2 participants included chills (19 participants, 10.5%), fatigue (10 participants, 5.5%), lymphadenopathy, injection site pain, and pyrexia (9 participants each, 5.0%), arthralgia, (8 participants, 4.4%), myalgia, (7 participants, 3.9%), headache, (5 participants, 2.8%), diarrhea, (4 participants, 2.2%), and injection site bruising, (3 participants, 1.7%). Of these AEs, severe events were reported in

3 of 19 participants with chills, 5 of 10 participants with fatigue, 4 of 9 participants with pyrexia, 4 of the 8 participants with arthralgia, and 4 of the 7 participants with myalgia. There were no related serious AEs (SAEs) reported in the Phase 1 CMV, HMPV/PIV3, or Zika vaccine studies.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart.

2.1.2 Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific binding antibody (bAb).

2.2 Secondary Objective

The secondary objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

2.3 Exploratory Objectives

The exploratory objectives are the following:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29)
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age. The study schematic is presented in Figure 1 and the Schedule of Events is presented in Table 7.

Two dose levels, 50 µg and 100 µg, will be evaluated in this study, based in part on initial safety data from the Phase 1 DMID study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo (Figure 1).

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment (Figure 2). Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC; Section 6.1.1).

In addition to the SMC's review, prior to expansion in Cohort 2, there will be a pause for the review of the following:

- Safety data through Day 7 from the sentinel group of Cohort 2
- All available safety data from Cohort 1

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

Figure 1: Study Flow Schema

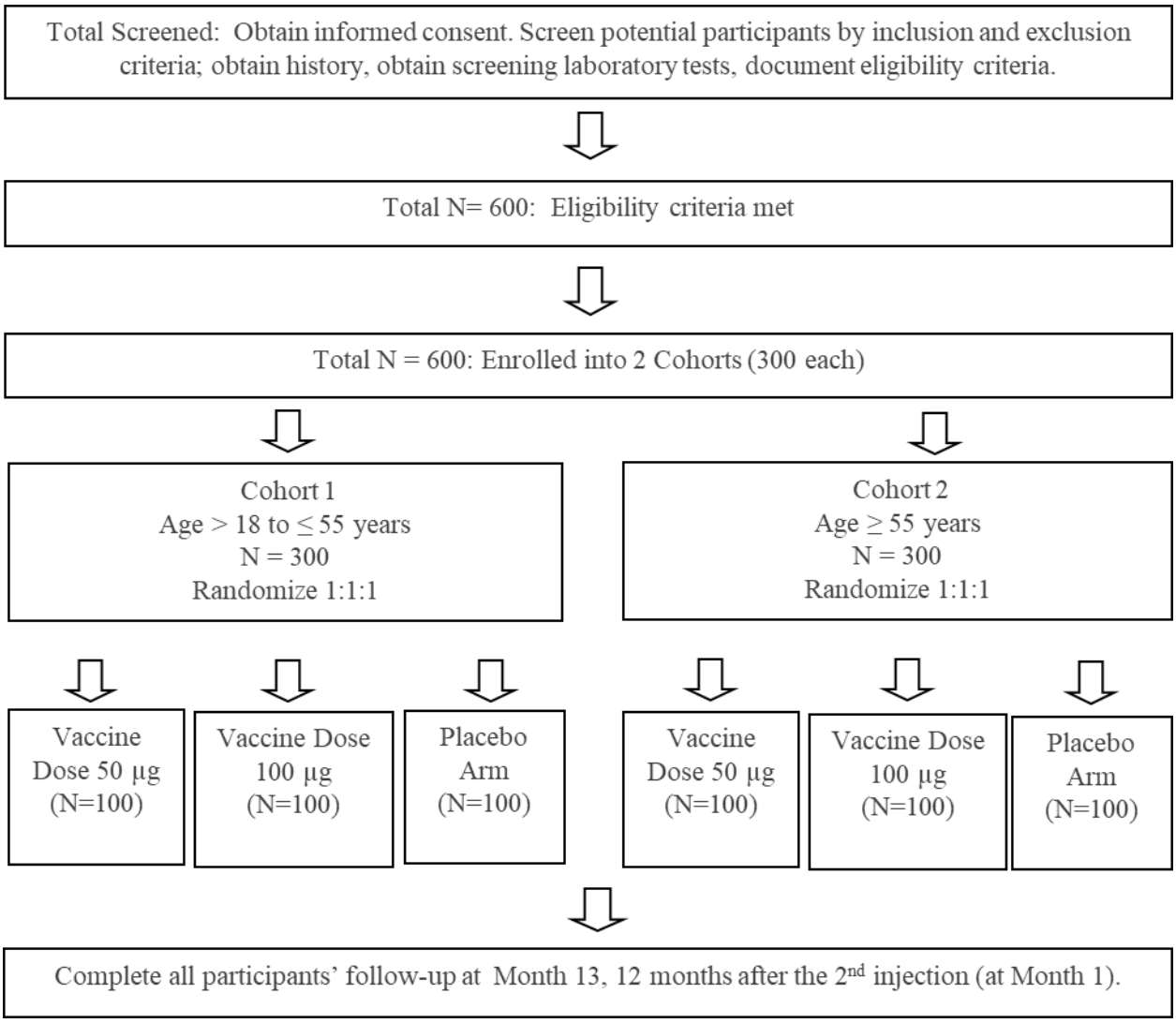
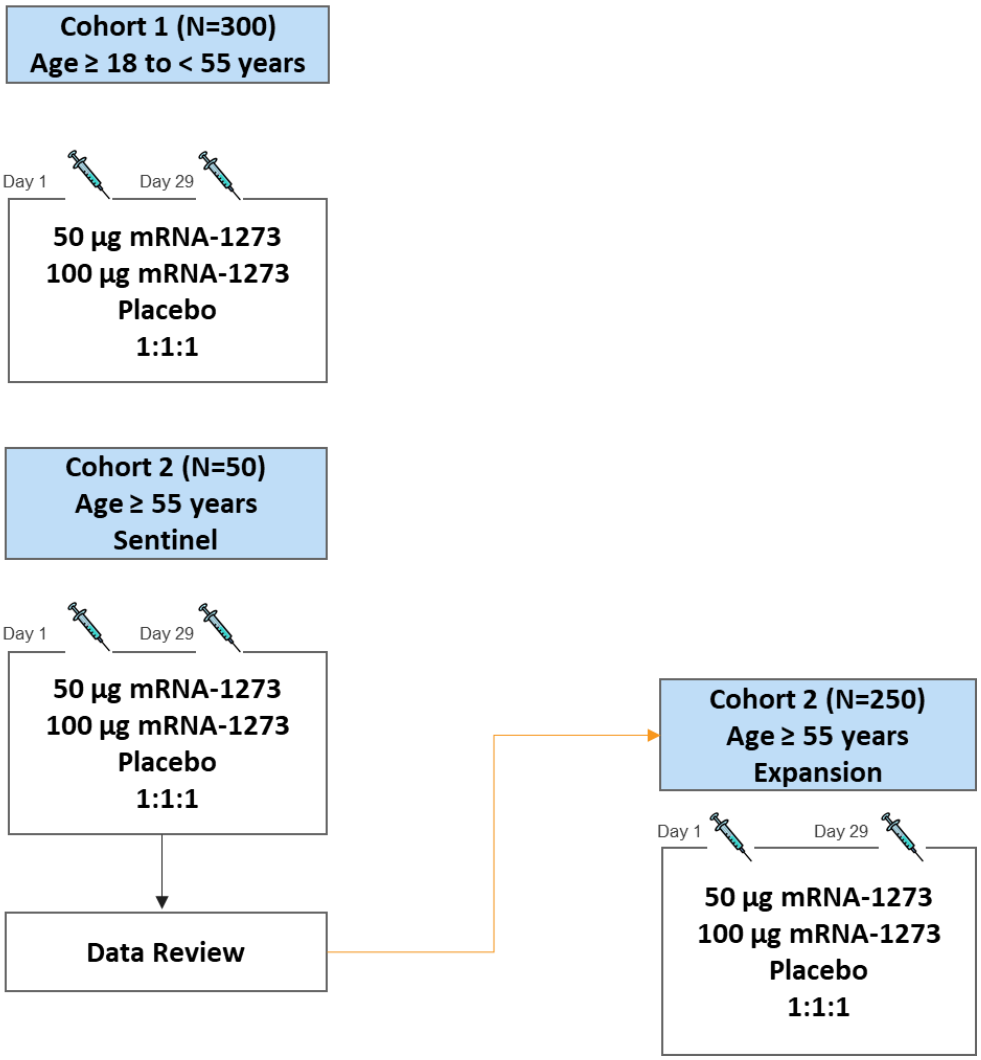


Figure 2: Sentinel and Expansion Cohort Schema



The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled participant contacts approximately every 2 weeks after Day 57 to collect medically attended adverse events (MAAEs), AEs leading to withdrawal, SAEs, concomitant medications associated with these events, receipt of non-study vaccinations, exposure to someone with known COVID-19 or SARS-CoV-2 infection, and participant experience of COVID-19 symptoms (Table 7). Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363, each participant will complete a questionnaire in an electronic diary (eDiary) that will be reviewed by study site personnel. Safety telephone calls will occur every 4 weeks from Day 85 through Day 165 and from Day 237 through Day 377. The study duration will be approximately 14 months for each participant: a screening period

of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment (Section 3.5.1).

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 ml IM injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment (Section 3.4.5).

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. Section 4.7 describes the planned study analyses.

The end of study (EOS) is defined as the release of the last testing result of samples collected at Visit 9 or the completion of the last participant’s last visit, whichever occurs later. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within a provided eDiary. Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at scheduled study visits during the study for safety and immunogenicity assessments or other medical concerns, according to the investigator’s judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Detailed information on all statistical analysis of data is presented in Section 4.6.2.

3.1.1 Rationale for Dose Selection

In this study, the 2 dose levels of mRNA-1273 tested in participants will be 50 µg, and 100 µg, based on assessment of available safety and immunogenicity data from the Phase 1 DMID study and Phase 1 studies of mRNA-1647 and mRNA-1443 (Section 1.1).

The Phase 1 DMID study, an open-label dose ranging study of mRNA-1273 in healthy adult male and non-pregnant female participants in 3 age groups: age 18 to 55 years, inclusive (45 participants); age 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants) is currently ongoing. Participants in each age cohort will be randomly assigned to 1 of 3 dose levels of mRNA-1273: 25 µg, 100 µg, and 250 µg. Each participant will receive an IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed for 12 months after the second injection.

As of 14 May 2020, 15 participants in each of the 3 dose levels of the 18 to 55-year age cohort had received at least 1 dose of mRNA-1273. Recruitment of participants in the 2 older-age cohorts is ongoing. There have been no SAEs and no triggering of study pause rules. A review of preliminary solicited local and systemic adverse reactions in participants in the 18 to 55-year age cohort after the second injection showed 3 participants in the 100 µg dose group who reported severe local adverse reactions (grade 3 erythema and induration) and 3 participants in the 250 µg dose group who reported severe systemic adverse reactions (fever, fatigue, feverishness, myalgia, and nausea). These adverse reactions resolved within 24 hours and were not assessed as serious.

The 50 µg and 100 µg doses proposed for this Phase 2a study fall within the doses being evaluated in the Phase 1 DMID study.

3.1.2 Rationale for Study Design

The 2 age cohorts in this Phase 2a study, ≥ 18 to < 55 years old and ≥ 55 years old, were established to better understand the relationships among dose, tolerability, and immunogenicity in different age groups, one being healthy older adults. The older cohort in this Phase 2a study corresponds to the 2 older age cohorts in the Phase 1 DMID study.

Because there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 3.4.5).

The Phase 1 DMID study is small (105 participants at 3 dose levels) and does not incorporate a placebo. Having a sample size of 600 participants in this Phase 2a study and including a placebo will help to improve understanding of AEs.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and post-injection blood samples for antibody analysis through 12 months after the last dose of investigational product. In addition, participants will have nasopharyngeal swab samples collected at Day 1 and Day 29 before the injections, and at Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasopharyngeal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and polymerase chain reaction (PCR). Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Since it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the nasopharyngeal swab samples collected before study injection may help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

3.2 Selection of Study Population

Healthy male or female participants will be enrolled at study sites in the US or its territories.

3.2.1 Inclusion Criteria

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 18 years of age or older at the time of consent (Screening Visit, Day 0).
2. Understands and agrees to comply with the study procedures and provides written informed consent.
3. According to the assessment of the investigator, is in good general health and can comply with study procedures.
4. Body mass index (BMI) of 18 kg/m^2 to 30 kg/m^2 (inclusive) at the Screening Visit (Day 0).
5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as

amenorrhea for ≥ 12 consecutive months prior to Screening (Day 0) without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

    - Has a negative pregnancy test at Screening (Day 0) and on the day of the first injection (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).
    - Is not currently breastfeeding.

    Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:

    - Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
    - Intrauterine device
    - Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
    - Sterilization of a female participant's monogamous male partner prior to entry into the study

    Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception and refrain from sperm donation from the time of the first injection and through 3 months after the last injection.

    Adequate contraception for male participants is defined as:

    - Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
    - Use of barrier methods and spermicide
    - History of surgical sterilization

Male participants with partners who have become pregnant prior to Screening are eligible to participate in the study.

3.2.2 Exclusion Criteria

Participants meeting any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known exposure to someone with SARS-CoV-2 infection or COVID-19.
2. Travel outside of the US in the 28 days prior to the Screening Visit (Day 0).
3. Pregnant or breastfeeding.
4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
5. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
6. Current treatment with investigational agents for prophylaxis against COVID-19.
7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
8. Is a healthcare worker or a member of an emergency response team.
9. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).
10. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
11. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of Screening.

12. Known history of hypertension, or systolic blood pressure > 150 mm Hg in participants in Cohort 1 (≥ 18 to < 55 years old) or systolic blood pressure > 160 mm Hg in participants in Cohort 2 (≥ 55 years old) at the Screening Visit (Day 0).

13. Known history of hypotension or systolic blood pressure < 85 mm Hg at the Screening Visit (Day 0).

14. Diabetes mellitus

15. Diagnosis of chronic pulmonary disease (eg, chronic obstructive pulmonary disease, asthma)

16. Chronic cardiovascular disease

17. Resides in a nursing home

18. Grade 1 or higher toxicity on clinical safety laboratory testing at the Screening Visit (Day 0)

19. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.

20. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to the Screening Visit (Day 0) (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the Screening Visit (Day 0).

21. Anticipating the need for immunosuppressive treatment at any time during participation in the study.

22. Positive serology for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies identified at the Screening Visit (Day 0).

23. History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine.

24. Bleeding disorder considered a contraindication to IM injection or phlebotomy.

25. Diagnosis of malignancy within previous 10 years (excluding non-melanoma skin cancer).

26. Has received or plans to receive a licensed vaccine ≤ 28 days prior to the first injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after any study injection. Licensed influenza vaccines may be received more than 14 days before or after any study injection.

27. Receipt of systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (Day 0) or plans for receipt during the study.

28. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.

29. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.

30. Is an immediate family member or household member of study personnel

3.2.3 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In the event an eligible participant was not enrolled as a result of a cohort being full and the participant having surpassed their 28-day screening period, the investigator may rescreen the participant for enrollment by assigning the participant a new identification number and repeating all screening procedures (Section 3.3.4).

3.2.4 Participant Restrictions During the Study

3.2.4.1 General and Dietary

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

3.3 Withdrawal of Participants From the Study or Study Dosing

3.3.1 Participant Withdrawal From the Study

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS electronic case report form (eCRF).

Potential reasons for withdrawing a participant from the study include the following:

- SAE
- AE (non-SAE)
- Protocol violation (specify)
- Consent withdrawal (document reason)
- Lost to follow-up
- Other (specify)

3.3.2 Handling Withdrawal From the Study

When a participant withdraws or is withdrawn from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These participants will be requested to complete the EOS assessments scheduled for Day 394 (Month 13).

3.3.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's study source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (eg, study site visit, telephone call).

3.3.4 Replacements

Any participant who is withdrawn, who is significantly outside the allowed injection window, or who is lost to follow-up from the study may be replaced at the Sponsor's discretion.

3.3.5 Participant Withdrawal From Study Dosing

Every reasonable attempt will be made to follow up with participants for safety throughout the entire study period, even if further injection is withheld or the participant misses one or more visits. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all scheduled visits and assessments. (Table 7).

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to investigational product (Section 3.5.8.9) and is of Grade 3 (severe) or greater severity (Appendix 3)
- Experiences an AE or SAE that, in the judgment of the investigator, requires study vaccine withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly attributed to study vaccine
- Experiences generalized urticaria related to the study vaccine

The reason(s) for withdrawal from further injection will be recorded.

3.4 Study Dosing Groups

3.4.1 Method of Assigning Participants to Dosing Groups

There are 2 age cohorts in this study: participants ≥ 18 to < 55 years old in Cohort 1 and participants ≥ 55 years old in Cohort 2. Within each age cohort, approximately 300 participants will be randomly assigned in 1:1:1 ratio to receive mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules. Only the unblinded pharmacy personnel (Section 3.4.5) will have controlled access to which arm the participant is randomly assigned.

Dose group assignment in each cohort and stratification within each cohort is summarized in Table 1.

Table 1: Dose Group Assignment

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Total			**600**

3.4.2 Investigational Product Administration

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 100 µg, or saline placebo. Preferably, vaccine should be administered into the nondominant arm. The second dose of investigational product should be administered in the same arm as the first dose.

The investigational product will be prepared for injection as a single 0.5 mL dose for each participant based on the cohort and randomization assignment, as detailed in the mRNA-1273-P201 Pharmacy Manual. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform investigational product accountability, dose preparation, and investigational product administration. The investigator will designate an unblinded clinical team member to provide oversight to the administration of investigational

product so that it proceeds according to the procedures stipulated in this study protocol and the mRNA-1273-P201 Pharmacy Manual. Study-specific training will be provided.

At each visit when investigational product is administered, participants will be monitored for a minimum of 60 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (Schedule of Events, Table 7).

Eligibility for subsequent investigational product injection is determined by following the criteria outlined in Section 3.4.2.2.

The study site will be appropriately staffed, staff will be trained on emergency resuscitation, and will have stocked rescue medications (such as epinephrine, steroids, antihistamines, and intravenous fluids) should any severe reaction (eg, anaphylaxis or urticaria) occur that requires immediate intervention.

The rules for pausing dosing are provided in Section 3.4.2.1.

3.4.2.1 Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause (Table 2).

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than injection	≥ 3
3	ICU admissions in Cohort 1 due to SARS-CoV-2 infection	≥ 3
4	ICU admissions in Cohort 2 due to SARS-CoV-2 infection	≥ 6

Abbreviations: AE = adverse event; ICU = intensive care unit; SAE = serious adverse event.

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold event is adjudicated by the Safety Monitoring Committee (SMC; Section 6.1.1).

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event potentially meeting any pause rule criterion. The Sponsor will inform the SMC (Section 6.1.1) of any event potentially meeting

any pause rule criterion. The SMC will review all available study data to adjudicate such events in accordance with the SMC charter.

The Sponsor will also actively monitor the following and provide them to the SMC for review as they become available:

- Instances of study halting rules triggered in the Phase 1 DMID study (NCT04283461)
- Histopathological data suggestive of vaccine-enhanced disease in ongoing nonclinical studies

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

3.4.2.2 Contraindications to Subsequent Injection

Prior to receiving a second injection, participants will be reassessed to ensure that they continue to meet eligibility requirements as outlined below.

The following events in a participant constitute absolute contraindications to any further administration of the investigational product to that participant. If any of these events occur during the study, the participant must not receive additional doses of vaccine but will be encouraged to continue study participation for safety through 12 months following last injection (Section 3.3.5).

- Diagnosed COVID-19. If COVID-19 is suspected, further administration of investigational product must be withheld until COVID-19 test results are available.
- Anaphylaxis or systemic hypersensitivity reaction following the administration of vaccine.
- Any SAE judged by investigator or Sponsor to be related to study vaccine.
- Pregnancy
- Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the participant if he/she continues to participate in the study.

The following events constitute contraindications to administration of study vaccine at certain points in time, and if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the Schedule of

Events (Table 7), or the participant may be withdrawn from dosing at the discretion of the investigator (Section 3.3.5):

- Acute moderate or severe infection with or without fever at the time of injection
- Fever, defined as body temperature ≥ 38.0°C (100.4°F) at the time of injection

Participants with a minor illness without fever, as assessed by the investigator, can be administered investigational product. Participants with a fever of 38.0°C (100.4°F) or higher will be contacted within the time window acceptable for participation and reevaluated for eligibility.

3.4.3 Identity of Investigational Product

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 Injection is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

3.4.4 Management of Investigational Product

3.4.4.1 Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the investigational product
- Confirming the appropriate labeling of mRNA-1273 Injection, so that it complies with the legal requirements of the US

The investigator is responsible for acknowledging the receipt of the investigational product by a designated staff member at the site, including the following:

- Confirming that the investigational product was received in good condition

- Confirmation that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming whether the Sponsor has authorized the investigational product for use
- Ensuring the appropriate dose level of mRNA-1273 Injection is properly prepared using aseptic technique

Further description of the investigational product and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the investigational product are described in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.2 Packaging and Labeling

The Sponsor will provide the investigator and study site with adequate quantities of mRNA-1273. The sterile vaccine product is packaged in a 2-mL glass vial with a 0.6-mL fill volume. mRNA-1273 vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future participant identification purposes.

mRNA-1273 Injection will be packaged and labeled in accordance with the standard operating procedures (SOPs) of the Sponsor or of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, guidelines for Quality System Regulations, and applicable regulations.

The Sponsor or Sponsor's designee will supply the 0.9% sodium chloride injection for use as both a placebo and a diluent to mRNA-1273. The 0.9% sodium chloride bears a commercial label and does not contain study-specific identification.

3.4.4.3 Storage

mRNA-1273 vaccine must be stored at -60°C to -90°C (-76°F to -130°F) in a secure area with limited access (unblinded pharmacy staff only) and protected from moisture and light until it is prepared for administration (Section 3.4.2). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There must be an available back-up freezer. The freezers must be connected to a back-up generator. In addition, vaccine accountability study staff (eg, the unblinded pharmacy personnel) are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1273 vaccine that was not

temperature controlled during shipment or during storage to the unblinded site monitor. Such mRNA-1273 will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

The 0.9% sodium chloride injection (USP) should be stored at 20ºC to 25ºC (68ºF to 77ºF) in a restricted access area.

3.4.4.4 Investigational Product Accountability

It is the investigator's responsibility that the unblinded pharmacy personnel maintain accurate records in an investigational product accountability log of receipt of all investigational product, inventory at the site, dispensing of mRNA-1273 and placebo, study injections, and return to the Sponsor or alternative disposition of used/unused products.

An unblinded site monitor will review the inventory and accountability log during site visits and at the completion of the study. Additional details are found in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.5 Handling and Disposal

An unblinded site monitor will reconcile the investigational product during the conduct and at the end of the study for compliance. Once fully reconciled at the site at the end of the study, the investigational product can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Investigational product may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be completed and sent to the Sponsor or designee.

3.4.5 Blinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of investigational product to either the participant or the blinded study site

personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the investigational product accountability monitors. They will have responsibilities to ensure that sites are following all proper investigational product accountability, preparation, and administration procedures.
- A primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. A limited number of Sponsor and clinical research organization (CRO) personnel will be unblinded to perform the primary study analysis and prepare a final Clinical Study Report (CSR), including individual listings. The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the investigational product in a secure location that is not accessible or visible to other study staff. A blinding label over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different than placebo. Only delegated unblinded site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

3.4.6 Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for the primary study analyses as outlined in Section 4.7.

3.4.7 Dosing Compliance

All doses of investigational product will be administered at the study site under direct observation of unblinded pharmacy personnel and appropriately recorded (date and time) in the eCRF. Unblinded pharmacy personnel will confirm that the participant has received the entire dose of vaccine. If a participant does not receive vaccine or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Participants who miss the second injection due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all safety and immunogenicity assessments required through the scheduled EOS.

The study site is responsible for ensuring participants comply with the study windows allowed. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Table 7). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (eg, clinical laboratory testing, eDiary review for reactogenicity, immunologic testing, as applicable).

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

3.4.8.2 Concomitant Medications and Therapies

At each study visit, study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the first study injection.
- All concomitant medications and non-study vaccinations taken through 28 days after each injection. Antipyretics and analgesics taken prophylactically (ie, taken in the

absence of any symptoms in anticipation of an injection reaction) will be recorded as such.

- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each study injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the postinjection study visits or via other participant interactions (eg, telephone calls).

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis (analysis sets are described in Section 4.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- A licensed vaccine administered during the period from 28 days before through 28 days after each study injection, except for any licensed influenza vaccine that was administered more than 14 days before or after any study injection.
- Immunoglobulins and/or any blood products administered during the study period.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

3.5 Study Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 5.3). Participants will undergo study procedures at the time points specified in the Schedule of Events (Table 7).

A participant also can be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

3.5.1 Assessment for SARS-CoV-2 Infection

Study participants will have nasopharyngeal swab samples collected for SARS-CoV-2 testing at time points specified in the Schedule of Events (Table 7).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect a nasopharyngeal swab sample to ascertain the presence of SARS-CoV-2 via PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020c)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case. All findings will be recorded in the eCRF.

If scheduled, a study site illness visit may include assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasopharyngeal swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. Blood samples will be collected for potential future immunologic assessment of SARS-CoV-2 infection.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant's primary care physician of the diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a blood sample will be collected for potential future immunologic assessment of SARS-CoV-2 infection.

If participants are confirmed to have SARS-CoV-2 infection, and are asymptomatic, the investigator will notify the participant's primary care physician and local health authority, as per local regulations. If the participant had known exposure to COVID-19 (e.g., exposure to someone with confirmed COVID-19 disease), it will be captured in the COVID-19 exposure form, and the participant will be discontinued from future study treatment only, and will continue to follow all other study assessments as outlined in the protocol. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

Any confirmed SARS-CoV-2 infection occurring in participants, except asymptomatic infection diagnosed at Day 1, will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

3.5.2 Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 3.5.8.4) on Day 1.

At each injection visit, participants will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants will record data into the eDiary starting approximately 1 hour after injection under supervision of the study site staff to ensure successful entry of assessments. The site staff will perform any retraining as necessary. Study participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 3.5.8.4, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in the eDiary until resolution. Adverse reactions recorded in diaries beyond Day 7 should be reviewed by study site staff either during the next scheduled telephone call or at the next study site visit (Table 7).
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on a day of injection or for the 6 subsequent days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. The participant will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

Any new safety information reported during safety telephone calls or at site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF.

Study site staff will review eDiary data with participants at the Day 8 and Day 36 visits.

The eDiary will also be used after the Day 57 visit to capture the occurrence of AEs, MAAEs, SAEs, or AEs leading to study withdrawal. Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363 (Table 7), the eDiary will prompt the participant to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since in contact with the study site.

- Known exposure to someone with known COVID-19 or SARS-CoV-2 infection.
- Any experience of symptoms of COVID-19.
- Any MAAEs or SAEs

If an eDiary record results in identification of relevant safety events according to the study period or of symptoms of COVID-19, a follow-up safety call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 3.5.3) as the procedure for safety follow-up approximately every 2 weeks after the Day 57 visit (Table 7).

3.5.3 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls are scheduled to occur every 4 weeks from Day 85 through Day 165 and from Day 237 through Day 377 (Table 7). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AEs leading to study withdrawal, concomitant medications associated with those events, and any non-study vaccinations (Section 3.5.8.6). In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone contact.

3.5.4 Safety Laboratory Assessments

Laboratory tests will be performed by the central laboratory, unless otherwise specified. Screening safety laboratory tests will include complete blood count with differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (ALP), blood urea nitrogen/creatinine, prothrombin time (PT), and partial thromboplastin time (PTT). These safety laboratory tests are to be repeated at Day 29 and Day 57 only for Cohort 2 (≥ 55 years of age).

Additional tests include the following:

- A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine administration (Day 1 and Day 29). At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

- If not documented in a female participant's medical records, an FSH test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.
- Hepatitis B surface antigen, hepatitis C virus antibody, and HIV virus (types 1 and 2) antibody at the Screening Visit (Day 0).

3.5.5 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, blood samples for immunogenicity assessment will be collected before administration of vaccine. The following analytes will be measured:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 S protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow further testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

The ELISA and measurement of nAb titers will be performed in a laboratory designated by the Sponsor.

For participants who provide consent (Section 5.3), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoV.

3.5.6 Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant are 66 mL for 1 day, 182 mL for 28 days, and 398 mL for the complete study (Table 3).

Table 3: Maximum Blood Sampling Volumes per Participant by Visit

Study Visit Day	D0	D1	D15	D29	D43	D57	D209	D394	Total
Safety laboratory tests	16 mL			16[1] mL		16[1] mL			48 mL
Immunogenicity assays		50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	350 mL
Total	**16 mL**	**50 mL**	**50 mL**	**66 mL**	**50 mL**	**66 mL**	**50 mL**	**50 mL**	**398 mL**

Abbreviation: D = Day.

[1] Only participants in Cohort 2 will have blood sampled for safety laboratory tests at Day 29 and Day 57.

3.5.7 Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 3.5.8.4) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 3.5.2).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs (Section 3.5.8.4).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study.
- MAAEs from Day 1 through Day 394 or withdrawal from the study.
- SAEs from Day 1 through Day 394 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 3.5.1).

3.5.8 Safety Definitions

3.5.8.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to vaccine or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test result (hematology, clinical chemistry, or PT/PTT) or other safety assessment (eg, electrocardiogram, radiological scan, vital sign measurement), including one that worsens from baseline and is considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after mRNA-1273 vaccine administration even though it may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the investigational product caused the AE (Section 3.5.8.4). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the investigational product and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.2 Medically Attended Adverse Event

An MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner (HCP). This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, SARS-CoV-2 infection [Section 3.5.1]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be fully reported on the MAAE page of the eCRF.

3.5.8.3 Serious Adverse Event

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study vaccine.
- Is life-threatening
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission.
  Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Congenital anomaly or birth defect
- Medically important event
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered

serious. 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.

3.5.8.4 Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after vaccine administration. The eDiary (Section 3.5.2) will solicit participant reporting of ARs using a structured checklist. Participants will record such occurrences in an eDiary on the day of each vaccine administration and for the 6 days after a day of injection.

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, body temperature (potentially fever), and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following occurs within 7 days after study injection:

- Severe (Grade 3) local or systemic ARs (Table 4),
- Presence of any rash, or
- Presence of any underarm swelling or tenderness on the same side as the injection arm

The purpose of the contact is to assess the nature of AR, including assessment of potential pause rules. In the event that rash or underarm swelling or tenderness on the same side as the injection arm is reported, the participant will be asked to return to the study site for assessment by the investigator.

The investigator will review, confirm, and Grade reactogenicity according to the grading scales presented in Table 4, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution. Adverse reactions

recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit. All solicited ARs (local and systemic) will be considered causally related to injection.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous	Requires emergency room visit or hospitalization for hypotensive shock

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
		24 hours		hydration	
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F
Rash*	No rash	Localized rash, without associated symptoms	Maculopapular rash, covering < 50% body surface area	Generalized urticarial, covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis, eg, Stevens-Johnson syndrome or erythema multiforme

* Grading for rash and Grade 4 events per Investigator assessment (with exception of fever)

In case of any rash episode observed within 7 days after study injection, the participants will be instructed to contact the study site within 24 hours. During participant evaluation, the investigator should categorize the rash as one of the following:

- Rash no longer present and history not consistent with urticaria.
- Rash no longer present but history is consistent with urticaria.
- Rash present but clinical findings are not consistent with urticaria. Alternative diagnosis should be specified as an AE.
- Rash present and clinical findings consistent with urticaria.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded as an AE in the participant's Adverse Event eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days post-injection
- Solicited local or systemic AR that leads to participant withdrawal from vaccine

- Solicited local or systemic AR that otherwise meets the definition of an SAE
- Solicited AR with a toxicity score of Grade 3 or greater

An unsolicited AE is any AE reported by the participant that is either not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but it starts outside the protocol-defined post injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.5 Pregnancy

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 3.5.8.7).

3.5.8.6 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor. Unsolicited AEs will be captured from Day 1 through 28 days after each dose up to Day 57 (±5 days), Both MAAEs and SAEs will be captured from Day 1 throughout entire study duration (Day 394 for all participants), as specified in the Schedule of Events (Table 7). Any AEs occurring before receipt of the vaccine will be analyzed separately from TEAEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically-related changes in their well-being according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, data from clinical laboratory test results, physical examination findings, or other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

3.5.8.7 Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to vaccine or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes cohort, type of event, time of onset, investigator-specified assessment of severity and relationship to vaccine, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.8.3) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the vaccine caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341
- SAE Fax line (USA and Canada): +1-866-599-1342

3.5.8.8 Assessment of Severity

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 3.5.8.3), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities and will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or Grade 4 using the following criteria:

- Mild (Grade 1): These events do not interfere with the participant's daily activities.
- Moderate (Grade 2): These events cause some interference with the participant's daily activities but do not require medical intervention.
- Severe (Grade 3): These events prevent the participant's daily activity and require medical intervention.
- Grade 4: These events require an emergency room visit or hospitalization.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic solicited ARs (Table 4), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for clinical and laboratory abnormalities are presented in Appendix 2 (Table 8 and Table 9, respectively) and will be graded if outside of the reference range for the laboratory utilized.

3.5.8.9 Assessment of Causality

The investigator's assessment of an AE's relationship to vaccine is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the vaccine caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: There is not a reasonable possibility of a relationship to the investigational product. Participant did not receive the investigational product OR temporal sequence of the AE onset relative to administration of the investigational product is not reasonable OR the AE is more likely explained by another cause than the investigational product.
- Related: There is a reasonable possibility of a relationship to the investigational product. There is evidence of exposure to the investigational product. The temporal sequence of

the AE onset relative to the administration of the investigational product is reasonable. The AE is more likely explained by the investigational product than by another cause.

3.5.8.10 Follow-up of Adverse Events

All AEs, SAEs, and MAAEs must be reported in detail on the appropriate page of the eCRF and followed until the event is resolved or stable or judged by the investigator to be not clinically significant.

3.5.9 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, vital sign measurements will be collected once before vaccine administration and at least 1 hour after vaccine administration (before participants are discharged from the study site).

Febrile participants at Day 1 and Day 29 visits (fever is defined as a body temperature $\geq$ 38.0°C/100.4°F) may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities (Table 8) of Grade 3 or greater, the abnormal value and Grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.5.10 Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Schedule of Events (Table 7). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as a MAAE.

Symptom-directed physical examinations may be performed at other timepoints at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

Body mass index will be calculated at the Screening Visit (Day 0) only.

4 STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or Clinical Study Report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

4.1 Blinding and Responsibility for Analyses

Blinding during the study will be managed as described in Section 3.4.5. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Planned data presentation for unblinded SMC review are described in Section 6.1.

A limited number of Sponsor and CRO personnel will be unblinded to perform the primary analysis and prepare a final Clinical Study Report (CSR) after all participants have completed Day 57 study procedures (Section 3.4.5). The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study.

Planned study analyses and data presentation for unblinded SMC review are described in Section 4.7 and Section 6.1, respectively. At each analysis, pre-identified Sponsor members will be unblinded to review treatment level results as defined in the study Data Blinding Plan. Unblinded data presentation or analysis for SMC review will be handled by the CRO unblinded team of statisticians and programmers, who are not involved in study design. A strict firewall between the CRO blinded and unblinded teams will be maintained during study conduct. Sponsor personnel who have access to review unblinded results will be documented. Sponsor and CRO personnel involved in the ongoing review and oversight of safety and immunogenicity will remain blinded, as will study investigators and personnel at the study sites. The results of the primary analysis will not be shared with the investigators before completion of the study.

4.2 Hypothesis Testing

There is no hypothesis testing in this study.

4.3 Analysis Endpoints

4.3.1 Primary Endpoints

4.3.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.
- Unsolicited AEs through 28 days after each injection.
- MAAEs through the entire study period.
- SAEs throughout the entire study period.
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only).
- Vital sign measurements and physical examination findings.

4.3.1.2 Primary Immunogenicity Endpoint

- Level of SARS-CoV-2-specific binding antibody (bAb) measured by ELISA on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13).

4.3.2 Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

- Titer of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13).
- Seroconversion on Day 29 (M1), Day 43, Day 57 (M2), Day 209 (M7), and Day 394 (M13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) to equal to or above LOD or LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers.

4.3.3 Exploratory Endpoints

The exploratory endpoints are the following:

- Serum titers of S protein-specific binding Ig assessed by class and subclass and nAb in serum.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum
- Clinical severity and immune response of participants infected by SARS-CoV-2
- Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect non-vaccine antigens of SARS-CoV-2.

4.4 Analysis Populations

4.4.1 Randomized Set

The Randomized Set consists of all participants who are randomly assigned in the study, regardless of the participants' treatment status in the study.

4.4.2 Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomly assigned and received any study injection, and contribute any solicited AR data; ie, have at least one post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment group corresponding to the study injection they actually received.

4.4.3 Safety Set

The Safety Set consists of all randomly assigned participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the treatment group corresponding to the study injection they actually received for the analysis of safety data using the Safety Set.

4.4.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who a) receive any study injection, b) have baseline (Day 1) data available for those analyses that require baseline

data, and c) have at least one post-injection assessment for the analysis endpoint. Participants will be included in the treatment group to which they were randomly assigned.

4.4.5 Per-Protocol Set

The Per-Protocol (PP) Set consists of all FAS participants who meet all of the following criteria:

- Complied with the injection schedule
- Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective
- Did not have SARS-CoV-2 infection
- Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the treatment group to which they were randomly assigned.

4.5 Sample Size Determination

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. Table 5 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. The 2-sided 95% CI is estimated (0.01%, 1.4%) at sample size of 400 with 1 participant reporting an AE. Furthermore, a sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Table 5: 95% Confidence Interval for One Participant with AE and the Lowest Detectable Incidence Rate at 95% Probability in Selected Sample Size

Sample Size Receiving mRNA-1273	Rate and 95% CI (%) at One Participant with AE			Lowest Detectible Rate (%) with ≥95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75

Abbreviations: AE = adverse event; CI = confidence interval.

4.6 Statistical Methods

There are 2 age cohorts in this study: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). All analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise.

4.6.1 Summary of Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by treatment group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

4.6.2 Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA for adverse reaction terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash, solicited ARs, and vital signs (Table 4).

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area

- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher SARs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided and Table 6 summarizes analysis strategy for safety parameters.

Table 6: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by system organ class and preferred term coded by MedDRA.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, treatment group, and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the SAP.

4.6.3 Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set. For each age cohort, if the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint (Section 4.3.1.2), geometric mean (GM) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint (Section 4.3.2), geometric mean titer (GMT) of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the LOD or LLOQ will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb levels/titers may be performed.

4.6.4 Exploratory Analyses

Exploratory analyses may include the following:

- Descriptive summaries of the relative proportions of S protein-specific serum Igs and nAb during the study. Subclass analysis of specific IgG may be performed.

- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study

- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study

4.7 Study Analyses

No interim analysis is planned for this study.

4.7.1 Primary Study Analysis

A primary analysis of safety and immunogenicity data will be performed after all participants have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. Results of this analysis will be presented in a final CSR, including individual listings.

4.7.2 End of Study Analysis

The final analysis of all endpoints will be performed after all participants have completed Month 13 study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an EOS CSR, including individual listings.

Additional information can be found in the SAP.

4.8 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonized tripartite guideline E6(R2): GCP and current SOPs. The eCRFs will be utilized and accessed through iMedidata® via the internet. This EDC system is validated and compliant with US Title 21 of CFR Part 11. Each person involved with the study will have an individual identification code and password that allow for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Due to safety review requirements, study sites must follow the data entry and availability instructions provided by Sponsor in the study readiness trainings. As a quality measure, timeliness of data entry and data query resolution will be followed closely. Other issues of data

quality that may hinder safety review or pose a concern with patient safety will be brought to the attention of the Sponsor or CRO, with appropriate awareness to the SMC if needed.

5 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study and may be pursuant to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

5.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

5.2 Institutional Review

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

5.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to

study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study, be allowed to read the approved ICF, and be given answers to any questions. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF. Separate counseling and consent may be provided for HIV testing as applicable per local laws or regulations.

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoV.

The investigator or designee will provide a copy of the ICF to the participant. The original form shall be maintained in the participant's medical records at the site.

5.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to Sponsor according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

5.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor, the CRO, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, the CRO, nor the study site is financially responsible for further treatment of the disease under study.

5.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

5.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

5.8 Data Collection

5.8.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic case report forms are accessed through iMedidata® via the internet. This EDC system is validated and compliant with 21 CFR 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

5.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

5.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

5.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

5.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the vaccine. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

5.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

6 STUDY MANAGEMENT

6.1 Monitoring

Ongoing safety monitoring will be performed in a blinded manner by the CRO's medical monitor, the Sponsor's medical monitor, and the individual site investigators throughout the study.

6.1.1 Safety Monitoring Committee

Safety oversight will be under the direction of an SMC composed of external independent consultants with relevant expertise. Members of the SMC will be independent from the study conduct and free of conflict of interest. The SMC will meet on a regular basis to assess safety throughout the study conduct. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SMC. Details regarding the SMC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The SMC will convene on an ad hoc basis if any of the pause rules, described in Section 3.4.2.1, are met. The SMC will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

6.1.2 Monitoring of the Study

The study monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The monitor will be blinded to dose assignment. A separate unblinded study monitor will be responsible for vaccine accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

6.2 Management of Protocol Amendments and Deviations

6.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

6.2.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Major protocol deviations are defined as exclusionary from the analysis according to the protocol objectives and endpoints. Protocol deviations will be documented by the study monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of such deviations.

6.3 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last participant completes the last visit (includes the EOS Visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the CSR.

6.4 Clinical Study Reports

Whether the study is completed or prematurely terminated, the Sponsor will ensure that CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory

requirement(s). The Sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSRs. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

The final CSR will be prepared based on the primary analysis of safety and immunogenicity data, which is based on cleaned and locked data collected from all participants from Day 0 through the Day 57 visit (Section 4.7.1).

The EOS CSR will be based on an analysis of all data collected from Day 0 through Day 394. The Sponsor will provide the investigator(s) with the final approved EOS CSR.

7 APPENDICES

7.1 Appendix 1: Schedule of Events

The Schedule of Events is presented in Table 7.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening, Day 1, and Day 29 visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Screening, Day 1, and Day 29 visits), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls (Table 7).

Table 7: Schedule of Events

Visit Number	0	1	2	3	4	5	6	7			8			9
Type of Visit	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0			M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	-3/ +7	+3	±3	-3/ +7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	14	28/0	7	14	28	-	-	180	-	-	365
ICF, demographics, concomitant medications, medical history	X													
Confirm participant meets inclusion and exclusion criteria	X	X												
Blood for safety laboratory tests[4]	X				X[4]			X[4]						
Blood for viral serology (hepatitis B, hepatitis C, HIV [1 and 2])	X													
Physical examination including vital signs[5]	X	X	X	X	X	X	X	X			X			X
Pregnancy testing[6]	X	X			X									
Randomization		X												
Study injection (including 60-minute post-dosing observation period)		X			X									
Blood for vaccine immunogenicity[7]		X		X	X		X	X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[8]		X			X			X						
eDiary activation for recording solicited adverse reactions (7 days)[9]		X			X									
Review of eDiary			X			X								

Visit Number	0	1	2	3	4	5	6	7			8			9
Type of Visit	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0			M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	-3/ +7	+3	±3	-3/ +7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	14	28/0	7	14	28	-	-	180	-	-	365
Follow-up safety calls[10]									X			X		
Recording of Unsolicited AEs		X	X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[12]		X	X	X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[12]		X	X	X	X	X	X	X	X		X	X		X
Recording of concomitant medications and non-study vaccinations[13]		X	X	X	X	X	X	X						
Study completion														X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ; C = clinic visit; CBC = complete blood count; D = day; HIV = human immunodeficiency virus; ICF = informed consent form; M = month; MAAE = medically attended AE; SC = safety (telephone) call; SFU = Safety Follow Up; PCR = PT = prothrombin time; PTT = partial thromboplastin time; Q = every; SAE = serious adverse event.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (FDA March 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. The Day 0 visit may be performed over multiple visits if within the 28-day screening window.

2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for adverse events and concomitant medications (e.g. as defined in scheduled safety telephone calls). Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site as a result of

the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).

3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 -3/+7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. When the extended window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.
4. Safety follow-up via eDiary questionnaire will be performed every 4 weeks starting at Day 71 to Day 183 and again starting at Day 223 to Day 363.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks starting at Day 85 to Day 197 and again starting at Day 237 to Day 377.
6. Safety laboratory tests include the following: CBC with differential, AST, ALT, total and direct bilirubin, alkaline phosphates, BUN/creatinine, PT/PTT. Safety laboratory tests are to be repeated at Day 29 and Day 57 **only for Cohort 2 (≥ 55 years old).**
7. Physical examination: a full physical examination, including height and weight, will be performed at Day 1, Day 29 and Day 57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as a MAAE. Vital signs are to be collected pre and post-dosing on days of injection (Day 1 and Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator a pregnancy test either via blood or point-of-care urine test can be performed. Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the investigator.
9. Sample must be collected prior to dosing on days of injection (Day 1 and Day 29).
10. The nasopharyngeal swab sample will be used to ascertain the presence of SARS-CoV-2 via PCR.
11. Diary entries will be recorded by the participant at approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit.
12. Trained site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any non-study vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
13. All concomitant medications and non-study vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).

7.2 Appendix 2: Toxicity Grading Scale Tables

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 8 and Table 9, respectively. Note that for laboratory abnormalities, grading only occurs if the values are outside of the normal values established by the clinical laboratory. For study-specific laboratory normal ranges and associated toxicity grades, refer to the laboratory manual and provided toxicity grade communications.

Table 8: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Abbreviation: ER = emergency room.

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)**	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER = emergency room.

Note that fever is classified under systemic reactions for grading purposes.

* Participant should be at rest for all vital sign measurements.

** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise (unusual tiredness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized myalgia (muscle ache or pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized arthralgia (joint ache or pain)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviations: ER = emergency room; IV = intravenous.

* Oral temperature; no recent hot or cold beverages or smoking.

Sources: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

Table 9: Tables for Laboratory Abnormalities

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)**
Blood urea nitrogen (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (female) (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease (cell/mm^3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease (cell/mm^3)	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm^3)	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils (cell/mm^3)	650 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT; increase by factor	> 1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	> 1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Laboratory abnormality grading occurs only when the values fall beyond the normal ranges established by the local laboratory.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007). Note that the criteria for Grade 1 PT and PTT have been adjusted from the source table: instead of >= 1.0 x ULN, both criteria are > 1.0 x ULN. Grade 1 will not be used for hematology values due to the large overlap with normal values at the central laboratory.

7.3 Appendix 3: Protocol Amendment History

The document history table for this protocol and the Protocol Amendment Summary of Changes Table for the current Amendment 2 is located directly before the Table of Contents.

A description of Amendment 1 is presented in this appendix.

Amendment 1, 18 May 2020:

Main Rationale for the Amendment:

The main purpose of this amendment was to incorporate the following modifications requested by the FDA Center for Biologics Evaluation and Research:

- Enhance monitoring of participants who are confirmed to have SARS-CoV-2 infection.
- Include a convalescent visit for participants with confirmed SARS-CoV-2 infection.
- Explore the mRNA-1273 vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection.
- Updated the Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to extend the follow-up to a full 12-month period after the second injection on Day 29 (Month 1).
- Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.

The summary of changes table provided here describes the major changes made in Amendment 1, including the sections modified and the corresponding rationale. Minor editorial or formatting changes are not included in this summary table.

Summary of Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated protocol version and date	Revised version and date of protocol
Title page, Signature page, and header	Updated the protocol title	Revised to reflect the current purpose of the study
Synopsis and Section 2.3 Exploratory Objectives	Added an exploratory objective to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection	Request from the Health Authority
Synopsis, Section 2.3 Exploratory Objectives, Section 4.3.3 Exploratory Endpoints, Section 4.6.4 Exploratory Analyses	Revised wording for the exploratory objective/endpoint regarding spike protein-specific serum immunoglobulin class and subclass and neutralizing antibody in serum	Editorial change
Synopsis, Section 3.1 Study Design, Study Flow Schema (Figure 1), Sentinel and Expansion Cohort Schema (Figure 2), Section 3.1.1 Rationale for Dose Selection, 3.4.1 Method of Assigning Participants to Dosing Groups. Dose Group Assignment (Table 1), 3.4.2 Investigational Product Administration, 4.5 Sample Size Determination	Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg	Decreased based on the preliminary findings of the Phase 1 DMID study
Synopsis and Section 3.1 Study Design	Deleted collection of nasopharyngeal swab samples at the Screening Visit (Day 0)	Editorial update for consistency with Schedule of Events (Table 7)
Synopsis and Section 3.1 Study Design	Deleted the number of visits at which participants will have blood samples collected	Editorial update to avoid confusion as blood samples will be collected at different visits for safety and vaccine immunogenicity assessments
Synopsis; Section 3.1 Study Design, Section 3.5.6 Blood Sampling Volumes (Table 3), Section 3.5.7 Safety Assessments, Section 3.5.8.6 Eliciting and Documenting Adverse Events, Section 4.3.1.2 Primary Immunogenicity Endpoint, Section 4.3.2 Secondary Endpoints, Section 4.7 Interim Analyses, Section 6.4 Clinical Study Reports, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to allow for 6-month and 12-month intervals, respectively, after the second injection on Day 29 (Month 1)	Request from the Health Authority

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 3.1 Study Design, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated the biweekly safety telephone calls from Day 211 through Day 351 to Day 223 through Day 377	Consequent to the change made to the Day 209 Visit (Request from the Health Authority)
Synopsis, Section 3.1 Study Design, Section 3.1.2 Rationale for Study Design, Section 3.5.1 Assessment for SARS-CoV-2 Infection, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated nasal swab to nasopharyngeal swab	Clarified the type of swab to be performed
Section 3.1.1 Rationale for Dose Selection	Updated enrollment and preliminary safety data from the ongoing Phase 1 DMID study	Updated based on the preliminary findings of the Phase 1 DMID study
Section 3.2.1 Inclusion Criteria	Updated inclusion criterion #7 to exclude sperm donations through 3 months after the last injection	Update to align with the informed consent form on refraining male participants from sperm donation through 3 months after the last injection based on IRB feedback to the ICF
Section 3.3.2 Handling Withdrawal From the Study	Updated the scheduled end-of study assessments at Day 394 (Month 13) to allow for a 12-month interval after the second vaccination on Day 29 (Month 1)	Request from the Health Authority
Section 3.4.5 Blinding	Updated the method to maintain the blind of the dosing assignment from opaque sleeve to blinding label	Operational change in cases for which opaque sleeves are not used
Section 3.5.1 Assessment for SARS-CoV-2 Infection	• Added more intense monitoring of participants who are confirmed to have SARS-CoV-2 infection (ie, notification of the participant's primary care physician by the investigator and recording of confirmed SARS-CoV-2 infection as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome) • Added a convalescent visit with blood collection after diagnosis of SARS-CoV-2 infection	Request from the Health Authority
Section 3.5.1 Assessment for SARS-CoV-2 Infection and Section 3.5.8.2 Medically Attended Adverse Event	Deleted "or COVID-19"	Editorial update for internal consistency
Section 4.3.3 Exploratory Endpoints	Included a new exploratory endpoint to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection	Request from the Health Authority

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Deleted that Day 0 and Day 1 visits may be combined the same day	Editorial update of template text, which did not apply to this protocol
	Corrected sequential footnote numbering in the schedule of events (Table 7)	Editorial update
	Included a header row titled "Days Since Most Recent Vaccination"	Update to clarify that the visits are relative to the most recent injection

Abbreviation: ICF = informed consent form; IRB = Institutional Review Board; MAAE = medically attended adverse event

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Signature Page for VV-CLIN-000833 v1.0

Approval	Brett Leav Clinical 06-Jul-2020 21:15:32 GMT+0000

Approval	Charbel Haber Regulatory 06-Jul-2020 21:18:46 GMT+0000

Approval	Tal Zaks Clinical 07-Jul-2020 15:04:54 GMT+0000

Approval	Conor Knightly Clinical 07-Jul-2020 15:58:27 GMT+0000

Signature Page for VV-CLIN-000833 v1.0

CLINICAL STUDY PROTOCOL

A PHASE 2a, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, DOSE-CONFIRMATION STUDY TO EVALUATE THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF MRNA-1273 SARS-COV-2 VACCINE IN ADULTS AGED 18 YEARS AND OLDER

IND NUMBER: 19745
PROTOCOL NUMBER: mRNA-1273-P201

Sponsor:	ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139
Sponsor Contact:	Tal Zaks, MD, PhD, Chief Medical Officer ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-209-5906 e-mail: (b) (6) @modernatx.com

Amendment Number:	3
Date of Amendment 3:	02 Sep 2020
Date of Amendment 2:	01 Jul 2020
Date of Amendment 1:	18 May 2020
Date of Original Protocol:	22 Apr 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice.

Signature Page

PROTOCOL TITLE:	A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
PROTOCOL NUMBER:	mRNA-1273-P201
AMENDMENT NUMBER:	3
AMENDMENT 3 DATE:	02 Sep 2020

See eSignature and date signed on last page of document.

Tal Zaks, MD, PhD
Chief Medical Officer
ModernaTX, Inc.

Date

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Investigator	Date

Printed Name of Investigator

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	**02 Sep 2020**
Amendment 2	01 Jul 2020
Amendment 1	18 May 2020
Original Protocol	22 Apr 2020

Amendment 3, 02 Sep 2020: Current Amendment

Main Rationale for the Amendment:

The main purpose of this amendment is to clarify that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit. The summary of changes table describes the major changes made in Amendment 3 relative to Amendment 2, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, Synopsis, and header	Updated the protocol version and date	Reflect the new version and date of the protocol.
Synopsis, Section 3.1 Study Design	Deleted repeated text about Safety Monitoring Committee review before expansion in Cohort 2.	Editorial removal of redundant text.
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7.1 Primary Study Analysis	Added information about potential participant populations to be included in the primary analysis of safety and immunogenicity after completion of Day 57 procedures.	Clarification that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit.
Synopsis, Section 4.6.2 Safety Analyses	Revisions to clarify that separate summaries of Grade 3 or higher solicited ARs are not planned.	Clarification of planned safety analyses.
Section 3.5.2 Use of Electronic Diaries, Section 7.1 Appendix 1: Schedule of Events (Table 7)	Added clarification about site follow-up of relevant safety events from eDiary entries (includes revisions to Footnote 12).	Clarification that follow-up by telephone of relevant safety events from eDiary entries is not the same as scheduled safety follow-up telephone calls.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The acceptable window around the Day 29 visit has been clarified as + 7 days with no negative visit window.	Correction to reflect the minimum interval between vaccine administrations of 28 days.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The footnotes and footnote numbering have been updated to accommodate the footnotes that were added with Amendment 2.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 4 has been revised to clarify that study days for safety follow-up are relative to Day 1 vaccine administration.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 5 has been revised to explain how to handle potential visit window overlap related to Visit 8.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 10 has been revised to clarify the timing of nasopharyngeal swab samples on vaccination days.	Editorial clarification.

Abbreviations: AE = adverse event; AR = adverse reaction; MAAE = medically attended adverse event; SAE = serious adverse event.

IRB and Regulatory Authority Approval

A copy of this amended protocol will be sent to the institutional review board (IRB) and regulatory authority.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	**mRNA-1273-P201**
Title:	A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older
Study Phase:	2
Study Sites:	Approximately 10 study sites in the United States or its territories.
Objectives:	Primary: • To evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart • To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific binding antibody (bAb) Secondary: • To evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb) Exploratory: • To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum • To describe the ratio or profile of specific bAb relative to nAb in serum • To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29) • To characterize the clinical profile and immune response of participants infected by SARS-CoV-2 • To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

Study Design and Methodology:

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age.

Two dose levels (50 µg and 100 µg) will be evaluated in this study, based in part on initial safety data from the Phase 1 Division of Microbiology and Infectious Diseases (DMID) study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo.

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment. Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC).

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled participant contacts approximately every 2 weeks after Day 57 to collect medically attended adverse events (MAAEs), adverse events (AEs) leading to withdrawal, SAEs, concomitant medications associated with these events, receipt of non-study vaccinations, exposure to someone with known COVID-19 or SARS-CoV-2 infection, and participant experience of COVID-19 symptoms. Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363, each participant will complete a questionnaire in an electronic diary (eDiary) that will be reviewed by study site personnel. Safety telephone calls will occur every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that

suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment.

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 mL intramuscular (IM) injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment.

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. There are 2 planned analyses.

The end of study (EOS) is defined as the release of the last testing result of samples collected at Visit 9 or the completion of the last participant's last visit, whichever occurs later. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited adverse reactions (ARs) within a provided eDiary. Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at scheduled study site visits during the study for safety and immunogenicity assessments or other medical concerns according to the investigator's judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Study Population:

Participants (males and females 18 years of age or older at time of consent) will be included in the study if they are in good health according to the assessment of the investigator and can comply with study procedures. Negative pregnancy tests will be required at Screening and before vaccine administration for female participants of childbearing potential. The full lists of inclusion and exclusion criteria are provided in the body of the protocol.

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and

6 subsequent days); solicited ARs will be recorded daily using eDiaries.

- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days); unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study.
- MAAEs from Day 1 through Day 394 or withdrawal from the study.
- SAEs from Day 1 through Day 394 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.

Immunogenicity Assessments:

Immunogenicity assessments will include the following:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 spike protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Investigational Product, Dosage, and Route of Administration:

The mRNA-1273 vaccine is a lipid nanoparticle (LNP) dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available). mRNA-1273 is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 100 µg, or saline placebo. Preferably, vaccine should be administered

into the nondominant arm. The second dose of vaccine should be administered in the same arm as the first dose.

Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform vaccine accountability, dose preparation, and vaccine administration.

Sample Size:

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. A sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Statistical Methods:

General Considerations: All analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

Safety: Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) for Adverse Reaction Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials is used in this study with modification for rash, solicited ARs, and vital signs.

Rash will be graded in the following manner:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area

- Grade 4 = generalized exfoliative, ulcerative, or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized. A 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, treatment group, and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the statistical analysis plan (SAP).

Demographic variables (eg, age, height, weight, and body mass index (BMI)) and baseline characteristics will be summarized by treatment group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variables, and number and percentage for categorical variables).

Immunogenicity: The analyses of immunogenicity will be based on the Per-Protocol (PP) Set. For each age cohort, if the number of participants in the Full Analysis Set (FAS) and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint, geometric mean (GM) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding

95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint, geometric mean titer (GMT) of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the limit of detection (LOD) or lower limit of quantification (LLOQ) will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb levels/titers may be performed.

Study Analyses

A primary analysis of safety and immunogenicity data will be performed after participants have completed Day 57 study procedures. This primary analysis may be performed when all participants in Cohort 1 and the Cohort 2 sentinel group have completed Day 57 study procedures and/or when all participants in Cohort 1 and Cohort 2 have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. A limited number of Sponsor and clinical research organization personnel will be unblinded to perform the primary study analysis and prepare a final Clinical Study Report (CSR), including individual listings. The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study.

The EOS analysis of all endpoints will be performed after all participants have completed Month 13 study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an EOS CSR, including individual listings.

Date of Protocol Amendment 3: 02 Sep 2020

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
bAb	binding antibody
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics and Evaluation Research
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CoV	coronavirus
CRO	contract research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunoabsorbent assay
EOS	end of study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	geometric mean
GMFR	geometric mean fold-rise

Abbreviation	Definition
GMP	Good Manufacturing Practice
GMT	geometric mean titer
HCP	healthcare practitioner
hDPP4	dipeptidyl peptidase 4
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LOD	limit of detection
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger RNA
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no adverse effect level
PCR	polymerase chain reaction
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PIV3	parainfluenza virus type 3
PP	per-protocol
PT	prothrombin time
PTT	partial thromboplastin time
S	spike
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy)hexyl) amino) octanoate
SMC	Safety Monitoring Committee
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
USP	United States Pharmacopeia
VRC	Vaccine Research Center
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are zoonotic, meaning they are transmitted between animals and people.

An outbreak of the CoV disease (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 200 other countries and territories, including the United States (WHO 2020). A CoV ribonucleic acid was quickly identified in some of these patients.

As of 20 Apr 2020, the World Health Organization (WHO) reported more than 2,314,621 confirmed cases and 157,847 deaths globally and have therefore made the assessment that COVID-19 can be characterized as a pandemic (WHO 2020). As of 20 Apr 2020, the US Centers for Disease Control and Prevention (CDC) reported 746,625 confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with 39,083 attributed and probable deaths (CDC 2020a). The CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease (CDC 2020b).

There is currently no vaccine against SARS-CoV-2. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapeutic currently exists. Therefore, there is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease.

ModernaTX, Inc., has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is 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. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). 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) into a prefusion conformation. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P expresses well and is in the prefusion conformation (Wrapp et al 2020).

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). Two dose levels will be chosen for evaluation in this Phase 2 study, based on the data from the Phase 1 DMID study (Section 3.1.1). The development of this vaccine is being accelerated as, if it is demonstrated safe and immunogenic, it may be used to address the current COVID-19 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273.

1.2 Nonclinical Studies in Development of mRNA-1273

Nonclinical studies in mice, at National Institutes of Health's Vaccine Research Center (VRC), part of the NIAID, have demonstrated that CoV S proteins are immunogenic and that vaccines encoding S proteins, including DNA and mRNA delivery platforms, are protective in animals. The S proteins of closely related beta-CoVs stabilized by the 2P mutation, including HKU1, MERS, SARS, and WIV1, are potent immunogens in mice (Pallesen et al 2017).

The VRC and the Sponsor produced mRNA expressing the MERS S-2P protein sequence and compared to it to mRNA expressing wild-type S protein in dipeptidyl peptidase 4 (hDPP4) mice. The mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 µg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in hDPP4 mice and were protected from MERS challenge.

Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and the Sponsor designed mRNA expressing a membrane-anchored SARS-CoV-2 S protein stabilized with

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

In support of development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

To estimate the generalized tissue distribution and tissue half-life of mRNA-1273, the biodistribution of mRNA-1647, a novel mRNA-based CMV vaccine formulated in a mixture of the same 4 lipids as mRNA-1273, was evaluated. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1273 and mRNA-1647) are expected to distribute similarly. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen.

The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102-containing LNP matrix encapsulating mRNA constructs encoding for various antigens have been evaluated in multiple Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies in Sprague Dawley rats followed by a 2-week recovery period. The Sponsor considers that the toxicity associated with mRNA vaccines formulated in LNP formulations is driven primarily by the LNP composition and to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the similar and consistent toxicity profile observed in these GLP studies at intramuscular (IM) doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix, differing only by the encapsulated mRNA sequence(s). Thus, the aggregate toxicity results from these studies supports the development of mRNA-1273. All doses administered in these GLP-compliant repeat dose toxicity studies in rats were tolerated. Test article related in-life observations observed at ≥ 9 µg/dose included reversible or reversing erythema and edema at the injection site and transient increases in body temperature at 6 hours post dose returning to baseline 24 hours postdose. The lowest no adverse effect level (NOAEL) determined across the aggregate of the completed studies was 89 µg/dose.

In GLP-compliant studies, SM-102 was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in SM-102-containing LNPs (mRNA-1706, which encodes the Zika virus pre-membrane and envelope polypeptide), induced statistically

significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.3 Clinical Studies With Lipid Nanoparticle mRNA Vaccines

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in the dose-ranging Phase 1 DMID study of healthy adults at least 18 years of age (Section 3.1.1).

As of March 2020, there have been 8 clinical studies initiated across the Sponsor's infectious disease vaccine platform with over 1,000 participants receiving at least one dose of an mRNA vaccine. mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated in 3 indications: prophylactic protection against CMV (NCT03382405), hMPV/PIV3 (NCT03392389), and Zika virus (NCT04064905). As of January 6, 2020, approximately 365 participants were dosed with either an SM-102-containing lipid vaccine or placebo (doses ranging from 10 to 300 µg) across 3 Phase 1 studies. Of the 365 participants dosed, 264 participants experienced at least 1 solicited adverse reaction (AR). The most common solicited events were pain (28% of total events reported), headache (15%), fatigue (15%), myalgia (13%), arthralgia (9%), nausea (7%), chills (6%), fever (4%), erythema (2%), and swelling (2%). The majority of the events were of Grade 1 to 2 with approximately 9% being reported as Grade 3. The most common Grade 3 events were pain, myalgia, fatigue, headache, and chills. Grade 3 events were typically recorded on Day 1 or Day 2 following vaccination, with most occurring on Day 2 and resolving by Day 6. In the hMPV/PIV3 Phase 1 study, which is unblinded, unsolicited related adverse events (AEs) included mild to moderate chills, hot flush, diarrhea, pyrexia, temperature intolerance, white blood cell increased, headache, and rash erythematous, as well as severe injection site pain, prothrombin time prolonged, and myalgia. All of the severe events occurred at the 300 µg × 2 dose level. In the blinded Phase 1 CMV study, unsolicited related AEs in more than 2 participants included chills (19 participants, 10.5%), fatigue (10 participants, 5.5%), lymphadenopathy, injection site pain, and pyrexia (9 participants each, 5.0%), arthralgia (8 participants, 4.4%), myalgia (7 participants, 3.9%), headache (5 participants, 2.8%), diarrhea (4 participants, 2.2%), and injection site bruising (3 participants, 1.7%). Of these AEs, severe events were reported in 3 of 19 participants with chills, 5 of 10 participants with fatigue, 4 of 9 participants with pyrexia, 4 of 8 participants with arthralgia, and 4 of 7 participants with myalgia.

There were no related serious AEs (SAEs) reported in the Phase 1 CMV, hMPV/PIV3, or Zika vaccine studies.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart.

2.1.2 Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the level of specific binding antibody (bAb).

2.2 Secondary Objective

The secondary objective is to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered in 2 doses 28 days apart, as assessed by the titer of neutralizing antibody (nAb).

2.3 Exploratory Objectives

The exploratory objectives are the following:

- To profile S protein-specific serum immunoglobulin (Ig) class and subclass and nAb in serum
- To describe the ratio or profile of specific bAb relative to nAb in serum
- To describe initial immunogenicity responses following the first dose (Day 1) and prior to the second dose (Day 29)
- To characterize the clinical profile and immune response of participants infected by SARS-CoV-2
- To evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study will be randomized, observer-blind, and placebo-controlled, with adult participants at least 18 years of age. The study schematic is presented in Figure 1 and the Schedule of Events is presented in Table 7.

Two dose levels, 50 µg and 100 µg, will be evaluated in this study, based in part on initial safety data from the Phase 1 DMID study of mRNA-1273. The study will include 2 age cohorts: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). Approximately 600 participants will receive either mRNA-1273 vaccine or saline placebo control according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants will receive mRNA-1273 50 µg, 100 participants will receive mRNA-1273 100 µg, and 100 participants will receive saline placebo (Figure 1).

The study will be initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment (Figure 2). Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 will be reviewed by the Safety Monitoring Committee (SMC; Section 6.1.1).

If no safety concerns are found, expansion enrollment (N=250) of Cohort 2 will proceed.

Figure 1: Study Flow Schema

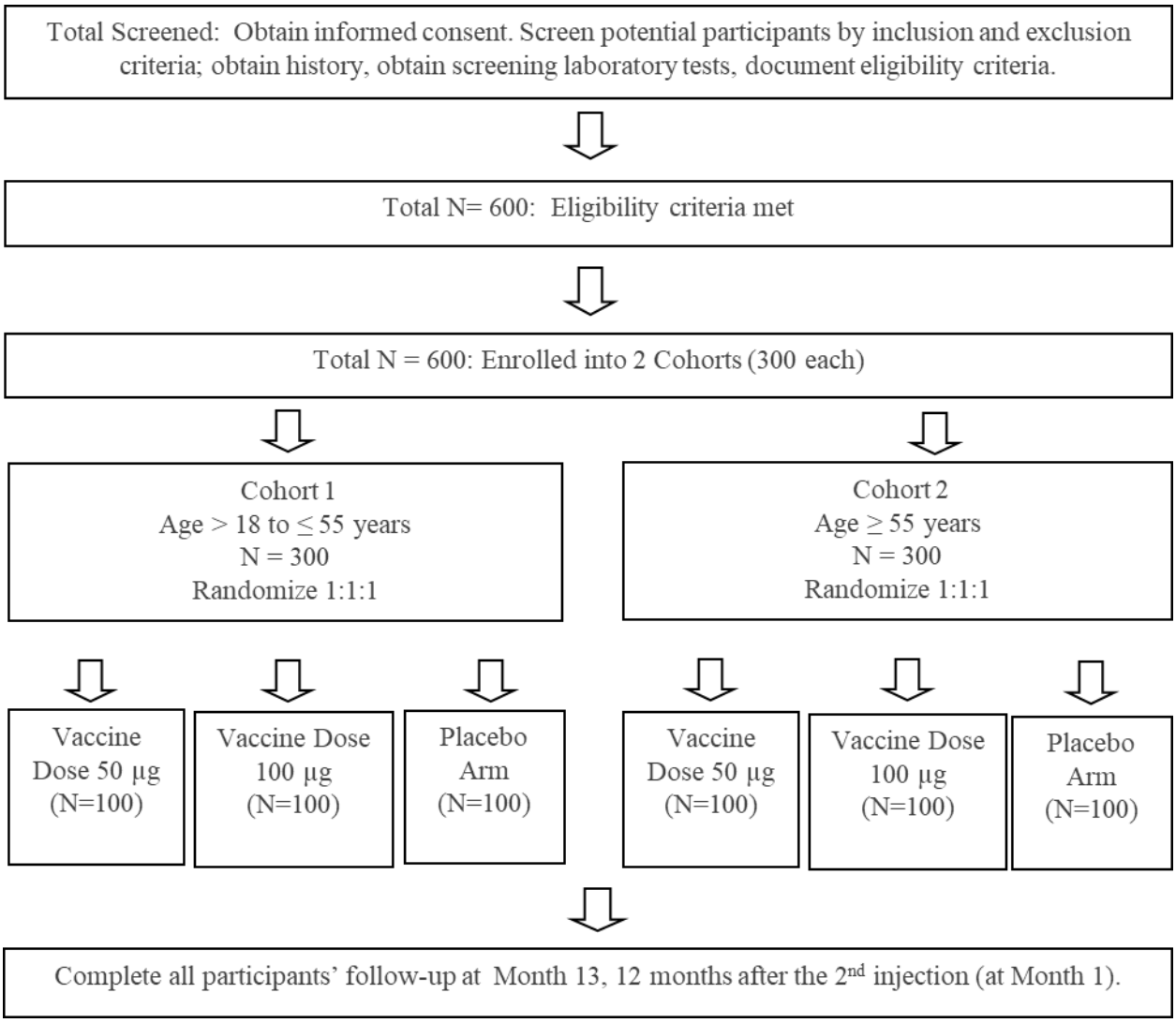
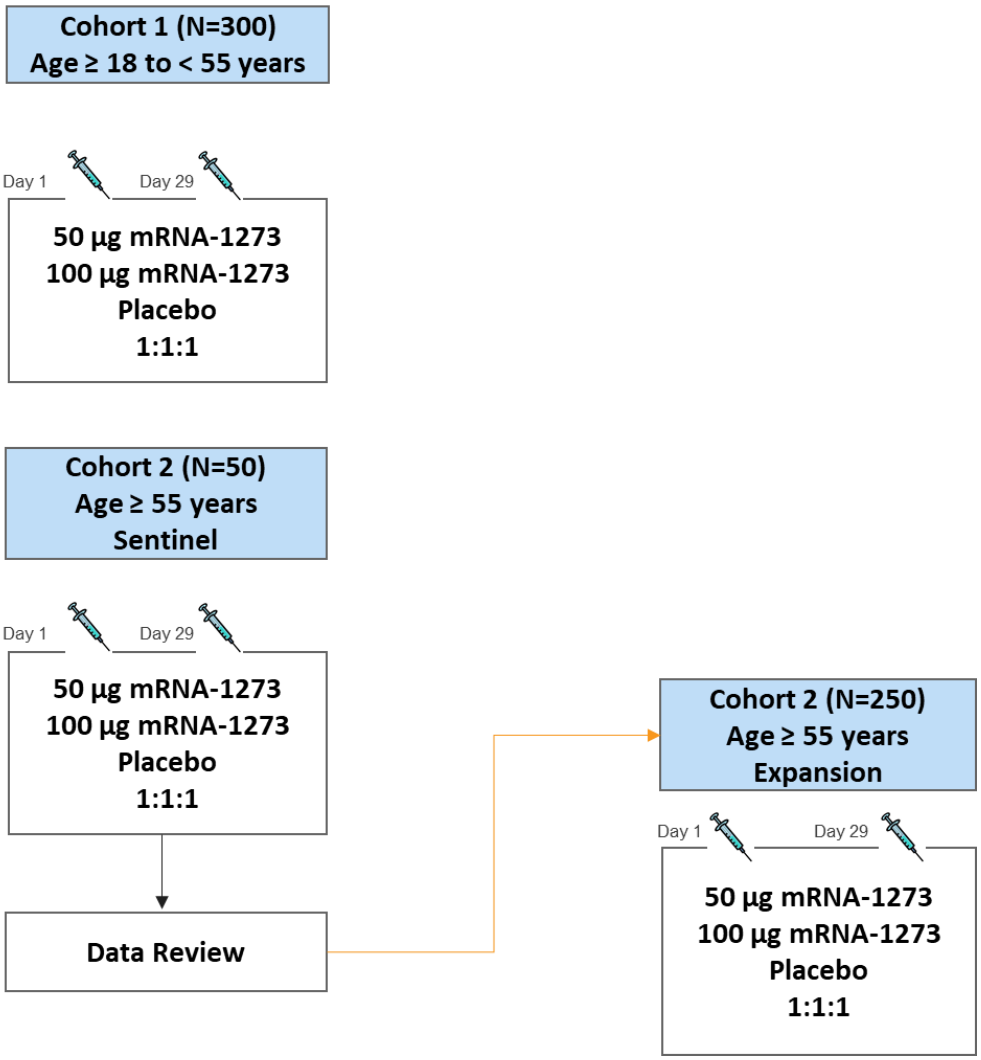


Figure 2: Sentinel and Expansion Cohort Schema



The full study comprises 10 scheduled study site visits: Screening, Day 1, Day 8, Day 15, Day 29 (Month 1), Day 36, Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled participant contacts approximately every 2 weeks after Day 57 to collect medically attended adverse events (MAAEs), AEs leading to withdrawal, SAEs, concomitant medications associated with these events, receipt of non-study vaccinations, exposure to someone with known COVID-19 or SARS-CoV-2 infection, and participant experience of COVID-19 symptoms (Table 7). Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363, each participant will complete a questionnaire in an electronic diary (eDiary) that will be reviewed by study site personnel. Safety telephone calls will occur every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of

13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12 months after the second dose of vaccine on Day 29 (Month 1).

To test for the presence of SARS-CoV-2, nasopharyngeal swab samples will be collected at Day 1, Day 29, and Day 57. During the course of the study, participants meeting pre-specified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment (Section 3.5.1).

Each participant will receive 2 injections of mRNA-1273 or placebo by 0.5 mL IM injection on Day 1 and Day 29. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel who will not participate in any other aspects of the study. The remainder of the study staff, all participants, and Sponsor personnel (or its designees) will remain blinded to dosing assignment (Section 3.4.5).

All participants will be followed for safety and reactogenicity and provide pre- and post-injection blood specimens for immunogenicity through 12 months after the last dose of investigational product. Section 4.7 describes the planned study analyses.

The end of study (EOS) is defined as the release of the last testing result of samples collected at Visit 9 or the completion of the last participant’s last visit, whichever occurs later. Participants are considered to have completed the study if they complete the final visit on Day 394 (Month 13), 12 months after the second injection on Day 29 (Month 1).

At each dosing visit, participants will be instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within a provided eDiary. Solicited ARs will be assessed for 7 days (the day of injection and the following 6 days) after each injection and unsolicited AEs will be assessed for 28 days after each injection; SAEs and MAAEs will be assessed throughout the study.

Participants will have blood sampled at scheduled study visits during the study for safety and immunogenicity assessments or other medical concerns, according to the investigator’s judgment. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Detailed information on all statistical analysis of data is presented in Section 4.6.2.

3.1.1 Rationale for Dose Selection

In this study, the 2 dose levels of mRNA-1273 tested in participants will be 50 µg, and 100 µg, based on assessment of available safety and immunogenicity data from the Phase 1 DMID study and Phase 1 studies of mRNA-1647 and mRNA-1443 (Section 1).

The Phase 1 DMID study, an open-label dose-ranging study of mRNA-1273 in healthy adult male and non-pregnant female participants in 3 age groups: age 18 to 55 years, inclusive (45 participants); age 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants) is currently ongoing. Participants in each age cohort will be randomly assigned to 1 of 3 dose levels of mRNA-1273: 25 µg, 100 µg, and 250 µg. Each participant will receive an IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed for 12 months after the second injection.

As of 14 May 2020, 15 participants in each of the 3 dose levels of the 18 to 55-year age cohort had received at least 1 dose of mRNA-1273. Recruitment of participants in the 2 older age cohorts is ongoing. There have been no SAEs and no triggering of study pause rules. A review of preliminary solicited local and systemic ARs in participants in the 18 to 55-year age cohort after the second injection showed 3 participants in the 100 µg dose group who reported severe local ARs (Grade 3 erythema and induration) and 3 participants in the 250 µg dose group who reported severe systemic ARs (fever, fatigue, feverishness, myalgia, and nausea). These ARs resolved within 24 hours and were not assessed as serious.

The 50 µg and 100 µg doses proposed for this Phase 2a study fall within the doses being evaluated in the Phase 1 DMID study.

3.1.2 Rationale for Study Design

The 2 age cohorts in this Phase 2a study, ≥ 18 to < 55 years old and ≥ 55 years old, were established to better understand the relationships among dose, tolerability, and immunogenicity in different age groups, one being healthy older adults. The older cohort in this Phase 2a study corresponds to the 2 older age cohorts in the Phase 1 DMID study.

Because there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 3.4.5).

The Phase 1 DMID study is small (105 participants at 3 dose levels) and does not incorporate a placebo. Having a sample size of 600 participants in this Phase 2a study and including a placebo will help to improve understanding of AEs.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and post-injection blood samples for antibody analysis through 12 months after the last dose of investigational product. In addition, participants will have nasopharyngeal swab samples collected at Day 1 and Day 29, before the

injections, and at Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasopharyngeal swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and polymerase chain reaction (PCR). Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

Since it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the nasopharyngeal swab samples collected before study injection may help discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

3.2 Selection of Study Population

Healthy male or female participants will be enrolled at study sites in the US or its territories.

3.2.1 Inclusion Criteria

Each participant must meet all of the following criteria during the screening period and at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 18 years of age or older at the time of consent (Screening Visit, Day 0).

2. Understands and agrees to comply with the study procedures and provides written informed consent.

3. According to the assessment of the investigator, is in good general health and can comply with study procedures.

4. Body mass index (BMI) of 18 kg/m^2 to 30 kg/m^2 (inclusive) at the Screening Visit (Day 0).

5. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening (Day 0) without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

- Has a negative pregnancy test at Screening (Day 0) and on the day of the first injection (Day 1).
- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
- Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).
- Is not currently breastfeeding.

Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male participants engaging in activity that could result in pregnancy of sexual partners must agree to practice adequate contraception and refrain from sperm donation from the time of the first injection and through 3 months after the last injection.

   Adequate contraception for male participants is defined as:

   - Monogamous relationship with a female partner using an intrauterine device or hormonal contraception (described above)
   - Use of barrier methods and spermicide
   - History of surgical sterilization

   Male participants with partners who have become pregnant prior to Screening are eligible to participate in the study.

3.2.2 Exclusion Criteria

Participants meeting any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known exposure to someone with SARS-CoV-2 infection or COVID-19.

2. Travel outside of the US in the 28 days prior to the Screening Visit (Day 0).

3. Pregnant or breastfeeding.

4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

5. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.

6. Current treatment with investigational agents for prophylaxis against COVID-19.

7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.

8. Is a healthcare worker or a member of an emergency response team.

9. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).

10. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).

11. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of Screening.

12. Known history of hypertension, or systolic blood pressure > 150 mm Hg in participants in Cohort 1 (≥ 18 to < 55 years old) or systolic blood pressure > 160 mm Hg in participants in Cohort 2 (≥ 55 years old) at the Screening Visit (Day 0).

13. Known history of hypotension or systolic blood pressure < 85 mm Hg at the Screening Visit (Day 0).

14. Diabetes mellitus.

15. Diagnosis of chronic pulmonary disease (eg, chronic obstructive pulmonary disease, asthma).

16. Chronic cardiovascular disease.

17. Resides in a nursing home.

18. Grade 1 or higher toxicity on clinical safety laboratory testing at the Screening Visit (Day 0).

19. Current or previous diagnosis of immunocompromising condition, immune-mediated disease, or other immunosuppressive condition.

20. Received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the Screening Visit (Day 0) (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the Screening Visit (Day 0).

21. Anticipating the need for immunosuppressive treatment at any time during participation in the study.

22. Positive serology for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibodies identified at the Screening Visit (Day 0).

23. History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine.

24. Bleeding disorder considered a contraindication to IM injection or phlebotomy.

25. Diagnosis of malignancy within previous 10 years (excluding non-melanoma skin cancer).

26. Has received or plans to receive a licensed vaccine ≤ 28 days prior to the first injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after any study injection. Licensed influenza vaccines may be received more than 14 days before or after any study injection.

27. Receipt of systemic immunoglobulins or blood products within 3 months prior to the Screening Visit (Day 0) or plans for receipt during the study.

28. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.

29. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.

30. Is an immediate family member or household member of study personnel.

3.2.3 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In the event an eligible participant was not enrolled as a result of a cohort being full and the participant having surpassed their 28-day screening period, the investigator may rescreen the participant for enrollment by assigning the participant a new identification number and repeating all screening procedures (Section 3.3.4).

3.2.4 Participant Restrictions During the Study

3.2.4.1 General and Dietary

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

3.3 Withdrawal of Participants From the Study or Study Dosing

3.3.1 Participant Withdrawal From the Study

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS electronic case report form (eCRF).

Potential reasons for withdrawing a participant from the study include the following:

- SAE
- AE (non-SAE)
- Protocol violation (specify)
- Consent withdrawal (document reason)
- Lost to follow-up
- Other (specify)

3.3.2 Handling Withdrawal From the Study

When a participant withdraws or is withdrawn from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These participants will be requested to complete the EOS assessments scheduled for Day 394 (Month 13).

3.3.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's study source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed. Date of withdrawal/lost to follow-up should be the date of last contact with the participant where safety status of the participant was assessed (eg, study site visit, telephone call).

3.3.4 Replacements

Any participant who is withdrawn, who is significantly outside the allowed injection window, or who is lost to follow-up from the study may be replaced at the Sponsor's discretion.

3.3.5 Participant Withdrawal From Study Dosing

Every reasonable attempt will be made to follow up with participants for safety throughout the entire study period, even if further injection is withheld or the participant misses one or more visits. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all scheduled visits and assessments. (Table 7).

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 3.2.2)
- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to investigational product (Section 3.5.8.9) and is of Grade 3 (severe) or greater severity (Appendix 2)
- Experiences an AE or SAE that, in the judgment of the investigator, requires study vaccine withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly attributed to study vaccine
- Experiences generalized urticaria related to the study vaccine

The reason(s) for withdrawal from further injection will be recorded.

3.4 Study Dosing Groups

3.4.1 Method of Assigning Participants to Dosing Groups

There are 2 age cohorts in this study: participants ≥ 18 to < 55 years old in Cohort l and participants ≥ 55 years old in Cohort 2. Within each age cohort, approximately 300 participants will be randomly assigned in 1:1:1 ratio to receive mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules. Only the unblinded pharmacy personnel (Section 3.4.5) will have controlled access to which arm the participant is randomly assigned.

Dose group assignment in each cohort and stratification within each cohort is summarized in Table 1.

Table 1: Dose Group Assignment

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Total			**600**

3.4.2 Investigational Product Administration

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29, with a 28-day interval between doses. Each injection will have a volume of 0.5 mL and contain mRNA-1273 50 µg, mRNA-1273 100 µg, or saline placebo. Preferably, vaccine should be administered into the nondominant arm. The second dose of investigational product should be administered in the same arm as the first dose.

The investigational product will be prepared for injection as a single 0.5 mL dose for each participant based on the cohort and randomization assignment, as detailed in the mRNA-1273-P201 Pharmacy Manual. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform investigational product accountability, dose preparation, and investigational product administration. The investigator will designate an unblinded clinical team member to provide oversight to the administration of investigational product so that it

proceeds according to the procedures stipulated in this study protocol and the mRNA-1273-P201 Pharmacy Manual. Study-specific training will be provided.

At each visit when investigational product is administered, participants will be monitored for a minimum of 60 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (Schedule of Events, Table 7).

Eligibility for subsequent investigational product injection is determined by following the criteria outlined in Section 3.4.2.2.

The study site will be appropriately staffed, staff will be trained on emergency resuscitation, and will have stocked rescue medications (such as epinephrine, steroids, antihistamines, and intravenous fluids) should any severe reaction (eg, anaphylaxis or urticaria) occur that requires immediate intervention.

The rules for pausing dosing are provided in Section 3.4.2.1.

3.4.2.1 Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause (Table 2).

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any SAE or Grade 4 AE that cannot be reasonably attributed to a cause other than injection	≥ 3
3	ICU admissions in Cohort 1 due to SARS-CoV-2 infection	≥ 3
4	ICU admissions in Cohort 2 due to SARS-CoV-2 infection	≥ 6

Abbreviations: AE = adverse event; ICU = intensive care unit; SAE = serious adverse event; SARS-Cov-2 = severe acute respiratory syndrome coronavirus that causes COVID-19.

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold event is adjudicated by the Safety Monitoring Committee (SMC; Section 6.1.1).

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event potentially meeting any pause

rule criterion. The Sponsor will inform the SMC (Section 6.1.1) of any event potentially meeting any pause rule criterion. The SMC will review all available study data to adjudicate such events in accordance with the SMC charter.

The Sponsor will also actively monitor the following and provide them to the SMC for review as they become available:

- Instances of study halting rules triggered in the Phase 1 DMID study (NCT04283461)
- Histopathological data suggestive of vaccine-enhanced disease in ongoing nonclinical studies

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

3.4.2.2 Contraindications to Subsequent Injection

Prior to receiving a second injection, participants will be reassessed to ensure that they continue to meet eligibility requirements as outlined below.

The following events in a participant constitute absolute contraindications to any further administration of the investigational product to that participant. If any of these events occur during the study, the participant must not receive additional doses of vaccine but will be encouraged to continue study participation for safety through 12 months following last injection (Section 3.3.5).

- Diagnosed COVID-19. If COVID-19 is suspected, further administration of investigational product must be withheld until COVID-19 test results are available.
- Anaphylaxis or systemic hypersensitivity reaction following the administration of vaccine.
- Any SAE judged by investigator or Sponsor to be related to study vaccine.
- Pregnancy
- Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the participant if he/she continues to participate in the study.

The following events constitute contraindications to administration of study vaccine at certain points in time, and if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the Schedule of Events (Table 7), or the participant may be withdrawn from dosing at the discretion of the investigator (Section 3.3.5):

- Acute moderate or severe infection with or without fever at the time of injection
- Fever, defined as body temperature ≥ 38.0°C (100.4°F) at the time of injection

Participants with a minor illness without fever, as assessed by the investigator, can be administered investigational product. Participants with a fever of 38.0°C (100.4°F) or higher will be contacted within the time window acceptable for participation and reevaluated for eligibility.

3.4.3 Identity of Investigational Product

The mRNA-1273 vaccine is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 Injection is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, USP.

3.4.4 Management of Investigational Product

3.4.4.1 Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the investigational product
- Confirming the appropriate labeling of mRNA-1273 Injection, so that it complies with the legal requirements of the US

The investigator is responsible for acknowledging the receipt of the investigational product by a designated staff member at the site, including the following:

- Confirming that the investigational product was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming whether the Sponsor has authorized the investigational product for use

- Ensuring the appropriate dose level of mRNA-1273 Injection is properly prepared using aseptic technique

Further description of the investigational product and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the investigational product are described in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.2 Packaging and Labeling

The Sponsor will provide the investigator and study site with adequate quantities of mRNA-1273. The sterile vaccine product is packaged in a 2-mL glass vial with a 0.6-mL fill volume. mRNA-1273 vaccine will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future participant identification purposes.

mRNA-1273 Injection will be packaged and labeled in accordance with the standard operating procedures (SOPs) of the Sponsor or of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, guidelines for Quality System Regulations, and applicable regulations.

The Sponsor or Sponsor's designee will supply the 0.9% sodium chloride injection for use as both a placebo and a diluent to mRNA-1273. The 0.9% sodium chloride bears a commercial label and does not contain study-specific identification.

3.4.4.3 Storage

mRNA-1273 vaccine must be stored at -60°C to -90°C (-76°F to -130°F) in a secure area with limited access (unblinded pharmacy staff only) and protected from moisture and light until it is prepared for administration (Section 3.4.2). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of freezer malfunction. There must be an available back-up freezer. The freezers must be connected to a back-up generator. In addition, vaccine accountability study staff (eg, the unblinded pharmacy personnel) are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1273 vaccine that was not temperature controlled during shipment or during storage to the unblinded site monitor. Such mRNA-1273 will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

The 0.9% sodium chloride injection (USP) should be stored at 20ºC to 25ºC (68ºF to 77ºF) in a restricted access area.

3.4.4.4 Investigational Product Accountability

It is the investigator's responsibility that the unblinded pharmacy personnel maintain accurate records in an investigational product accountability log of receipt of all investigational product, inventory at the site, dispensing of mRNA-1273 and placebo, study injections, and return to the Sponsor or alternative disposition of used/unused products.

An unblinded site monitor will review the inventory and accountability log during site visits and after the completion of treatment. Additional details are found in the mRNA-1273-P201 Pharmacy Manual.

3.4.4.5 Handling and Disposal

An unblinded site monitor will reconcile the investigational product during the conduct and at the end of the study for compliance. Once fully reconciled at the site at the end of the study, the investigational product can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Investigational product may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be completed and sent to the Sponsor or designee.

3.4.5 Blinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of investigational product to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the investigational product accountability monitors. They will have responsibilities to

ensure that sites are following all proper investigational product accountability, preparation, and administration procedures.

- A primary analysis of safety and immunogenicity data will be performed after participants have completed Day 57 study procedures. This primary analysis may be performed when all participants in Cohort 1 and the Cohort 2 sentinel group have completed Day 57 study procedures and/or when all participants in Cohort 1 and Cohort 2 have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. A limited number of Sponsor and clinical research organization (CRO) personnel will be unblinded to perform the primary study analysis and prepare a final Clinical Study Report (CSR), including individual listings. The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the investigational product in a secure location that is not accessible or visible to other study staff. A blinding label over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different than placebo. Only delegated unblinded site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

3.4.6 Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for the primary study analysis as outlined in Section 4.7.

3.4.7 Dosing Compliance

All doses of investigational product will be administered at the study site under direct observation of unblinded pharmacy personnel and appropriately recorded (date and time) in the eCRF. Unblinded pharmacy personnel will confirm that the participant has received the entire dose of vaccine. If a participant does not receive vaccine or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Participants who miss the second injection due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine will remain in the study and complete all safety and immunogenicity assessments required through the scheduled EOS.

The study site is responsible for ensuring participants comply with the study windows allowed. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Table 7). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (eg, clinical laboratory testing, eDiary review for reactogenicity, immunologic testing, as applicable).

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

3.4.8.2 Concomitant Medications and Therapies

At each study visit, study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the first study injection.
- All concomitant medications and non-study vaccinations taken through 28 days after each injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.

- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each study injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the post-injection study visits or via other participant interactions (eg, telephone calls).

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis (analysis sets are described in Section 4.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- A licensed vaccine administered during the period from 28 days before through 28 days after each study injection, except for any licensed influenza vaccine that was administered more than 14 days before or after any study injection.
- Immunoglobulins and/or any blood products administered during the study period.

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the CRO's medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

3.5 Study Procedures

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 5.3). Participants will undergo study procedures at the time points specified in the Schedule of Events (Table 7).

A participant also can be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

3.5.1 Assessment for SARS-CoV-2 Infection

Study participants will have nasopharyngeal swab samples collected for SARS-CoV-2 testing at time points specified in the Schedule of Events (Table 7).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect a nasopharyngeal swab sample to ascertain the presence of SARS-CoV-2 via PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020c)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case. All findings will be recorded in the eCRF.

If scheduled, a study site illness visit may include assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasopharyngeal swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. Blood samples will be collected at all illness visits for potential future immunologic assessment of SARS-CoV-2 infection.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant's primary care physician of the diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a blood sample will be collected for potential future immunologic assessment of SARS-CoV-2 infection.

If participants are confirmed to have SARS-CoV-2 infection, and are asymptomatic, the investigator will notify the participant's primary care physician and local health authority, as per local regulations. If the participant had known exposure to COVID-19 (eg, exposure to someone with confirmed COVID-19 disease), it will be captured in the COVID-19 exposure form, and the participant will be discontinued from future study treatment only, and will continue to follow all other study assessments as outlined in the protocol. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

Any confirmed SARS-CoV-2 infection occurring in participants, except asymptomatic infection diagnosed at Day 1, will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

3.5.2 Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 3.5.8.4) beginning on Day 1.

At each injection visit, participants will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants will record data into the eDiary starting approximately 1 hour after injection under supervision of the study site staff to ensure successful entry of assessments. The site staff will perform any retraining as necessary. Study participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 3.5.8.4, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be reported in the eDiary until resolution. Adverse reactions

recorded in diaries beyond Day 7 should be reviewed by study site staff either during the next scheduled telephone call or at the next study site visit (Table 7).

- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on a day of injection or for the 6 subsequent days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. The participant will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

Any new safety information reported during safety telephone calls or at site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be described as an unsolicited event and therefore entered on the AE eCRF.

Study site staff will review eDiary data with participants at the Day 8 and Day 36 visits.

The eDiary will also be used after the Day 57 visit to capture the occurrence of AEs, MAAEs, SAEs, or AEs leading to study withdrawal. Every 4 weeks from Day 71 through Day 183 and from Day 223 through Day 363 (Table 7), the eDiary will prompt the participant to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since last in contact with the study site.
- Known exposure to someone with known COVID-19 or SARS-CoV-2 infection.
- Any experience of symptoms of COVID-19.
- Any MAAEs or SAEs.

If an eDiary record results in identification of relevant safety events according to the study period or of symptoms of COVID-19, the site will follow up with the participant via telephone and assess the need for an unscheduled visit.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 3.5.3) as the procedure for safety follow-up approximately every 2 weeks after the Day 57 visit (Table 7).

3.5.3 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls are scheduled to occur every 4 weeks from Day 85 through Day 197 and from Day 237 through Day 377 (Table 7). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AEs leading to study withdrawal, concomitant medications associated with those events, and any non-study vaccinations (Section 3.5.8.6). In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone contact.

3.5.4 Safety Laboratory Assessments

Laboratory tests will be performed by the central laboratory unless otherwise specified. Screening safety laboratory tests will include complete blood count with differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (ALP), blood urea nitrogen/creatinine, prothrombin time (PT), and partial thromboplastin time (PTT). These safety laboratory tests are to be repeated at Day 29 and Day 57 only for Cohort 2 (≥ 55 years of age).

Additional tests include the following:

- A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine administration (Day 1 and Day 29). At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.
- If not documented in a female participant's medical records, an FSH test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.

- Hepatitis B surface antigen, hepatitis C virus antibody, and HIV virus (types 1 and 2) antibody at the Screening Visit (Day 0).

3.5.5 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, blood samples for immunogenicity assessment will be collected before administration of vaccine. The following analytes will be measured:

- Serum bAb level against SARS-CoV-2 as measured by enzyme-linked immunosorbent assay (ELISA) specific to the SARS-CoV-2 S protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow further testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

The ELISA and measurement of nAb titers will be performed in a laboratory designated by the Sponsor.

For participants who provide consent (Section 5.3), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across the coronaviruses.

3.5.6 Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant are 66 mL for 1 day, 182 mL for 28 days, and 398 mL for the complete study (Table 3).

Table 3: Maximum Blood Sampling Volumes per Participant by Visit

Study Visit Day	D0	D1	D15	D29	D43	D57	D209	D394	Total
Safety laboratory tests	16 mL			16[1] mL		16[1] mL			48 mL
Immunogenicity assays		50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	50 mL	350 mL
Total	**16 mL**	**50 mL**	**50 mL**	**66 mL**	**50 mL**	**66 mL**	**50 mL**	**50 mL**	**398 mL**

Abbreviation: D = Day.

[1] Only participants in Cohort 2 will have blood sampled for safety laboratory tests at Day 29 and Day 57.

3.5.7 Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 3.5.8.4) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 3.5.2).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs (Section 3.5.8.4).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 394 or withdrawal from the study.
- MAAEs from Day 1 through Day 394 or withdrawal from the study.
- SAEs from Day 1 through Day 394 or withdrawal from the study.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 3.5.1).

3.5.8 Safety Definitions

3.5.8.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to vaccine or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Any abnormal laboratory test result (hematology, clinical chemistry, or PT/PTT) or other safety assessment (eg, electrocardiogram, radiological scan, vital sign measurement), including one that worsens from baseline and is considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after mRNA-1273 vaccine administration even though it may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the investigational product caused the AE (Section 3.5.8.4). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the investigational product and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol but starts outside the protocol-defined post-injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.2 Medically Attended Adverse Event

An MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner (HCP). This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, SARS-CoV-2 infection [Section 3.5.1]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be fully reported on the MAAE page of the eCRF.

3.5.8.3 Serious Adverse Event

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study vaccine.
- Is life-threatening
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Congenital anomaly or birth defect
- Medically important event
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. 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.

3.5.8.4 Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after vaccine administration. The eDiary (Section 3.5.2) will solicit participant reporting of ARs using a structured checklist. Participants will record such occurrences in an eDiary on the day of each vaccine administration and for the 6 days after a day of injection.

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, body temperature (potentially fever), and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following occurs within 7 days after study injection:

- Severe (Grade 3) local or systemic ARs (Table 4),
- Presence of any rash, or
- Presence of any underarm swelling or tenderness on the same side as the injection arm.

The purpose of the contact is to assess the nature of AR, including assessment of potential pause rules. In the event that rash or underarm swelling or tenderness on the same side as the injection arm is reported, the participant will be asked to return to the study site for assessment by the investigator.

The investigator will review, confirm, and grade reactogenicity according to the grading scales presented in Table 4, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after injection, the participant will be prompted to capture solicited local or systemic ARs in the eDiary until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the

following study visit. All solicited ARs (local and systemic) will be considered causally related to injection.

Table 4: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous	Requires emergency room visit or hospitalization for hypotensive shock

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*
		24 hours		hydration	
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F
Rash*	No rash	Localized rash, without associated symptoms	Maculopapular rash, covering < 50% body surface area	Generalized urticarial, covering > 50% body surface area	Generalized exfoliative, ulcerative or bullous dermatitis, eg, Stevens-Johnson syndrome or erythema multiforme

* Grading for rash and Grade 4 events per Investigator assessment (with exception of fever).

Sources: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

In case of any rash episode observed within 7 days after study injection, the participant will be instructed to contact the study site within 24 hours. During participant evaluation, the investigator should categorize the rash as one of the following:

- Rash no longer present and history not consistent with urticaria.
- Rash no longer present but history is consistent with urticaria.
- Rash present but clinical findings are not consistent with urticaria. Alternative diagnosis should be specified as an AE.
- Rash present and clinical findings consistent with urticaria.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded as an AE in the participant's Adverse Event eCRF:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days post-injection

- Solicited local or systemic AR that leads to participant withdrawal from vaccine administration
- Solicited local or systemic AR that otherwise meets the definition of an SAE
- Solicited AR with a toxicity score of Grade 3 or greater

An unsolicited AE is any AE reported by the participant that is either not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol, but starts outside the protocol-defined post-injection period for reporting solicited ARs (ie, for the 7 days after each injection).

3.5.8.5 Pregnancy

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 3.5.8.7).

3.5.8.6 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor. Unsolicited AEs will be captured from Day 1 through 28 days after each dose up to Day 57 (-3/+7 days). Both MAAEs and SAEs will be captured from Day 1 throughout entire study duration (Day 394 for all participants), as specified in the Schedule of Events (Table 7). Any AEs occurring before receipt of the vaccine will be analyzed separately from TEAEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically-related changes in their well-being according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, data from clinical laboratory test results, physical examination findings, or other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

3.5.8.7 Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to vaccine or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes cohort, type of event, time of onset, investigator-specified assessment of severity and relationship to vaccine, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.8.3) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the vaccine caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341
- SAE Fax line (USA and Canada): +1-866-599-1342

3.5.8.8 Assessment of Severity

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 3.5.8.3), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant’s daily activities and will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or Grade 4 using the following criteria:

- Mild (Grade 1): These events do not interfere with the participant's daily activities.
- Moderate (Grade 2): These events cause some interference with the participant's daily activities but do not require medical intervention.
- Severe (Grade 3): These events prevent the participant's daily activity and require medical intervention.
- Grade 4: These events require an emergency room visit or hospitalization.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic solicited ARs (Table 4), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for clinical and laboratory abnormalities are presented in Appendix 2 (Table 8 and Table 9, respectively) and will be graded if outside of the reference range for the laboratory utilized.

3.5.8.9 Assessment of Causality

The investigator's assessment of an AE's relationship to vaccine is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the vaccine caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: There is not a reasonable possibility of a relationship to the investigational product. Participant did not receive the investigational product OR temporal sequence of the AE onset relative to administration of the investigational product is not reasonable OR the AE is more likely explained by another cause than the investigational product.
- Related: There is a reasonable possibility of a relationship to the investigational product. There is evidence of exposure to the investigational product. The temporal sequence of the AE onset relative to the administration of the investigational product is reasonable. The AE is more likely explained by the investigational product than by another cause.

3.5.8.10 Follow-up of Adverse Events

All AEs, SAEs, and MAAEs must be reported in detail on the appropriate page of the eCRF and followed until the event is resolved or stable or judged by the investigator to be not clinically significant.

3.5.9 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the Schedule of Events (Table 7). On Day 1 and Day 29, vital sign measurements will be collected once before vaccine administration and at least 1 hour after vaccine administration (before participants are discharged from the study site).

Febrile participants at Day 1 and Day 29 visits (fever is defined as a body temperature ≥ 38.0°C/100.4°F) may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities (Table 8) of Grade 3 or greater, the abnormal value and grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.5.10 Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Schedule of Events (Table 7). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as a MAAE.

Symptom-directed physical examinations may be performed at other timepoints at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

Body mass index will be calculated at the Screening Visit (Day 0) only.

4 STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

4.1 Blinding and Responsibility for Analyses

Blinding during the study will be managed as described in Section 3.4.5. The Sponsor Biostatistics department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Details regarding unblinded SMC review are described in Section 6.1.

A limited number of Sponsor and CRO personnel will be unblinded to perform the primary analysis and prepare a final CSR after participants have completed Day 57 study procedures (Section 3.4.5). This primary analysis may be performed when all participants in Cohort 1 and the Cohort 2 sentinel group have completed Day 57 study procedures and/or when all participants in Cohort 1 and Cohort 2 have completed Day 57 study procedures. The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study.

Planned study analyses and data presentation for unblinded SMC review are described in Section 4.7 and Section 6.1, respectively. At each analysis, pre-identified Sponsor members will be unblinded to review treatment level results as defined in the study Data Blinding Plan. Unblinded data presentation or analysis for SMC review will be handled by the CRO unblinded team of statisticians and programmers, who are not involved in study design. A strict firewall between the CRO blinded and unblinded teams will be maintained during study conduct. Sponsor personnel who have access to review unblinded results will be documented. Sponsor and CRO personnel involved in the ongoing review and oversight of safety and immunogenicity will remain blinded, as will study investigators and personnel at the study sites. The results of the primary analysis will not be shared with the investigators before completion of the study.

4.2 Hypothesis Testing

There is no hypothesis testing in this study.

4.3 Analysis Endpoints

4.3.1 Primary Endpoints

4.3.1.1 Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic ARs through 7 days after each injection.
- Unsolicited AEs through 28 days after each injection.
- MAAEs through the entire study period.
- SAEs throughout the entire study period.
- Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only).
- Vital sign measurements and physical examination findings.

4.3.1.2 Primary Immunogenicity Endpoint

- Level of SARS-CoV-2-specific bAb measured by ELISA on Day 1, Day 29 (Month 1), Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13).

4.3.2 Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- Titer of SARS-CoV-2-specific nAb on Day 1, Day 29 (Month 1), Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13).
- Seroconversion on Day 29 (Month 1), Day 43, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13) as measured by an increase of SARS-CoV-2-specific nAb titer either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) to equal to or above LOD or LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers.

4.3.3 Exploratory Endpoints

The exploratory endpoints are the following:

- Serum titers of S protein-specific binding Ig assessed by class and subclass and nAb in serum.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum.
- Clinical severity and immune response of participants infected by SARS-CoV-2.
- Number of cases and incidence of confirmed SARS-CoV-2 infection using an assay designed to detect non-vaccine antigens of SARS-CoV-2.

4.4 Analysis Populations

4.4.1 Randomized Set

The Randomized Set consists of all participants who are randomly assigned in the study, regardless of the participants' treatment status in the study.

4.4.2 Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomly assigned and received any study injection, and contribute any solicited AR data; ie, have at least one post-baseline solicited safety (eDiary) assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment group corresponding to the study injection they actually received.

4.4.3 Safety Set

The Safety Set consists of all randomly assigned participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the treatment group corresponding to the study injection they actually received for the analysis of safety data using the Safety Set.

4.4.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who a) receive any study injection, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-injection assessment for the analysis endpoint. Participants will be included in the treatment group to which they were randomly assigned.

4.4.5 Per-Protocol Set

The Per-Protocol (PP) Set consists of all FAS participants who meet all of the following criteria:

- Complied with the injection schedule
- Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective
- Did not have SARS-CoV-2 infection
- Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective

The PP Set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the treatment group to which they were randomly assigned.

4.5 Sample Size Determination

There is no hypothesis testing in this study. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1273.

Approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level. Table 5 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. The 2-sided 95% CI is estimated (0.01%, 1.4%) at sample size of 400 with 1 participant reporting an AE. Furthermore, a sample size of 400 has at least a 95% probability to observe at least 1 participant with an AE at a true 0.75% AE rate.

Table 5: 95% Confidence Interval for One Participant with AE and the Lowest Detectable Incidence Rate at 95% Probability in Selected Sample Size

Sample Size Receiving mRNA-1273	Rate and 95% CI (%) at One Participant with AE			Lowest Detectible Rate (%) with ≥95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75

Abbreviations: AE = adverse event; CI = confidence interval.

4.6 Statistical Methods

There are 2 age cohorts in this study: Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). All analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise.

4.6.1 Summary of Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by treatment group for each age cohort (when appropriate) by descriptive statistics (mean, standard deviation for continuous variables, and number and percentage for categorical variables).

4.6.2 Safety Analyses

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA for adverse reaction terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash, solicited ARs, and vital signs (Table 4).

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area

- Grade 4 = generalized exfoliative, ulcerative, or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by age cohort unless otherwise specified.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided. Table 6 summarizes the analysis strategy for safety parameters.

Table 6: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	
Any SAE	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Abbreviations: AE = adverse event; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; SAE = serious adverse event.

Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by system organ class and preferred term coded by the Medical Dictionary for Regulatory Activities.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by age cohort, treatment group, and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

Further details will be described in the SAP.

4.6.3 Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set. For each age cohort, if the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint (Section 4.3.1.2), geometric mean (GM) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold-rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint (Section 4.3.2), geometric mean titer (GMT) of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by treatment group and age cohort. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the LOD or LLOQ will be replaced by 0.5 × LOD or 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as a change of nAb titer from below the LOD or LLOQ to equal to or above LOD or LLOQ (respectively), or a 4-times or higher titer ratio in participants with pre-existing nAb titers.

Exploratory analyses of each dose level of mRNA-1273 versus placebo on bAb and nAb levels/titers may be performed.

4.6.4 Exploratory Analyses

Exploratory analyses may include the following:

- Descriptive summaries of the relative proportions of S protein-specific serum Igs and nAb during the study. Subclass analysis of specific IgG may be performed.
- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study.
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.

4.7 Study Analyses

No interim analysis is planned for this study.

4.7.1 Primary Study Analysis

A primary analysis of safety and immunogenicity data will be performed after participants have completed Day 57 study procedures. This primary analysis may be performed when all participants in Cohort 1 and the Cohort 2 sentinel group have completed Day 57 study procedures and/or when all participants in Cohort 1 and Cohort 2 have completed Day 57 study procedures. All data relevant to the primary study analysis through Day 57 will be cleaned (ie, data that are as clean as possible) and locked. Results of this analysis will be presented in a final CSR, including individual listings.

4.7.2 End of Study Analysis

The final analysis of all endpoints will be performed after all participants have completed Month 13 study procedures and after the database is cleaned and locked. Results of this analysis will be presented in an EOS CSR, including individual listings.

Additional information can be found in the SAP.

4.8 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonized tripartite guideline E6(R2): GCP and current SOPs. The eCRFs will be utilized and accessed through iMedidata® via the internet. This EDC system is validated and compliant with US Title 21 of CFR Part 11. Each person involved with the study

will have an individual identification code and password that allow for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Due to safety review requirements, study sites must follow the data entry and availability instructions provided by the Sponsor in the study readiness trainings. As a quality measure, timeliness of data entry and data query resolution will be followed closely. Other issues of data quality that may hinder safety review or pose a concern with patient safety will be brought to the attention of the Sponsor or CRO, with appropriate awareness to the SMC if needed.

5 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study and may be pursuant to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

5.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

5.2 Institutional Review

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

5.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to study-

related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study, be allowed to read the approved ICF, and be given answers to any questions. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF. Separate counseling and consent may be provided for HIV testing as applicable per local laws or regulations.

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across the coronaviruses.

The investigator or designee will provide a copy of the ICF to the participant. The original form shall be maintained in the participant's medical records at the site.

5.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to Sponsor according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

5.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor, the CRO, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, the CRO, nor the study site is financially responsible for further treatment of the disease under study.

5.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

5.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

5.8 Data Collection

5.8.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for participants treated as part of the research under this protocol.

The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic case report forms are accessed through iMedidata® via the internet. This EDC system is validated and compliant with 21 CFR 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

5.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

5.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

5.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

5.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the vaccine. These documents should be retained for a longer period, however, if

required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

5.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

6 STUDY MANAGEMENT

6.1 Monitoring

Ongoing safety monitoring will be performed in a blinded manner by the CRO's medical monitor, the Sponsor's medical monitor, and the individual site investigators throughout the study.

6.1.1 Safety Monitoring Committee

Safety oversight will be under the direction of an SMC composed of external independent consultants with relevant expertise. Members of the SMC will be independent from the study conduct and free of conflict of interest. The SMC will meet on a regular basis to assess safety throughout the study conduct. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the SMC. Details regarding the SMC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The SMC will convene on an ad hoc basis if any of the pause rules, described in Section 3.4.2.1, are met. The SMC will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

6.1.2 Monitoring of the Study

The study monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The monitor will be blinded to dose assignments. A separate unblinded study monitor will be responsible for vaccine accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.3 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event

of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

6.2 Management of Protocol Amendments and Deviations

6.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

6.2.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Major protocol deviations are defined as exclusionary from the analysis according to the protocol objectives and endpoints. Protocol deviations will be documented by the study monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of such deviations.

6.3 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last participant completes the last visit (includes the EOS Visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the CSR.

6.4 Clinical Study Reports

Whether the study is completed or prematurely terminated, the Sponsor will ensure that CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSRs. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

The final CSR will be prepared based on the primary analysis of safety and immunogenicity data, which is based on cleaned and locked data collected from participants from Day 0 through the Day 57 visit (Section 4.7.1).

The EOS CSR will be based on an analysis of all data collected from Day 0 through Day 394. The Sponsor will provide the investigator(s) with the final approved EOS CSR.

7 APPENDICES

7.1 Appendix 1: Schedule of Events

The Schedule of Events is presented in Table 7. Reasons and procedures for possible unscheduled visits are provided in Section 3.5 and Section 3.5.1.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening, Day 1, and Day 29 visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Screening, Day 1, and Day 29 visits), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls (Table 7).

Table 7: Schedule of Events

Visit Number	0	1	2	3	4	5	6	7			8			9
Type of Visit	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0			M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	+7	+3	±3	-3/ +7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	14	28/0	7	14	28	-	-	180	-	-	365
ICF, demographics, concomitant medications, medical history	X													
Confirm participant meets inclusion and exclusion criteria	X	X												
Blood for safety laboratory tests[6]	X				X[4]			X[4]						
Blood for viral serology (hepatitis B, hepatitis C, HIV [1 and 2])	X													
Physical examination including vital signs[7]	X	X	X	X	X	X	X	X			X			X
Pregnancy testing[8]	X	X			X									
Randomization		X												
Study injection (including 60-minute post-dosing observation period)		X			X									
Blood for vaccine immunogenicity[9]		X		X	X		X	X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[10]		X			X			X						
eDiary activation for recording solicited adverse reactions (7 days)[11]		X			X									
Review of eDiary			X			X								

Visit Number	0	1	2	3	4	5	6	7			8			9
Type of Visit	C	C	C	C	C	C	C	C	SFU		C	SFU		C
Month Timepoint		M0			M1			M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D15[2]	D29[3]	D36[2, 3]	D43[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	-28		+3	±3	+7	+3	±3	-3/ +7	±2	±3	±14	±2	±3	±14
Days Since Most Recent Injection	-	0	7	14	28/0	7	14	28	-	-	180	-	-	365
Follow-up safety calls[12]										X			X	
Recording of unsolicited AEs		X	X	X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE		X	X	X	X	X	X	X	X[12]	X	X	X[12]	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE		X	X	X	X	X	X	X	X[12]	X	X	X[12]	X	X
Recording of concomitant medications and non-study vaccinations[13]		X	X	X	X	X	X	X						
Study completion														X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = clinic visit; CBC = complete blood count; D = day; HIV = human immunodeficiency virus; ICF = informed consent form; M = month; MAAE = medically attended AE; SC = safety (telephone) call; SFU = Safety Follow Up; PCR = polymerase chain reaction; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event.

Note: In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

1. The Day 0 visit may be performed over multiple visits if within the 28-day screening window.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to come on site for a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for adverse events and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all non-dosing visits except for Screening if a participant cannot come to the study site as a result of

the COVID-19 pandemic. Home visits must be permitted by the site IRB and the participant via informed consent and have prior approval from the Sponsor (or its designee).

3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 +7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. When the extended window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.
4. Safety follow-up via eDiary questionnaire will be performed every 4 weeks starting at Day 71 to Day 183 and again starting at Day 223 to Day 363. These study days are relative to Day 1 vaccine administration and are not affected by the timing of the second vaccine administration.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks starting at Day 85 to Day 197 and again starting at Day 237 to Day 377. There is potential overlap of the Day 197 safety telephone call and Visit 8 due to their respective visit windows. As such, the safety telephone call on Day 197 only needs to be performed if the participant is scheduled to complete Visit 8 after Day 200.
6. Safety laboratory tests include the following: CBC with differential, AST, ALT, total and direct bilirubin, ALP, BUN/creatinine, PT/PTT. Safety laboratory tests are to be repeated at Day 29 and Day 57 **only for Cohort 2 (≥ 55 years old).**
7. Physical examination: A full physical examination, including height and weight, will be performed at Day 1, Day 29, and Day 57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be collected pre- and post-dosing on days of injection (Day 1 and Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be administered investigational product at the discretion of the investigator.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator a pregnancy test either via blood or point-of-care urine test can be performed. Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the investigator.
9. Sample must be collected prior to dosing on days of injection (Day 1 and Day 29).
10. The nasopharyngeal swab sample, collected prior to vaccination on days of injection (Day 1 and Day 29), will be used to ascertain the presence of SARS-CoV-2 via PCR.
11. Diary entries will be recorded by the participant starting approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection. Any solicited AR that is ongoing beyond Day 7 will be reported in the eDiary until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either during the next telephone call or at the next study site visit.
12. Trained site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any non-study vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. Sites will collect this information for diary days only if diary responses indicate the need for follow-up via telephone.
13. All concomitant medications and non-study vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).

7.2 Appendix 2: Toxicity Grading Scale Tables

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 8 and Table 9, respectively. Note that for laboratory abnormalities, grading only occurs if the values are outside of the normal values established by the clinical laboratory. For study-specific laboratory normal ranges and associated toxicity grades, refer to the laboratory manual and provided toxicity grade communications.

Table 8: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Abbreviation: ER = emergency room.

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)**	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER = emergency room.

Note that fever is classified under systemic reactions for grading purposes.

* Participant should be at rest for all vital sign measurements.

** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40.0 102.1 – 104.0	> 40.0 > 104.0
Nausea/vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/malaise (unusual tiredness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized myalgia (muscle ache or pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized arthralgia (joint ache or pain)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviations: ER = emergency room; IV = intravenous.

* Oral temperature; no recent hot or cold beverages or smoking.

Sources: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for clinical abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

Table 9: Tables for Laboratory Abnormalities

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)**
BUN (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
ALP; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests – ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of the normal range.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007).

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (female) (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease (cell/mm^3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease (cell/mm^3)	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm^3)	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils (cell/mm^3)	650 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT; increase by factor	> 1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	> 1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell.

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Laboratory abnormality grading occurs only when the values fall beyond the normal ranges established by the local laboratory.

Source: Guidance for industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; tables for laboratory abnormalities (DHHS 2007). Note that the criteria for Grade 1 PT and PTT have been adjusted from the source table: instead of ≥ 1.0 x ULN, both criteria are > 1.0 x ULN. Grade 1 will not be used for hematology values due to the large overlap with normal values at the central laboratory.

7.3 Appendix 3: Protocol Amendment History

The document history table for this protocol and the Protocol Amendment Summary of Changes table for the current Amendment 3 is located directly before the Table of Contents.

Descriptions of Amendments 1 and 2 are presented in this appendix.

7.3.1 Amendment 2, 01 Jul 2020

Main Rationale for the Amendment:

The main purpose of this amendment was to change the statistical analysis plan by removing interim analyses and defining the Primary Study Analysis and End of Study Analysis. The summary of changes table describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated the protocol version and date	Reflect the new version and date of the protocol.
Synopsis, Section 3.1 Study Design, Section 3.5.2 Use of Electronic Diaries, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (including text, Table 7, and footnotes to Table 7)	Added eDiary questionnaires to the procedure for safety follow-up after the Day 57 visit, with completion of eDiary questionnaires alternating with safety telephone calls approximately every 2 weeks after the Day 57 visit.	Reduce the burden on study site personnel of completing safety follow-up by telephone.
Synopsis, Section 3.1 Study Design, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (footnote 12)	Added exposure to someone with known COVID-19 or SARS-CoV-2 infection and participant experience of COVID-19 symptoms to the list of events queried during scheduled safety telephone calls.	Improve surveillance for incidence of COVID-19 during the study.
Synopsis, Section 3.1 Study Design	End of Study definition was amended.	Minor clarification to define the End of Study.
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7 Study Analyses, Section 4.7.1 Primary Study Analysis, Section 4.7.2 End of Study Analysis, Section 6.4 Clinical Study Reports	Added descriptions of the Primary Study Analysis and End of Study Analysis and respective clinical study reports, replacing descriptions of interim analyses and reports. The synopsis contains a new section.	Eliminate interim analyses in favor of a focus on the primary analysis.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 4.6 Statistical Methods	Stated that all analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise.	Previous versions of the protocol had not included the overall analysis in statement of the standard scope of analysis.
Synopsis, Section 4.6.3 Immunogenicity Analyses	For the primary immunogenicity endpoint, geometric mean titer was changed to geometric mean.	Assays for bAb are under development. The reported values may or may not be titers; hence the protocol wording has been modified.
Section 3.5.1 Assessment for SARS-CoV-2 Infection	Added instructions for asymptomatic patients who have a confirmed SARS-CoV-2 infection.	To clarify the steps for the investigator to follow when a participant is confirmed to have SARS-CoV-2 infection but is asymptomatic.
Section 3.5.8.8 Assessment of Severity	Decoupled life-threatening and Grade 4 in the severity assessment.	To adhere to CDISC guidance and align with case report form page.
Section 3.5.8.8 Assessment of Severity	Added clarification on when an AE is defined as serious.	To clarify when an AE is defined as serious.

Abbreviations: AE = adverse event; bAb = binding antibody; CDISC = Clinical Data Interchange Standards Consortium; eDiary = electronic diary; SARS-Cov-2 = Severe Acute Respiratory Syndrome coronavirus that causes COVID-19.

7.3.2 Amendment 1, 18 May 2020

Main Rationale for the Amendment:

The main purpose of this amendment was to incorporate the following modifications requested by the FDA Center for Biologics Evaluation and Research:

- Enhance monitoring of participants who are confirmed to have SARS-CoV-2 infection.
- Include a convalescent visit for participants with confirmed SARS-CoV-2 infection.
- Explore the mRNA-1273 vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection.
- Update the Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to extend the follow-up to a full 12-month period after the second injection on Day 29 (Month 1).
- Decrease the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.

The summary of changes table describes the major changes made in Amendment 1, including the sections modified and the corresponding rationale. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated protocol version and date.	Revised version and date of protocol.
Title page, Signature page, and header	Updated the protocol title.	Revised to reflect the current purpose of the study.
Synopsis and Section 2.3 Exploratory Objectives	Added an exploratory objective to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.	Request from the Health Authority.
Synopsis, Section 2.3 Exploratory Objectives, Section 4.3.3 Exploratory Endpoints, Section 4.6.4 Exploratory Analyses	Revised wording for the exploratory objective/endpoint regarding spike protein-specific serum immunoglobulin class and subclass and neutralizing antibody in serum	Editorial change.
Synopsis, Section 3.1 Study Design, Study Flow Schema (Figure 1), Sentinel and Expansion Cohort Schema (Figure 2), Section 3.1.1 Rationale for Dose Selection, 3.4.1 Method of Assigning Participants to Dosing Groups. Dose Group Assignment (Table 1), 3.4.2 Investigational Product Administration, 4.5 Sample Size Determination	Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.	Decreased based on the preliminary findings of the Phase 1 DMID study.
Synopsis and Section 3.1 Study Design	Deleted collection of nasopharyngeal swab samples at the Screening Visit (Day 0).	Editorial update for consistency with Schedule of Events (Table 7).
Synopsis and Section 3.1 Study Design	Deleted the number of visits at which participants will have blood samples collected.	Editorial update to avoid confusion as blood samples will be collected at different visits for safety and vaccine immunogenicity assessments.
Synopsis; Section 3.1 Study Design, Section 3.5.6 Blood Sampling Volumes (Table 3), Section 3.5.7 Safety Assessments, Section 3.5.8.6 Eliciting and Documenting Adverse Events, Section 4.3.1.2 Primary Immunogenicity Endpoint, Section 4.3.2 Secondary Endpoints, Section 4.7 Interim Analyses, Section 6.4 Clinical Study Reports, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to allow for 6-month and 12-month intervals, respectively, after the second injection on Day 29 (Month 1).	Request from the Health Authority.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 3.1 Study Design, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated the biweekly safety telephone calls from Day 211 through Day 351 to Day 223 through Day 377.	Consequent to the change made to the Day 209 Visit (Request from the Health Authority).
Synopsis, Section 3.1 Study Design, Section 3.1.2 Rationale for Study Design, Section 3.5.1 Assessment for SARS-CoV-2 Infection, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated nasal swab to nasopharyngeal swab.	Clarified the type of swab to be performed.
Section 3.1.1 Rationale for Dose Selection	Updated enrollment and preliminary safety data from the ongoing Phase 1 DMID study.	Updated based on the preliminary findings of the Phase 1 DMID study.
Section 3.2.1 Inclusion Criteria	Updated inclusion criterion #7 to exclude sperm donations through 3 months after the last injection.	Update to align with the informed consent form on refraining male participants from sperm donation through 3 months after the last injection based on IRB feedback to the ICF.
Section 3.3.2 Handling Withdrawal From the Study	Updated the scheduled end of study assessments at Day 394 (Month 13) to allow for a 12-month interval after the second vaccination on Day 29 (Month 1).	Request from the Health Authority.
Section 3.4.5 Blinding	Updated the method to maintain the blind of the dosing assignment from opaque sleeve to blinding label.	Operational change in cases for which opaque sleeves are not used.
Section 3.5.1 Assessment for SARS-CoV-2 Infection	• Added more intense monitoring of participants who are confirmed to have SARS-CoV-2 infection (ie, notification of the participant's primary care physician by the investigator and recording of confirmed SARS-CoV-2 infection as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome). • Added a convalescent visit with blood collection after diagnosis of SARS-CoV-2 infection.	Request from the Health Authority.
Section 3.5.1 Assessment for SARS-CoV-2 Infection and Section 3.5.8.2 Medically Attended Adverse Event	Deleted "or COVID-19."	Editorial update for internal consistency.
Section 4.3.3 Exploratory Endpoints	Included a new exploratory endpoint to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.	Request from the Health Authority.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Deleted that Day 0 and Day 1 visits may be combined the same day.	Editorial update of template text, which did not apply to this protocol.
	Corrected sequential footnote numbering in the schedule of events (Table 7).	Editorial update.
	Included a header row titled "Days Since Most Recent Vaccination."	Update to clarify that the visits are relative to the most recent injection.

Abbreviation: DMID = Division of Microbiology and Infectious Diseases; ICF = informed consent form; IRB = Institutional Review Board; MAAE = medically attended adverse event; SARS-Cov-2 = Severe Acute Respiratory Syndrome coronavirus that causes COVID-19.

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