CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2
Protocol Number:	mRNA-1283-P201
Sponsor Name:	ModernaTX, Inc.
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Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number:	IND: 027196
Amendment 2 Date	31 Jan 2022
Amendment 1 Date	22 Oct 2021
Original Protocol Date:	01 Sep 2021

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title: A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2

Protocol Number: mRNA-1283-P201

Amendment Number 2

Amendment Date: 31 Jan 2022

Protocol accepted and approved by:

PPD	Date

ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2" and the most recent version of the Investigator's Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without institutional review board (IRB) approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	31 Jan 2022
Amendment 1	22 Oct 2021
Original Protocol	01 Sep 2021

Amendment 2, 31 Jan 2022: Current Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment

The main rational for this amendment is to add an open label study part (Part B) to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1283.529 booster vaccine - an omicron-specific booster vaccine candidate.

The summary of changes table provided here describes the changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationale. The synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol. Minor editorial and grammatical corrections were also made.

Summary of Major Changes from Original Protocol to Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature Page, Protocol Amendment Summary of Changes, and Header	• Updated the protocol version and date. • Added Protocol Amendment Summary of Changes for Amendment 1.	Updated to reflect the new version and date.
Throughout the protocol	• Addition of Study Part B to add mRNA-1283.529 booster doses to the protocol • Added language for Study Part A, designating the 6 treatment arms described in the original protocol as Part A	Updated to evaluate the safety, reactogenicity, and immunogenicity of the mRNA-1283.529 vaccine candidate at two dose levels
Section 1.2.3 (mRNA-1273.529)	• Section added with description of the mRNA-1273.529 vaccine candidate	Added to provide a description of the new vaccine candidate for Part B
Protocol Synopsis, Section 2 (Objectives and Endpoints)	• Addition of objectives and endpoints for Part B	Added to provide the descriptions of the objectives and endpoints of the new part of the study.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis, Section 4 (Study Population), Section 8.3 (Sample Size Determination)	• Changed Part A participant number from "approximately 420" to "up to 420."	Change reflects Part A and Part B targeted enrollment.
Protocol Synopsis, Section 4.1 (Inclusion Criteria)	1. Added language to inclusion criterion 6 to specify that mRNA-1273 refers specifically to the primary vaccine series	Updated for clarity.
Protocol Synopsis, Section 8.5.1 (Baseline Characteristics and Demographics), Section 8.5.2 (Efficacy Analysis), Section 8.5.3 (Safety Analyses), 8.5.4.1 (Analysis for the Primary Immunogenicity Objective), Section 8.5.4.2 (Analysis for the Secondary and Exploratory Immunogenicity Objectives), Section 8.5.5 (Subgroup Analyses)	2. Addition of references to Part A and Part B and statistical analyses and considerations for Part B	Updated to differentiate between Part A and B and to add the statistical analyses specific to Part B
Section 8.6.2 (Interim Analysis)	3. Section added to describe the conditions for the Part B interim analysis and the groups involved in the analysis	Added to allow for an interim analysis based on Part B of the study.
Section 10.1 Appendix 1: Schedule of Events	4. Added a Day 90 visit	Added to allow for a blood draw for humoral immunogenicity testing and a nasopharyngeal swab for COVID-19 testing.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1283 and mRNA-1283.211 vaccine candidates

Name of Active Ingredient: Part A - mRNA-1283 and mRNA-1283.211, respectively; Part B – mRNA-1283.529

Protocol Title: A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2

Protocol Number: mRNA-1283-P201

Study Period (months): Approximately 13 months

Phase of Development: Phase 2a

Estimated Date First Participant Enrolled: 29-Nov-2021

Estimated Date Last Participant Completed: 29-Nov-2022

Total Number of Sites: Up to 13 sites in the United States or its territories

Objectives and Endpoints:

The objectives that will be evaluated in this study and the endpoints and time points associated with each objective are provided in the table below:

Part A Objectives and Endpoints	
Objectives	**Endpoints**
Primary	
• To assess the safety and reactogenicity of the study vaccines	• Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period after vaccination • Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period after vaccination • Frequency of any serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal from study participation, and AEs of special interest (AESIs) from Day 1 to end of study (EoS)
• To assess the immunogenicity of the study vaccines	• Immune response of the study vaccine candidates against the ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and against SARS-CoV-2 variants, including B.1.351, at Day 29 by geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroresponse rate (SRR) • To compare the immune response elicited by the mRNA-1283 study vaccine candidates with the immune response elicited by the mRNA-1273 vaccine when administered as a booster, at Day 29 by GMT, GMFR, and SRR
Secondary	
• To evaluate the immunogenicity at all immunogenicity time points	• Immune response of the study vaccine candidates against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants at all immunogenicity time points by GMT, GMFR, and SRR
Exploratory	
• To characterize cellular immunogenicity	• Frequency, magnitude, and phenotype of antigen-specific B- and T-cells, to include B-cell and T-cell receptor repertoires

• To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed asymptomatic or symptomatic SARS-CoV-2 infection will be defined in participants: – Negative SARS-CoV-2 anti-nucleocapsid antibody blood test at Day 1 that becomes positive at Day 29 or later, OR – Positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swab
• To assess the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

Part B Objectives and Endpoints	
Objectives	**Endpoints**
Primary	
• To assess the safety and reactogenicity of the mRNA-1283.529 booster vaccine candidate	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period after vaccination • Frequency and severity of any unsolicited adverse AEs during the 28-day follow-up period after vaccination • Frequency of any SAEs, MAAEs, AEs leading to withdrawal from study participation, and AEs of special interest (AESIs) from Day 1 to EoS
• To assess the immunogenicity of the mRNA-1283.529 booster vaccine candidate as the second booster dose	• Immune response of the 1283.529 booster vaccine candidate against SARS CoV 2 Omicron variant (B.1.1.529), at Day 29 by geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroresponse rate (SRR)
Secondary	
• To assess the immunogenicity at all immunogenicity time points	• Immune response of the mRNA-1283.529 vaccine candidate against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants at all immunogenicity time points by GMT, GMFR, and SRR
Exploratory	
• To characterize cellular immunogenicity	• Frequency, magnitude, and phenotype of antigen-specific B- and T-cells, to include B-cell and T-cell receptor repertoires
• To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed asymptomatic or symptomatic SARS-CoV-2 infection will be defined in participants:

	– Negative SARS-CoV-2 anti-nucleocapsid antibody blood test at Day 1 that becomes positive at Day 29 or later, OR – Positive SARS-CoV-2 RT-PCR from nasopharyngeal swab
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

Overall Study Design:

This is a Phase 2a study that consists two parts: Part A is an observer-blind, stratified, randomized design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283, mRNA-1283.211, and potentially of other study vaccine candidates, administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273. Part B is an open-label design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283.529 administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273.

Part A of this study will assess whether a single dose of mRNA-1283 at three different dose levels CCI [redacted] or mRNA-1283.211 at two different dose levels CCI [redacted] will boost antibody responses to the Wuhan-Hu-1 (ancestral strain of the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) virus, and to the B.1.351 variant, and potentially other SARS-CoV-2 variants, and inform dose selection for mRNA-1283 booster vaccines for subsequent clinical evaluation. The study will include an active comparator group of participants who will receive mRNA-1273 CCI [redacted].

Participants in Part A who received the primary series of mRNA-1273 CCI [redacted] with appropriate documentation at least 6 months prior will be randomized 1:1:1:1:1:1 to receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or a single dose of the active comparator, mRNA-1273.

Part A Treatment Groups:

Treatment Group	Vaccine	Dose Level[1]	N
1	mRNA-1283	CCI [redacted]	70
2			70
3			70
4	mRNA-1283.211		70
5			70
6	mRNA-1273		70

[1] Dose levels for mRNA-1283.211 and mRNA-1273 are total mRNA in 1:1 ratio of mRNA-1283 and mRNA-1283.351 or mRNA-1273 and mRNA-1283.351, respectively.

Part B of this study will assess whether a single dose of mRNA-1283.529 at two different dose levels CCI [redacted] as the second booster after a first booster of mRNA-1273 CCI [redacted], at least 3 months prior, will boost antibody response to the ancestral strain of the SARS-CoV-2, the B1.1.529 variant, and potentially other SARS-CoV-2 variants, and inform dose selection for mRNA-1283.529 booster vaccine candidate for subsequent clinical evaluation.

Participants in Part B who received the primary series of mRNA-1273 CCI and a first booster of mRNA-1273 CCI at least 3 months prior will be enrolled in a 1:1 ratio to receive a single boost of mRNA-1283.529 as the second booster dose at one of two dose levels

Part B Treatment Groups:

Treatment Group	Vaccine	Dose Level	N
1	mRNA-1283.529	CCI	70
2		CCI	70

Enrollment in both parts of this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but no more than 50% of participants 56 years of age or older. Those with documented prior SARS-CoV-2 infection are eligible to participate if also previously vaccinated with mRNA-1273. Prior infection status will be confirmed by anti-nucleocapsid antibody testing of all participants.

Participants in both parts will have up to 6 study visits; 5 visits if screening and randomization are performed on the same day. Study vaccine will be administered as a single dose on Day 1. Additional safety and immunogenicity study visits will occur on Days 8 (safety call only), 15, 29, 181, and 366 (end of study [EoS]). Study visits will include scheduled safety phone calls every 2 weeks to collect MAAEs, AESIs, AEs leading to withdrawal, SAEs, and information about concomitant medications associated with these events, as well as to collect information about receipt of nonstudy vaccinations temporally associated with these events.

At the vaccination visit (Day 1), participants will be instructed how to document and report solicited ARs in a provided electronic diary. Solicited ARs will be assessed for 7 days after the injection (the day of injection and the following 6 days), and unsolicited AEs will be assessed for 28 days after each injection. Medically attended AEs, SAEs, AESIs, and AEs leading to withdrawal will be assessed throughout the study. All participants will be tested for the presence of SARS-CoV-2 anti-nucleocapsid antibodies at Days 1, 29, 181, and 366, as well as by nasopharyngeal swab RT-PCR on Days 1, 29, 181, and 366. Active surveillance for intercurrent or breakthrough SARS-CoV-2 infection will occur throughout the study and be reported as AEs (confirmed symptomatic infections will be reported as MAAEs if not an SAE). Symptomatic infection will be prompted by signs and symptoms meeting the US Centers for Disease Control and Prevention (CDC) case definition for coronavirus disease 2019 (COVID-19), as well as the clinical suspicion of the site investigator. Participants will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment. Participants will have blood sampled at scheduled study site visits (Days 1, 15, 29, 181, and 366) during the study for immunogenicity assessments or other medical concerns according to the investigator's judgment.

Participants may experience AEs, including symptoms of COVID-19, that necessitate an unscheduled visit. There may also be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms should be completed for each unscheduled visit. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

Safety Oversight: Blinded safety monitoring for this study will include study team members, inclusive of, at a minimum, the Sponsor medical monitor, Sponsor safety physician (from Pharmacovigilance), and contract research organization medical monitor. The study team will conduct ongoing safety reviews during the study and will be responsible for monitoring of safety concerns during the study, as described in the Safety Management Plan.

An independent Data Safety Monitoring Board, composed of external and independent subject matter experts and an unblinded statistician, will conduct unblinded reviews of safety data on an ad hoc basis as requested by the study team members.

An independent Cardiac Event Adjudication Committee that includes pediatric and adult cardiologists will review any suspect cases of myocarditis and pericarditis to determine if they meet CDC criteria of “probable” or “confirmed” events, and to assess severity.

Study Duration: Approximately 13 months for each participant.

Number of Participants: In Part A up to 420 participants previously vaccinated for COVID-19 with mRNA-1273 will receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or a single dose of the active comparator, mRNA-1273, in a 1:1:1:1:1:1 ratio, ie, up to 70 participants per treatment group. In Part B, up to 140 participants previously vaccinated with mRNA-1273 primary series and who also received an mRNA-1273 booster dose at least 3 months prior will receive a single boost of mRNA-1283.529 as the second booster dose at one of two dose levels in a 1:1 ratio, ie, up to 70 participants per dose level.

Study Eligibility Criteria:

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:

1. At least 18 years of age at the time of consent (Screening Visit).
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as bilateral tubal ligation > 1 year prior to screening, bilateral oophorectomy, hysterectomy, or menopause. Follicle-stimulating hormone level may be measured at the discretion of the investigator to confirm postmenopausal status.
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test on the day of vaccination (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
    - Has agreed to continue adequate contraception through 3 months following the last vaccine administration.
    - Is not currently breastfeeding.
    - Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration–approved contraceptive method in accordance with the product label.
6. Participant must have received their second dose of the mRNA-1273 primary series at least 6 months prior to screening and enrollment (Part A) or have received the mRNA-1273 series and an mRNA-1273 booster dose (50 ug) at least 3 months prior to screening and enrollment (Part B).

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study:

1. Had significant exposure to someone with SARS-CoV-2 infection or COVID-19 in the past 14 days, defined by the CDC as a close contact of someone who has COVID-19.
2. Is acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) less than 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled and will retain their initially assigned participant number.
3. Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care, to include significant change in therapy or hospitalization for worsening disease, at the discretion of the investigator.
4. 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.
5. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
6. Has a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus, immune-mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
7. Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to screening (for corticosteroids ≥ 10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.
8. Has received or plans to receive any licensed vaccine ≤ 28 days prior to the injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.
9. Has received systemic immunoglobulins or blood products within 3 months prior to the Screening Visit or plans to receive these during the study.
10. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
11. Plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.
12. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

Study Treatments:

Investigational Product, Dosage, and Mode of Administration:

The term "investigational product (IP)" refers to the mRNA-1283, mRNA-1283.211, mRNA-1283.529, and mRNA-1273 vaccines administered in this study.

The mRNA-1283 Drug Product is a lipid nanoparticle (LNP) dispersion containing a single messenger ribonucleic acid (mRNA) sequence that encodes a protein made up of 2 segments of the SARS-CoV-2 spike (S) protein: the N-terminal domain (NTD) and receptor-binding domain (RBD), which are linked together with a 7-amino-acid flexible linker. These three proteins (NTD, RBD, and linker) are attached to a 23-amino-acid transmembrane domain from influenza hemagglutinin (HATM) via a 5-amino-acid flexible linker. This entire protein makes up the NTD-RBD-HATM antigen and is encoded by mRNA-1283. The mRNA is combined in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: 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 (PEG-2000-DMG).

mRNA-1283 is provided as a sterile liquid for injection, as a white to off-white dispersion in appearance, at a concentration of 0.4 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate, at pH 7.5. mRNA-1283 is packaged in 2R US Pharmacopeia (USP) Type I borosilicate glass vials with a PLASCAP® vial seal containing a 13-mm FluroTec-coated plug stopper and has a 0.6-mL nominal fill volume.

mRNA-1273 is an LNP dispersion of an mRNA encoding the full-length prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs as described for mRNA-1283. mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM sodium acetate, at pH 7.5.

Each dose of IP will be prepared for each participant based on the treatment group. Each injection will have a volume of 0.25 mL. The vaccines will contain mRNA-1283 at the doses of CCI [redacted], mRNA-1283.211 at the doses of CCI [redacted], mRNA-1273 at the dose of CCI [redacted], and mRNA-1283.529 at the doses of CCI [redacted]. Vaccine preparation instructions are detailed in the mRNA-1283-P201 Pharmacy Manual.

Investigational product will be administered as an IM injection into the deltoid muscle on Day 1 according to the procedures specified in the Pharmacy Manual. Preferably, vaccine should be administered into the nondominant arm. Participants will be monitored for a

minimum of 30 minutes after vaccination. Assessments will include vital sign measurements and monitoring for local or systemic ARs.

Procedures and Assessments:

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant, according to the schedule of events (SoE):

- Solicited local and systemic ARs that occur during the 7 days following vaccination (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 vaccination (ie, the day of injection and 27 subsequent days).
- MAAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- AESIs from vaccination on Day 1 through EoS or withdrawal from the study.
- AEs leading to study participation withdrawal from Day 1 through EoS or withdrawal from the study.
- SAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- Vital sign measurements before and after vaccine administration
- Physical examination findings (if performed)
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

The incidence and severity of the above events will be monitored by the blinded study team members.

Immunogenicity Assessments:

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE. The following immunogenicity assessments will be measured:

- Serum binding antibody (bAb) level against SARS-CoV-2, as measured by ligand-binding assay specific to the SARS-CoV-2 S protein and the S protein RBD.
- Serum neutralizing antibody (nAb) level against SARS-CoV-2, as measured by pseudovirus neutralization assays.

- The above assays will include SARS-CoV-2 variant antigens, pseudotyped virus expressing SARS-CoV-2 S protein, or virus isolates to assess differences in immunologic responses to different SARS-CoV-2 variant S proteins.
- Testing for serologic markers for SARS-CoV-2 infection, as measured by anti-nucleocapsid antibodies detected by immunoassay at study enrollment (Day 1) and scheduled post-baseline time points.

Vaccine efficacy will not be formally assessed in this study, but active surveillance for COVID-19 and SARS-CoV-2 infection through monthly contact and scheduled blood collection will be performed.

Statistical Methods:

No formal hypotheses will be tested.

Sample Size Determination:

The sample size for this trial is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of each treatment group. In Part A, up to 420 participants will be randomized to 6 treatment arms in a 1:1:1:1:1:1 ratio to mRNA-1283 at three dose levels, mRNA-1283.211 at two dose levels, and mRNA-1273 at a single dose level, respectively (ie, up to 70 participants for each treatment group). In Part B, up to 140 participants will be enrolled in two treatment arms of mRNA-1283.529 in a 1:1 ratio. Enrollment in both parts of this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but not more than 50% of participants 56 years of age or older.

Analysis Sets:

Analysis sets are described below (same definition across part A and B if applicable)

Set	Description
Randomization Analysis Set (Part A)	The Randomization Analysis Set consists of all participants who are randomized. Randomization Analysis Set is applicable to Part A only.
Full Analysis Set (FAS)	The FAS consists of all randomized/enrolled (Part A: randomized, Part B: enrolled) participants who receive one dose of IP.
Per-Protocol (PP) Set for Immunogenicity	The PP Set for Immunogenicity consists of all participants in the FAS who receive the planned dose of IP and who have no major protocol deviations that impact key or critical data. The PP Set for Immunogenicity will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified.
Safety Set	The Safety Set consists of all randomized/enrolled (Part A: randomized, Part B: enrolled) participants who receive one dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the treatment group corresponding to the IP that they actually received.
Solicited Safety Set	The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the treatment group corresponding to the IP that they actually received.

Safety Analyses:

Part A and B:

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 treatment group. Participants will be included in the treatment group corresponding to the IP that they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs), unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after the single dose, and with Grade 3 or higher solicited AR will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR for each treatment group.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation will be summarized. Unsolicited AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

The number of events of solicited ARs, unsolicited AEs, SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be reported in summary tables accordingly. Vital signs and physical examination findings will be summarized. Pregnancy outcomes will also be summarized.

Immunogenicity Analyses:

Immunogenicity analyses will be performed based on the PP Set for Immunogenicity and provided by treatment group.

Analysis for the Primary Immunogenicity Objective:

Part A:

For the primary immunogenicity endpoints of levels of SARS-CoV-2–specific nAb and SARS-CoV-2–specific bAb against the SARS-CoV-2 prototype virus strain and against the variant strains including B.1.351, immune response of each treatment group will be assessed with respect to the mRNA-1273 CCI booster dose. An analysis of covariance (ANCOVA) model will be employed to compare immune response between each treatment group against

the mRNA-1273 CCI booster dose. Day 29 antibody titers (against prototype virus strain or the variant strain) will be included in the model as a dependent variable and treatment group variable (mRNA-1283 at each dose level, mRNA-1283.211 at each dose level, and mRNA-1273 CCI) will be included as fixed effect. The model will also adjust for age group (< 56, ≥ 56). The GMT will be estimated by the geometric least square mean (GLSM) from the model for each group and corresponding 95% CI will be provided. The ratio of GMTs for each treatment group with respect to mRNA-1273 CCI booster dose will be estimated by the ratio of GLSM from the model. The 95% CI for the ratio of GLSM will be provided to assess the between-groups difference (each treatment group against mRNA-1273 CCI booster dose) in immune response against the prototype strain (or B.1.351 variant strain).

The primary immunogenicity endpoints of the study will also be assessed by the vaccine seroresponse (definition to be provided in the statistical analysis plan [SAP]) against the SARS-CoV-2 prototype virus strain and against variant strains including B.1.351. The SRR with 95% CI at Day 29 will be summarized for each treatment group. The difference of SRRs and 95% CI at Day 29 will be calculated for mRNA-1283 at each dose level and mRNA-1283.211 at each dose level compared with mRNA-1273.

Part B:

The same analysis methods will be used to analyzed immunogenicity data for Part B, ANCOVA model will be used to compare immune response between treatment group CCI mRNA-1283.529) in Part B. Day 29 antibody titers (against variant strain B.1.1.529) will be included in the model as a dependent variable and treatment group variable (mRNA-1283.529 at each dose level) will be included as fixed effect. The model will also adjust for age group (< 56, ≥ 56). The GMT will be estimated by the GLSM from the model for each group and corresponding 95% CI will be provided. The ratio of GMTs for CCI mRNA-1283.529 with respect to CCI mRNA-1283.529 will be estimated by the ratio of GLSM from the model. The 95% CI for the ratio of GLSM will be provided to assess the between-groups difference in immune response against B.1.1.529.

SRR against B.1.1.529 with 95% CI at Day 29 will be summarized for each mRNA-1283.529 dose level . The difference of SRRs and 95% CI at Day 29 between two dose levels will also be calculated.

Analysis for the Secondary and Exploratory Immunogenicity Objectives:

Part A and B:

Immunogenicity, SARS-CoV-2–specific bAb and nAb, will be assessed at multiple time points in this study; however, Day 29, 28 days after booster dose, is the time point of primary interest.

For each of the antibodies of interest, eg, levels of SARS-CoV-2–specific bAb and SARS-CoV-2–specific nAb, the GMT or level with corresponding 95% CI at each time point and geometric mean folder rise of post-baseline/baseline titers or levels with corresponding 95% CI at each post-baseline time point will be provided by treatment group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values, then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: number of participants (n), median, minimum, and maximum.

The SRR of each treatment group against the prototype strain and variant strain, defined as the percentage of participants achieving seroresponse against the prototype strain and variant strain, respectively, will be provided for each treatment group with the 95% CI calculated using the Clopper-Pearson method at each post-baseline time point.

Subgroup Analyses:

Part A and B:

Subgroup analyses may include age and SARS-CoV-2 infection status at baseline depending on the sample size in a subgroup. Details will be provided in the SAP.

Efficacy Analysis:

Part A and B:

No pre-specified efficacy analysis will be performed. Exploratory analyses of symptomatic and asymptomatic SARS-CoV-2 infection by treatment group may be performed.

Planned Analyses:

Primary Analysis

The primary analysis of safety and immunogenicity will be conducted after Part A participants have completed their Day 29 visit assessments. The primary analysis will be performed by a separate team of unblinded programmers and statisticians. The analysis, including any cases of COVID-19, will be presented by treatment group. With the exception of appropriately delegated unblinded study staff, vaccine administrators, and monitors, all personnel involved in the conduct of the trial will remain blinded to individual treatment assignment until

unblinding. Investigators will be blinded until after the final database lock for final analysis. The protocol may be amended to further assess or confirm dose selection based on results of this analysis.

Interim Analysis

The interim analysis of safety and immunogenicity will be conducted after Part B participants have completed their Day 29 visit assessments. The interim analysis will be performed by study team programmers and statisticians.

Final Analysis

The final analysis of all endpoints will be performed after all participants (Part A and Part B) have completed all planned study procedures. Results of this analysis will be presented in a final clinical study report (CSR), including individual listings. The final CSR will include full analyses of all safety and immunogenicity data through Day 366 (Month 12).

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LIST OF ABBREVIATIONS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
CDC	US Centers for Disease Control and Prevention
CEAC	cardiac event adjudication committee
CFR	Code of Federal Regulations
cMRI	cardiac magnetic resonance imaging
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG/EKG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMFR	geometric mean fold rise
GMT	geometric mean titer

Abbreviation or Specialist Term	Definition
HATM	hemagglutinin
HCP	healthcare practitioner
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IM	intramuscular
IP	investigational product
IRB	institutional review board
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NP	nasopharyngeal
NTD	N-terminal domain
PEG-2000-DMG	1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PP	Per-Protocol
RBD	receptor-binding domain
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoE	schedule of events
SRR	seroresponse rate

Abbreviation or Specialist Term	Definition
USP	US Pharmacopeia
VOC	variant of concern
WHO	World Health Organization

GLOSSARY OF TERMS

Term/Concept	Definition
Adequate female contraception	Consistent and correct use of a Food and Drug Administration–approved contraceptive method in accordance with the product label.
AE	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
AESI	An AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required. A list of the AESIs pertinent to this study is provided in Section 10.4 (Appendix 4).
AR	Any AE for which there is a reasonable possibility that the vaccine caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine and the AE. Solicited ARs are defined in Section 7.4.3.
Anaphylaxis	An acute hypersensitivity reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Characteristics of anaphylaxis are provided in Section 7.4.4.
Asymptomatic SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of COVID-19 symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test at time of enrollment.
COVID-19 symptoms	• Fever (temperature ≥ 38.0°C [100.4°F]) or chills • Cough • Shortness of breath and/or difficulty breathing • Fatigue • Muscle or body aches • Headache • New loss of taste and/or smell • Sore throat, congestion, or runny nose • Nausea or vomiting

Term/Concept	Definition
	• Diarrhea
Phase 3 study (mRNA-1273-P301) definition of COVID-19	The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
End of Study (EoS)	Completion of the last visit of the last participant in the study or last scheduled procedure, as shown in the schedule of events (Table 8) for the last participant in the study.
Lost to follow-up (LTFU)	A participant who repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site.
MAAE	An AE that leads to an unscheduled visit to a healthcare provider.
Nonchildbearing potential	Surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to screening without an alternative medical cause).
Screen failures	Participants who consent to participate in the clinical study but are not subsequently assigned to treatment.
SAE	An AE is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes (see Section 7.4.2 for further details of each criterion): • Death • Is life-threatening • Inpatient hospitalization or prolongation of existing hospitalization • Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • Congenital anomaly or birth defect • Medically important event.

Term/Concept	Definition
Symptomatic COVID-19	The presence of one of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample.
Unsolicited AE	Any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, 7 days after vaccination).
Women of childbearing potential	Women of childbearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see Section 10.3, Appendix 3).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = US Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. INTRODUCTION

1.1. Study Rationale

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 and severe acute respiratory syndrome (SARS). An outbreak of a novel coronavirus (coronavirus disease 2019 [COVID-19], later designated severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) initially emerged in Wuhan, Hubei Province, China in December 2019. The World Health Organization (WHO) declared COVID-19 a pandemic on 11 Mar 2020, which continues to have major global public health impact with more than 200 million cases and 4.2 million deaths as of 10 Aug 2021 (WHO 2021).

ModernaTX, Inc. (the Sponsor)'s scalable messenger ribonucleic acid (mRNA)/lipid nanoparticle (LNP) technology platform allowed for a rapid response to the pandemic and was used to develop mRNA-1273, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes for the full-length SARS-CoV-2 spike (S) protein of the Wuhan-Hu-1 SARS-CoV-2 virus, modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the S protein into a prefusion conformation. Having achieved the primary endpoint in a pivotal Phase 3 study conducted in persons at high risk for SARS-CoV-2 infection, in December 2020, mRNA-1273 was granted Emergency Use Authorization (EUA) for the prevention of COVID-19 for individuals 18 years of age and older based on the demonstration of efficacy and safety in a pivotal Phase 3 trial (Baden et al 2021).

In addition to mRNA-1273, the Sponsor is using its mRNA-based platform to develop additional SARS-CoV-2 mRNA vaccine candidates that may have improved stability and/or may be as immunogenic as mRNA-1273 at a lower dose level. mRNA-1283 encodes for a protein made up of 2 segments, the SARS-CoV-2 N-terminal domain (NTD) and receptor-binding domain (RBD), which are linked together with a 7-amino-acid flexible linker. These three proteins (NTD, RBD, and linker) are attached to a 23-amino-acid transmembrane domain from influenza hemagglutinin (HATM) via a 5-amino-acid flexible linker. This entire protein makes up the NTD-RBD-HATM antigen and is encoded by mRNA-1283. The mRNA-1283-P101 Phase 1 study is ongoing (NCT04813796).

Over the course of the pandemic, SARS-CoV-2 variants have emerged and are likely to continue to emerge, some of which may prove to have some level of escape from immunity associated with previous infection or vaccination. The emergence of variants of concern (VOCs) or interest, as defined by the WHO (WHO 2021), are associated with increased infectivity and a reduction in the ability of convalescent sera or sera from vaccinated subjects to neutralize these emergent strain variants. Mutations occurring in the RBD are of particular concern, as this site includes the

dominant neutralization epitopes on the S protein, and these mutations could impact the effectiveness of antibodies elicited by infection or vaccination in neutralizing the virus (Greaney et al 2021).

These recent evolutionary events indicate that SARS-CoV-2 has the capacity to develop more efficient transmission between human hosts (Martin et al 2021) and vaccination strategies to control the virus need to be responsive to this evolution. A SARS-CoV-2 variant, B.1.1.7, rapidly spread from southeast England around the globe. Relative to the Wuhan viral isolate, B.1.1.7 includes 8 mutations located in the S protein, including the N501Y mutation occurring in the RBD. Early analyses indicate that B.1.1.7 has a substantial fitness advantage over other currently circulating lineages. The B.1.351 variant emerged in South Africa, and the P.1 lineage has recently been reported in Brazil. For the P.1 lineage, there are at least 11 mutations located in the S protein, 3 of which (K417N, E484K, and N501Y) are found in the RBD. More recently, SARS-CoV-2 variants emerged in India, and the B.1.617.2 variant (Delta variant) containing 2 mutations in the RBD (L452R and T478K) is now circulating globally. In vitro characterization of sera from individuals recently vaccinated with the 2-dose regimen of the Moderna COVID-19 vaccine at the 100 µg dose showed that the Moderna COVID-19 vaccine (mRNA-1273) produced neutralizing titers against key emerging variants tested, including B.1.1.7, B.1.351, and B.1.617.2 (Wang et al 2021, Wu et al 2021, Choi et al 2021). The studies showed no significant reduction in neutralizing titers against the B.1.1.7 relative to the prototype Wuhan-Hu-1 strain and a 2.1-fold reduction versus B.1.617.2; however, a greater than 6-fold reduction in neutralizing titers was observed against the B.1.351 variant relative to the Wuhan-Hu-1. There is clinical and epidemiologic evidence that these VOCs have increased virulence, resulting in higher rates of hospitalization and death (Abdool Karim et al 2021), and there is evidence of reduced vaccine efficacy against the B.1.351 virus from Phase 3 clinical trials with non-mRNA-based vaccines that enrolled participants in South Africa (Madhi et al 2021, Shinde et al 2021). Evidence of effectiveness for an mRNA-based vaccine was recently published, which demonstrated protection against the B.1.351 and B.1.1.7 variants after implementation of an mRNA COVID-19 vaccine in Qatar (Abu-Raddad et al 2021).

Based on the data acquired for mRNA-1273, available under the EUA, and leveraging the flexible nature of the mRNA-technology, the Sponsor is evaluating multiple mRNA vaccines to address emerging variants. The ongoing pandemic and waning or reduced immunity from vaccines or previous infection against VOCs necessitate the development of vaccines and vaccination strategies that induce broader protection to decrease morbidity, mortality, and transmission. Based on the available data and the potential importance to maintain efficacy against the prototype strain or variants more closely related to the B.1.351 strain, the Sponsor has developed a multivalent mRNA-1283 vaccine (mRNA-1283.211) composed of equal amounts of the mRNA-1283 prototype vaccine and mRNA-1283.351, which encodes for the B.1.351 RBD

and NTD of the SARS-CoV-2 S protein, to include in further evaluation of mRNA-1283 in a Phase 2a clinical trial.

Potent neutralizing antibodies (nAbs) to the RBD and NTD of SARS-CoV-2 have been described in the literature (Brouwer et al 2020, Liu et al 2020, Lv et al 2020) and support their inclusion in candidate vaccines for SARS-CoV-2. Animal challenge and protection studies have demonstrated protective responses elicited by RBD-based vaccines (Chen et al 2020, Yang et al 2020). The NTD and RBD are dominant targets for nAbs to SARS-CoV-2.

The primary objective of this study is to assess the immunogenicity and safety of mRNA-1283 and mRNA-1283.211 as a booster dose for those previously vaccinated with mRNA-1273.

1.2. Background and Overview

The Sponsor has developed a rapid-response, proprietary vaccine platform based on an 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.

1.2.1. mRNA-1283

In December 2020, mRNA-1273 was granted EUA for the prevention of COVID-19 for individuals 18 years of age and older based on the demonstration of efficacy and safety in a pivotal Phase 3 trial. The Sponsor is using its mRNA-based platform to develop mRNA-1283, a novel LNP-encapsulated, mRNA-based SARS-CoV-2 vaccine candidate that may have improved stability and/or may be as immunogenic as mRNA-1273 at a lower dose level.

1.2.2. mRNA-1283.211

This is a multivalent mRNA-1283 vaccine candidate composed of equal amounts of the mRNA-1283 prototype vaccine and mRNA-1283.351.

1.2.3. mRNA-1283.529

mRNA-1273.529 is a vaccine candidate containing an mRNA encoding for the RBD and NTD of the B.1.1.529 variant.

1.2.4. Nonclinical Studies

Previous nonclinical studies in Balb/c mice have been performed to evaluate dose ranging responses to mRNA-1283 (immunogenicity) versus mRNA-1273. These nonclinical studies in mice assessed immunogenicity by evaluating binding antibody (bAb) and nAb responses as well as Th1-directed CD4+ and CD8+ responses elicited by mRNA-1283. mRNA-1283 was shown to be immunogenic in Balb/c mice, demonstrating a bAb response and neutralization activity.

mRNA-1283–elicited CD4+ T-cells re-stimulated with S1 or S2 peptide pools exhibited a Th1-dominant response (production of interferon-γ, interleukin-2, tumor necrosis factor-α), as well as CD8+ T cells, particularly at higher immunogen doses.

The Sponsor has conducted preclinical evaluation of mRNA-1283 that has been modified to encode the SARS-CoV-2 B.1.351 VOC, which indicates reduced neutralization activity to the prototype strain. This loss of neutralizing activity is restored by a multivalent mRNA-1283.211 with mRNAs encoding both the prototype Wuhan-Hu-1 and B.1.351 sequences. Preclinical evaluations have also been performed to evaluate mRNA-1283 and mRNA-1283.211 as boosters in animals previously vaccinated with a 2-dose primary series of mRNA-1273 or mRNA-1283. All boosters significantly increase bAb and nAb titers, with mRNA-1283.211 increasing titers to the highest levels against the broadest panel of variants.

1.2.5. Clinical Studies

The mRNA-1283-P101 Phase 1 study is ongoing (NCT04813796).

1.3. Benefit/Risk Assessment

1.3.1. Known Potential Benefits

The following benefits may accrue to participants who receive the mRNA-1283 vaccines:

- The mRNA-1283 vaccines may provide an effective immune response against SARS-CoV-2 and VOCs.
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection and ongoing surveillance for COVID-19 throughout the study.
- The study will contribute to the development of a vaccine against COVID-19, a current pandemic disease.

1.3.2. Risks from Study Participation and Their Mitigation

Safety will be monitored throughout the study (Section 7.4).

The safety profile of mRNA-1283 has not been evaluated yet in clinical studies, although a Phase 1 study (NCT04813796) is ongoing.

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

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

Intramuscular (IM) injection with other mRNA vaccines manufactured by the Sponsor containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection.

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown. Further details are available in the mRNA-1283 Investigator's Brochure (IB).

mRNA-1273

The safety profile of mRNA-1273 is largely based on data from the pivotal Phase 3 study. The most frequently reported adverse reactions (ARs) after any dose in the vaccine group were pain at the injection site, fatigue, headache, myalgia, and chills. The most common solicited local AR was pain. The majority of local and systemic ARs had a median duration of 1 to 3 days. Overall, there was a higher reported rate of some ARs in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above.

Several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritus. These were most likely dermal hypersensitivity and were unlikely to represent a long-term safety concern. Hypersensitivity events included injection site rash and injection site urticaria, which are likely related to vaccination. There have been no cases of severe hypersensitivity or anaphylactic reactions reported immediately after vaccination in the trial to date. In the Post-Authorization setting, anaphylaxis has been reported following mRNA-1273 administration.

In addition, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with the Moderna COVID-19 vaccine. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Detailed

information about the known and expected benefits and risks of mRNA-1273 is provided in the IB.

1.3.3. Overall Benefit/Risk Conclusion

The evolving antigenic variation of SARS-CoV-2 underscores the urgent need for vaccination strategies that induce broader protection, specifically against VOCs with attendant risk of viral escape. The Sponsor is developing additional SARS-CoV-2 mRNA vaccine candidates that may have improved stability and/or may be as immunogenic as mRNA-1273 at a lower dose level. The present study will evaluate the safety and immunogenicity of these additional vaccine candidates.

2. OBJECTIVES AND ENDPOINTS

The objectives that will be evaluated in this study and the endpoints and time points associated with each objective are provided in Table 1.

Table 1: Part A Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of the study vaccine candidates	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period after vaccination • Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period after vaccination • Frequency of any serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal from study participation, and AEs of special interest (AESIs) from Day 1 to end of study (EoS)
• To assess the immunogenicity of the study vaccine candidates	• Immune response of the study vaccine candidates against the ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and against SARS-CoV-2 variants, including B.1.351, at Day 29 by geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroresponse rate (SRR) • To compare the immune response elicited by the mRNA-1283 study vaccine candidates with the immune response elicited by the mRNA-1273 vaccine when administered as a booster at Day 29 by GMT, GMFR, and SRR
Secondary	
• To evaluate the immunogenicity at all immunogenicity time points	• Immune response of the study vaccinecandidates against ancestral SARS-CoV-2 and against SARS-CoV-2 variants at all immunogenicity time points by GMT, GMFR, and SRR

Objectives	Endpoints
Exploratory	
• To characterize cellular immunogenicity	• Frequency, magnitude, and phenotype of antigen-specific B- and T-cells, to include B-cell and T-cell receptor repertoires
• To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed asymptomatic or symptomatic SARS-CoV-2 infection will be defined in participants: – Negative SARS-CoV-2 anti-nucleocapsid antibody blood test at Day 1 that becomes positive at Day 29 or later, OR – Positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swab
• To assess the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

Table 2: Part B Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of the mRNA-1283.529 booster vaccine candidate	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period after vaccination • Frequency and severity of any unsolicited AEs during the 28-day follow-up period after vaccination • Frequency of any SAEs, MAAEs, AEs leading to withdrawal from study participation, and AESIs from Day 1 to EoS
• To assess the immunogenicity of the mRNA-1283.529 booster vaccine candidate as the second booster dose	• Immune response of the mRNA-1283.529 booster vaccine candidate against SARS-CoV-2 Omicron variant (B.1.1.529) at Day 29 by GMT, GMFR, and SRR
Secondary	

Objectives	Endpoints
• To assess the immunogenicity at all immunogenicity time points	• Immune response of the mRNA-1283.529 vaccine candidate against the ancestral SARS-CoV-2 and against SARS-CoV-2 variants at all immunogenicity time points by GMT, GMFR, and SRR •
Exploratory	
• To characterize cellular immunogenicity	• Frequency, magnitude, and phenotype of antigen-specific B- and T-cells, to include B-cell and T-cell receptor repertoires
To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed asymptomatic or symptomatic SARS-CoV-2 infection will be defined in participants: – Negative SARS-CoV-2 anti-nucleocapsid antibody blood test at Day 1 that becomes positive at Day 29 or later, OR – Positive SARS-CoV-2 RT-PCR from nasopharyngeal swab
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

3. STUDY DESIGN

3.1. General Design

This is a Phase 2a study that consists two parts: Part A is an observer-blind, stratified, randomized design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283, mRNA-1283.211, mRNA-1273, and potentially of other study vaccine candidates administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273. Part B is an open-label design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283.529 administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273.

Part A of this study will assess whether a single dose of mRNA-1283 at three different doses CCI or mRNA-1283.211 at two different dose levels CCI will boost antibody responses to the Wuhan-Hu-1 (ancestral strain of SARS-CoV-2) virus, and to the B.1.351 variant, and potentially other SARS-CoV-2 variants, and it will also be used to select a dose for subsequent clinical evaluation. The study will include an active comparator group of participants who will receive mRNA-1273 CCI.

Participants in Part A who received the primary series of mRNA-1273 CCI with appropriate documentation at least 6 months prior will be randomized 1:1:1:1:1:1 to receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or a single dose of the active comparator, mRNA-1273 (**Error! Reference source not found.**).

Table 3: Part A Treatment Groups

Treatment Group	Vaccine	Dose Level[1]	N
1	mRNA-1283	CCI	70
2			70
3			70
4	mRNA-1283.211		70
5			70
6	mRNA-1273		70

[1] Dose levels for mRNA-1283.211 and mRNA-1273 are total mRNA in 1:1 ratio of mRNA-1283 and mRNA-1283.351 or mRNA-1273 and mRNA-1283.351, respectively.

Part B of this study will assess whether a single dose of mRNA-1283.529 as the second booster at two different dose levels CCI as the second booster after a first booster of mRNA-1273 CCI, at least 3 months prior, will boost antibody response to the ancestral strain of the SARS-CoV-2 virus, the B.1.1.529 variant, and potentially other SARS-CoV-2 variants, and

inform dose selection for mRNA-1283.529 booster vaccine candidate for subsequent clinical evaluation.

Participants in Part B who received the primary series of mRNA 1273 and who received a first booster dose of mRNA-1273 CCI at least 3 months prior will be enrolled in a 1:1 ratio to receive a single boost of mRNA 1283.529 at one of two dose levels (Table 4).

Table 4: Part B Treatment Groups

Treatment Group	Vaccine	Dose Level[1]	N
1	mRNA-1283.529	CCI	70
2		CCI	70

Enrollment in both parts of this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but not more than 50% of participants 56 years of age or older. Those with documented prior SARS-CoV-2 infection are eligible to participate if also previously vaccinated with mRNA-1273. Prior infection status will be confirmed by anti-nucleocapsid antibody testing of all participants.

The schedule of events (SoE) table is provided in Table 8. The SoE will be used for participants in both parts of the study. Participants will have up to 6 study visits; 5 visits if screening and randomization are performed on the same day. Study vaccine will be administered as a single dose on Day 1. Additional safety and immunogenicity study visits will occur on Days 8 (safety call only), 15, 29, 181, and 366 (EoS). Study visits will include scheduled safety phone calls every 2 weeks to collect MAAEs, AESIs, AEs leading to withdrawal, SAEs, and information about concomitant medications associated with these events, as well as to collect information about receipt of nonstudy vaccinations temporally associated with these events.

At the vaccination visit (Day 1), participants will be instructed how to document and report solicited ARs in a provided electronic diary (eDiary). Solicited ARs will be assessed for 7 days after the injection (the day of injection and the following 6 days), and unsolicited AEs will be assessed for 28 days after each injection. Medically attended AEs, SAEs, AESIs, and AEs leading to withdrawal will be assessed throughout the study. All participants will be tested for the presence of SARS-CoV-2 anti-nucleocapsid antibodies at Days 1, 29, 181, and 366, as well as by nasopharyngeal (NP) swab RT-PCR on Days 1, 29, 181, and 366. Active surveillance for intercurrent or breakthrough SARS-CoV-2 infection will occur throughout the study and be reported as AEs (confirmed symptomatic infections will be reported as MAAEs if not an SAE). Symptomatic infection will be prompted by signs and symptoms meeting the US Centers for Disease Control and Prevention (CDCb 2021) case definition for COVID-19 (05 Aug 2020 or most recent), as well as the clinical suspicion of the site investigator. Participants will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment. Participants will

have blood sampled at scheduled study site visits (Days 1, 15, 29, 181, and 366) during the study for immunogenicity assessments or other medical concerns according to the investigator's judgment.

Participants may experience AEs, including symptoms of COVID-19, that necessitate an unscheduled visit. There may also be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit. In addition, participants may have blood sampled at unscheduled visits for acute respiratory symptoms.

3.2. Scientific Rationale for Study Design

Part A of this study is designed as an observer-blind study. Part B of the study is designed as an open-label study.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection and post-injection blood samples for analysis of antibodies to nonvaccine antigens through 12 months after study injection. In addition, participants will have NP swab samples collected before vaccination on Day 1 as well as on Day 29, Day 181, and Day 366 (EoS). Furthermore, in case of any signs or symptoms or MAAEs suggesting SARS-CoV-2 infection in a participant, an additional NP swab sample and blood sample will be collected to confirm the diagnosis of SARS-CoV-2 via serology and RT-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 NP swab samples collected before study injection and the serologic assays performed for antibody responses to nonvaccine antigen(s) may help to discriminate between natural infection and vaccine-induced antibody responses, should such discrimination be needed.

3.3. Justification for Dose, Control Product, and Choice of Study Population

The safety and immunogenicity of mRNA-1283 vaccine is being assessed as a primary series administered in two doses administered 28 days apart at three different dose levels of CCI [redacted] in the mRNA-1283-P101 study. Data analysis has not been performed in that study. The dose levels for mRNA-1283 and mRNA-1283.211 were selected to assess the dose range for a booster dose indication based on data from pre-clinical studies of these vaccines and clinical data for mRNA-1273 administered as a booster dose.

This study will screen and enroll healthy adults, 18 years of age and above, who have previously been vaccinated with mRNA-1273.

3.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled procedure as shown in the SoE (Table 8).

The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure, as shown in the SoE (Table 8), for the last participant in the study.

4. STUDY POPULATION

In Part A, up to 420 participants previously vaccinated for COVID-19 with mRNA-1273 will receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or a single dose of the active comparator, mRNA-1273, in a 1:1:1:1:1:1 ratio, ie, up to 70 participants per treatment group.

In Part B, up to 140 participants will be enrolled in a 1:1 ratio to mRNA-1283.529 at two dose levels (ie, up to 70 participants for each treatment group).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria (Part A and Part B)

Each participant must meet all of the following criteria to be enrolled in this study:

1. At least 18 years of age at the time of consent (Screening Visit).
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as bilateral tubal ligation > 1 year prior to screening, bilateral oophorectomy, hysterectomy, or menopause. Follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test on the day of vaccination (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
    - Has agreed to continue adequate contraception through 3 months following the last vaccine administration.
    - Is not currently breastfeeding.
    - Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration (FDA)–approved contraceptive method in accordance with the product label.

6. Participant must have received their second dose of the mRNA-1273 primary series at least 6 months prior to screening and enrollment (Part A) or have received the mRNA-1273 series and an mRNA-1273 booster dose (50 ug) at least 3 months prior to screening and enrollment (Part B).

4.2. Exclusion Criteria (Part A and Part B)

Participants meeting any of the following criteria will be excluded from the study:

1. Had significant exposure to someone with SARS-CoV-2 infection or COVID-19 in the past 14 days, defined by the CDC (CDCa 2021) as a close contact of someone who has COVID-19.
2. Is acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) less than 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled and will retain their initially assigned participant number.
3. Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care, to include significant change in therapy or hospitalization for worsening disease, at the discretion of the investigator.
4. 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.
5. History of myocarditis, pericarditis, or myopericarditis within 2 months prior to Screening. Participants who have not returned to baseline after their convalescent period will also be excluded.
6. Has a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus, immune-mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
7. Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to screening (for corticosteroids ≥ 10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.
8. Has received or plans to receive any licensed vaccine ≤ 28 days prior to the injection (Day 1) or plans to receive a licensed vaccine within 28 days before or after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.
9. Has received systemic immunoglobulins or blood products within 3 months prior to the Screening Visit or plans to receive these during the study.

10. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
11. Plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.
12. Is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

4.3. Lifestyle Restrictions

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

4.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria, and information on any SAE that may have occurred from the time informed consent was obtained to the time of withdrawal.

5. STUDY TREATMENT

5.1. Investigational Products Administered

The term "investigational product (IP)" refers to the mRNA-1283, mRNA-1283.211, mRNA-1273, and mRNA-1283.529 vaccine candidates and mRNA-1273 vaccine administered in this study.

The mRNA-1283 Drug Product is an LNP dispersion containing a single mRNA sequence that encodes a protein made up of 2 segments of the SARS-CoV-2 S protein: the NTD and RBD, which are linked together with a 7-amino-acid flexible linker. These three proteins (NTD, RBD, and linker) are attached to a 23-amino-acid transmembrane domain from influenza HATM via a 5-amino-acid flexible linker. This entire protein makes up the NTD-RBD-HATM antigen and is encoded by mRNA-1283. The mRNA is combined in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: 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 (PEG-2000-DMG).

mRNA-1283 is provided as a sterile liquid for injection, as a white to off-white dispersion in appearance, at a concentration of 0.4 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate, at pH 7.5. mRNA-1283 is packaged in 2R US Pharmacopeia (USP) Type I borosilicate glass vials with a PLASCAP® vial seal containing a 13-mm FluroTec-coated plug stopper and has a 0.6-mL nominal fill volume.

mRNA-1273 is an LNP dispersion of an mRNA encoding the full-length prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs as described for mRNA-1283. mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM sodium acetate, at pH 7.5.

5.2. Randomization and Blinding

Randomization will be performed using an interactive response technology (IRT). Participants in Part A will be randomized in parallel according to a 1:1:1:1:1:1 ratio (Arm 1: Arm 2: Arm 3: Arm 4: Arm 5: Arm 6). Participants in Part B will be enrolled in the two arms sequentially. Enrollment in both parts of this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but not more than 50% of participants 56 years of age or older. All participants, study staff involved in participant assessment, and Sponsor personnel (or its designees) will be blinded to vaccination assignment until the EoS for Part A. Preparation of IP for administration will be conducted on site by an unblinded staff member who has no role in the observation or assessment of study participants. A limited number of Sponsor and/or contract research organization (CRO) personnel will be unblinded to perform Data Safety

Monitoring Board (DSMB) safety data reviews. Additional information regarding unblinding is provided in Section 5.3.8. Part B of the study is open-label and therefore unblinded.

5.3. Preparation/Handling/Storage/Accountability

5.3.1. Study Vaccine Preparation

Each dose of IP in Part Awill be prepared for each participant based on the treatment group. Each injection will have a volume of 0.25 mL. The vaccines will contain mRNA-1283 at the doses of CCI [redacted], mRNA-1283.211 at the doses of CCI [redacted], and mRNA-1273 at the dose of CCI [redacted].

Each dose of IP in Part B will be prepared for each participant based on the treatment group. Each injection will have a volume of 0.25 mL. The vaccines will contain mRNA-1283.529 at the doses of CCI [redacted].

Vaccine preparation instructions are detailed in the mRNA-1283-P201 Pharmacy Manual.

5.3.2. Study Vaccine Administration (Part A and Part B)

Investigational product will be administered as an IM injection into the deltoid muscle on Day 1. Preferably, vaccine should be administered into the nondominant arm.

On Day 1, participants will be monitored for a minimum of 30 minutes after vaccination. Assessments will include vital sign measurements and monitoring for local or systemic ARs as shown in the SoE (Table 8).

The study site will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either onsite resuscitation equipment or appropriate protocols for the rapid transport of a participant to a resuscitation area or facility are required.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP
- Confirming the appropriate labeling of the IP, so that it complies with the legal requirements of the United States

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the site, which includes the following:

- Confirming that the IP was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator’s designated storage location was appropriate

- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of IP are described in the mRNA-1283-P201 Pharmacy Manual.

5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of IP. Sterile mRNA-1283, mRNA-1283.211, and mRNA-1283.529 (0.4 mg/mL) are packaged in 2R glass vials with a 0.8-mL fill volume. Sterile mRNA-1273 (0.2 mg/mL) is packaged in 10R glass vials with a 6.3-mL fill volume. The IP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

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

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

5.3.5. Study Vaccine Storage

The mRNA-1283, mRNA-1283.211, and mRNA-1283.529 vaccine candidates must be stored at -90°C to -60°C (-130°F to -76°F) and the mRNA-1273 vaccines must be stored at -25°C to -15°C (-13°F to 5°F) in a secure area with limited access and protected from moisture and light until they are prepared for administration (Section 5.3.1). The freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup freezer. The freezer must be connected to a backup generator. In addition, IP accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any IP that was not temperature-controlled during shipment or storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods.

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

5.3.6. Study Vaccine Accountability

It is the investigator's responsibility that the IP accountability study staff maintain accurate records in an IP accountability log of receipt of all IP, site IP inventory, IP dispensing, IP injections, and return to the Sponsor or alternative disposition of used and unused IP vials.

A 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-1283-P201 Pharmacy Manual.

5.3.7. Study Vaccine Handling and Disposal

A site monitor will reconcile the IP inventory during the conduct and at the EoS for compliance. Once fully reconciled at the site at the EoS, the IP should be destroyed on site, if site procedures allow, or returned to a destruction depot per instruction of the Sponsor. Additional details are found in the mRNA-1283-P201 Pharmacy Manual.

5.3.8. Unblinding (Part A)

Part A of this study is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the EoS for Part A, with the following exceptions:

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare IP for all participants. These 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 IP 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 medically qualified study site personnel will administer the IP. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- The DSMB will review unblinded statistical outputs for ad hoc safety reviews triggered by pause rules, should this occur. See Section 10.2.11 for additional information on DSMB and safety review.
- The pre-identified Sponsor team members will become unblinded to treatment group after primary analysis, but not to individual study participant receipt of study vaccine.

Except in the case of a medical necessity, a participant's treatment assignment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the investigator will make every attempt to contact the CRO medical monitor to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblinding instances will be tracked via an audit trail in IRT and documented in the final study report.

5.4. Study Intervention Compliance

All doses of IP will be administered at the study site under direct observation of medically qualified study staff and appropriately recorded (date and time) in the eCRF. Qualified staff will confirm that the participant has received the entire dose of IP. If a participant does not receive IP or does not receive all of the planned dose, the reason for the missed dose will be recorded. Data will be reconciled with site accountability records to assess compliance.

5.5. Prior and Concomitant Medications (Part A and Part B)

5.5.1. 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.

5.5.2. Concomitant Medications and Therapies

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

- All nonstudy vaccinations administered within the period starting 28 days before the study injection.
- Seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).
- All concomitant medications and nonstudy vaccinations taken through 28 days after vaccination. 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 used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE or an MAAE.
- The 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 vaccination, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the post-injection study visits or via other participant interactions (eg, telephone calls).

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.

5.5.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses

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 evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 8.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP 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 ≥ 10 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).
- An authorized or licensed vaccine administered during the period from 28 days before through 28 days after vaccination, except for any licensed influenza vaccine that was administered 14 days before or after vaccination.

- Immunoglobulins and/or any blood products administered during the study period.

5.6. Intervention After the End of the Study

Study intervention will not be available to participants after the EoS.

6. DELAY OR DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1. Criteria for Delay of Vaccine Administration

Body temperature must be measured before vaccination. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for vaccination, the participant may be injected at a later date within the time window specified in the SoE (Table 8), or the participant may be discontinued from vaccination at the discretion of the investigator (Section 6.2):

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

Afebrile participants with minor illnesses can be vaccinated at the discretion of the investigator. Participants with a fever of 38.0°C (100.4°F) or higher will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of vaccination temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

6.2. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If a participant desires to withdraw from the study because of an AE, the investigator will attempt to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EoS eCRF.

Information related to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify)
- AESI (specify)

- SAE (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs and AESIs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow up with participants who are withdrawn from the study as a result of an SAE or AE until resolution of the event.

A participant withdrawing from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

6.3. Lost to Follow-up

A participant will be considered LTFU 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 clinic 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 LTFU, 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 medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

7. STUDY ASSESSMENTS AND PROCEDURES (PART A AND PART B)

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the SoE (Table 8). A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, 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.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window specified in the SoE (Table 8). 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.

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 home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoE (Table 8). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as a part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided that the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoE (Table 8).

- The Screening Visit and Day 1 visit may be completed on the same day.

7.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE (Table 8). The following immunogenicity assessments will be measured:

- Serum bAb level against SARS-CoV-2, as measured by ligand-binding assay specific to the SARS-CoV-2 S protein and the S protein RBD.
- Serum nAb level against SARS-CoV-2, as measured by pseudovirus neutralization assays.
- The above assays will include SARS-CoV-2 variant antigens, pseudotyped virus expressing SARS-CoV-2 S protein, or virus isolates to assess differences in immunologic responses to different SARS-CoV-2 variant S proteins.
- Testing for serologic markers for SARS-CoV-2 infection, as measured by anti-nucleocapsid antibodies detected by immunoassay at study enrollment (Day 1) and scheduled post-baseline time points.

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Measurement of bAb and nAb levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 10.2.6), 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 CoVs.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

7.2. Efficacy Assessments

Vaccine efficacy will not be formally assessed in this study, but active surveillance for COVID-19 and SARS-CoV-2 infection through monthly contact and scheduled blood collection (see Table 8) will be performed.

7.3. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoE (Table 8):

- Solicited local and systemic ARs (Section 7.4.3) that occur during the 7 days following vaccination (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 7.3.1).
- Unsolicited AEs observed or reported during the 28 days following vaccination (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 7.4.1.
- MAAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- AESIs from vaccination on Day 1 through EoS or withdrawal from the study.
- AEs leading to withdrawal from Day 1 through EoS .
- SAEs from vaccination on Day 1 through EoS or withdrawal from the study.
- Vital sign measurements before and after vaccine administration
- Physical examination findings (if performed)
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study (Section 7.4.6).

The incidence and severity of the above events will be monitored by the blinded study team members (Section 7.5).

7.3.1. 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 will be 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 7.4.3) on Day 1.

On Day 1 (vaccination day), participants will be instructed 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.

On Day 1 (vaccination day), participants will record data into the eDiary starting approximately 30 minutes after the injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. 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 7.4.3, that occur on the day of vaccination and during the 7 days after vaccination (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 it has resolved, and not to exceed 28 days after vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
- 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.
- Other measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever on Day 1 or for the next 6 days.

The eDiary will be the only source document 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 AR) 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 during the safety call 7 days after vaccination.

The eDiary will also be used every 2 weeks from Day 36 to Day 162 and from Day 202 to Day 342 to capture the occurrence of MAAEs, AESIs, SAEs, or AEs leading to withdrawal. 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, AESIs, 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.

Apart from the safety telephone calls described in Section 7.3.2 at Day 8 and every 2 weeks starting from Day 43 to Day 169 and from Day 209 to Day 349, each participant will complete a questionnaire in an eDiary for Day 36 to Day 162 and from Day 202 to Day 342 (Table 8). The eDiary responses will be reviewed by study site personnel and may result in a follow-up safety call by the site to the participant.

7.3.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants to assess body temperature and injection site reactions, respectively, for recording solicited ARs in the eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

7.3.2. Safety Telephone Call

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow an approved script, which will facilitate the collection of relevant safety information. There will be a safety telephone call on Day 8 for each participant to discuss their health and review their eDiary. Safety calls by the site to each participant will occur on Day 8 and every 2 weeks from Day 43 to Day 169 and from Day 209 to Day 349 (Table 8). The participant will be interviewed according to the script about the occurrence of AEs, MAAEs, AESIs, AEs leading to withdrawal, SAEs, concomitant medications associated with those events, and any nonstudy vaccinations temporally associated with these events (Section 7.4.7). In addition, study personnel will collect information on known participant exposure to someone

with COVID-19 or SARS-CoV-2 infection and on the participant's experience of COVID-19 symptoms. All safety information collected from the telephone call must be documented in the source documents as described by the participant and not documented on the script used for the safety telephone contact. As noted in Section 7.3.1, an unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

7.3.3. Laboratory Assessments

No routine safety laboratory assessments are planned for this study.

A point-of-care urine pregnancy test will be performed at Day 1 before vaccination. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. If postmenopausal status is not documented in a female participant's medical records, an FSH test to confirm may be performed at the Screening Visit, as necessary and at the discretion of the investigator, to confirm postmenopausal status.

7.3.4. 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 SoE (Table 8). Vital signs are to be collected pre- and post-vaccination on the day of injection (Day 1) only. 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 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses may be vaccinated at the discretion of the investigator.

7.3.5. Physical Examinations

A full physical examination, including height and weight, will be performed at Day 1 as indicated in the SoE (Table 8). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On the day of vaccination, before injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated.

7.3.6. Assessment for SARS-CoV-2 Infection

Participants will have NP samples collected for SARS-CoV-2 testing at time points specified in the SoE (Table 8).

A study illness visit or a consultation will be arranged within 24 hours or as soon as possible to collect an NP swab (Table 8, Unscheduled Visit [UNS]) to ascertain the presence of SARS-CoV-2 via RT-PCR if a participant experiences any of the following (the presence of any one of these symptoms lasting at least 48 hours [except for fever and/or respiratory symptoms]):

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDCb 2021), including:
  - Fever (temperature ≥ 38.0°C [100.4°F]) or chills (of any duration, including ≤ 48 hours)
  - Cough (of any duration, including ≤ 48 hours)
  - Shortness of breath and/or difficulty breathing (of any duration, including ≤ 48 hours)
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste and/or smell
  - Sore throat, congestion, or runny nose
  - Nausea or vomiting
  - Diarrhea
- MAAE suggesting a SARS-CoV-2 infection
- Clinical or radiographical evidence of pneumonia

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

It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 or mRNA-1283 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgment to decide whether an NP swab should be collected. The collection of an NP swab prior to the Day 1 vaccination can help ensure

that cases of COVID-19 are not overlooked. Any study participant reporting respiratory symptoms during the 7-day period after vaccination should be evaluated for COVID-19.

If scheduled, a study site illness visit may include additional assessments such as medical history, physical examination, and blood sampling for clinical laboratory testing. The NP swab sample may be tested by multiplex RT-PCR for respiratory viruses besides 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.

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. Participants who are hospitalized for COVID-19 without the opportunity for a clinic visit will also be considered cases, assuming that the symptomology criteria for COVID-19 are met and a respiratory sample is positive for SARS-CoV-2 by PCR at a Clinical Laboratory Improvement Amendments (CLIA)-certified or CLIA-certified waiver laboratory. Investigators are encouraged to try to obtain a respiratory sample during the course of hospitalization for submission to the study central laboratory, if feasible.

Symptomatic COVID-19 is defined by the presence of one of the CDC-listed symptoms (CDC 2021b) and a positive RT-PCR test on a respiratory sample. Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test result at the time of enrollment, with the serologic assay detecting previously resolved SARS-CoV-2 infections that may have occurred between visits, and the RT-PCR to detect active viral infection at the time of a visit. If participants are confirmed to have SARS-CoV-2 infection and are symptomatic or asymptomatic, the investigator will notify the participants' primary care physicians of the diagnosis and the local public health authorities as required per local regulations.

If the participant had known exposure to COVID-19 (eg, exposure to someone with a confirmed case of COVID-19), it will be captured in the COVID-19 exposure form, and the participant will continue to follow all remaining study assessments as scheduled. Likewise, participants with a confirmed case of COVID-19 will continue to follow all remaining study assessments as scheduled.

Any confirmed symptomatic COVID-19 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

7.4. Safety Definitions and Related Procedures

7.4.1. 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.

Events Meeting the Adverse Event Definition

- 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 vaccination even though they may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

- Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure).
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be 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 vaccine caused the AE (Section 7.4.3). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine 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 but starts outside the protocol-defined period for reporting solicited ARs (ie, 7 days after vaccination).

7.4.2. Serious Adverse Events

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 the IP.
- **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.

7.4.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 7.3.1). Participants will record such occurrences in an eDiary during the 7 days after vaccination (ie, the day of injection and 6 subsequent days).

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 5 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 vaccination, the participant will be prompted daily to capture solicited local or systemic AR in the eDiary until resolution. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed by the study staff either via phone call or at the next study visit. All solicited ARs (local and systemic) will be considered causally related to vaccination.

Table 5: 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

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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/ 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

Note: Events listed above but starting > 7 days after study injection will be recorded on the AE CRF. Causality for each event will be determined per assessment by the investigator.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff on the solicited AR page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP), to be recorded as an MAAE (Section 7.4.4)
- 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 otherwise meets the definition of an SAE

7.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory follow-up, COVID-19 [Section 7.3.6]) 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. Unsolicited AEs will be captured on the AE page of the eCRF.

All confirmed COVID-19 cases will be recorded as MAAEs.

All suspected cases of anaphylaxis should be recorded as MAAEs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours per Section 7.4.11. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as follows) should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:
  - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, and red and itchy eyes.
  - **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, and evidence of reduced peripheral circulation.
  - **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress,

persistent dry cough, hoarse voice, sensation of throat closure, sneezing, and rhinorrhea.

- **Gastrointestinal:** diarrhea, abdominal pain, nausea, and vomiting.

7.4.5. Adverse Event of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the investigator to the Sponsor is required. Such events may require further investigation to characterize and understand them. Section 10.4 (Appendix 4) provides a list of AESIs pertinent to vaccine mRNA-1273. All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the electronic data capture (EDC) system. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI and the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11).

7.4.5.1. Myocarditis and/or Pericarditis

Very rare events of myocarditis and/or pericarditis have been reported after vaccination with the mRNA-1273 vaccine. All suspected cases of probable and confirmed myocarditis, pericarditis or myopericarditis should be recorded as an AESI and reported as an SAE, if the event meets seriousness criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 7.4.11. The investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. For reporting purposes, any event suspicious for myocarditis, pericarditis, or myopericarditis should be reported as an AESI. The CDC case definition is displayed below as guidance (Gargano et al 2021). However, any suspected case should be reported, even if it does not fulfil the criteria to be identified as a probable or confirmed case of acute myocarditis, or as a case of acute pericarditis. These definitions are intended to serve as a guide to help reporting of suspected cases of myocarditis, pericarditis, or myopericarditis, but the diagnosis of suspected cases are left to the investigator's clinical judgment.

7.4.5.2. Acute Myocarditis Case Definition

Presence of ≥ 1 new or worsening of the following clinical symptoms:

- Chest pain/pressure/discomfort
- Dyspnea/shortness of breath/pain with breathing
- Palpitations

- Syncope

AND

For probable case:

≥ 1 new finding of:

- Troponin level above upper limit of normal (any type of troponin)
- Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis
  - To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of:
    - ST segment or T-wave abnormalities
    - Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias
    - AV nodal conduction delays or intraventricular conduction defects
- Abnormal cardiac function or wall motion abnormalities on echocardiogram
- Cardiac magnetic resonance imaging (cMRI) finding consistent with myocarditis (Ferreira et al 2018)

AND

- No other identifiable cause of the symptoms and findings

For confirmed case:

- Histopathologic confirmation of myocarditis (using Dallas criteria [Aretz 1987])

OR

- cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)

AND

- No other identifiable cause of the symptoms and findings

7.4.5.3. Acute Pericarditis Case Definition

Presence of ≥ 2 new or worsening of the following clinical features (Adler et al 2015):

- Acute chest pain (typically described as pain made worse by lying down, deep inspiration, or cough and relieved by sitting up or leaning forward, although other types of chest pain may occur)
- Pericardial rub on examination

- New ST-elevation or PR-depression on EKG
- New or worsening pericardial effusion on echocardiogram or cMRI

7.4.5.4. Case Definition of Myopericarditis

Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis.

An independent cardiac event adjudication committee (CEAC) that includes pediatric and adult cardiologists will review any suspect cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, which will then make a final decision on whether to suspend further enrollment and/or study vaccination based on assessment of the overall potential risk to study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

7.4.6. Recording and Follow-up of Pregnancy

Female participants who have a positive pregnancy test at screening should not be enrolled; participants who have a positive pregnancy test at any time during the study should receive no further vaccination with IP but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). 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.

7.4.7. 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.

Solicited ARs will be collected from Day 1 through 7 days after vaccination. Other (unsolicited) AEs will be collected from Day 1 through 28 days after vaccination.

The MAAEs, AESIs, AEs leading to withdrawal, and SAEs will be collected from participants as specified in the SoE (Table 8) until the end of their participation in the study. Any AEs occurring before receipt of IP will be analyzed separately from AEs occurring after receipt of the study vaccine.

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 (including COVID-19 symptoms) 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 nonstudy vaccinations.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 6.3).

7.4.8. Assessment of Intensity

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 7.4.2), 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. 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 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 Section 7.4.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation 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. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

7.4.9. Assessment of Causality

The investigator's assessment of an AE's relationship to IP 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 IP 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 IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

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

7.4.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP 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 type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, 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 of screening 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.

7.4.11. Reporting SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

Any AE considered serious by the investigator or that meets SAE criteria (Section 7.4.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in 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

Regulatory reporting requirements for SAEs are described in Section 7.4.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to IP or study procedures, or that caused the participant to discontinue the study.

Any SAE occurring after the EoS and considered to be caused by the study vaccine must be reported to the Sponsor.

7.4.12. Time Period and Frequency for Collecting AE, AESI, and SAE Information

Medical occurrences that begin before IP administration but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant
- Questioning the participant in an unbiased and nonleading manner

Solicited AEs will be collected from the day of injection through 6 days after vaccination. Other (unsolicited) AEs will be collected from the day of injection through 28 days after vaccination.

Serious AEs (including AESIs) will be collected from the start of IP administration until the last day of study participation.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE or AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11).

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to study drug discontinuation or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after EoS participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

7.4.13. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for

the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.4.14. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 6.3.

7.4.15. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious ARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

7.5. Safety Monitoring

Safety monitoring for this study will include an unblinded DSMB.

Blinded safety monitoring for this study will include study team members, inclusive of, at a minimum, the Sponsor medical monitor, Sponsor safety physician (from Pharmacovigilance), and CRO medical monitor. The study team will conduct ongoing safety reviews during the study and will be responsible to monitor for safety concerns during the study as described in the Safety Management Plan.

An independent CEAC that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity.

7.6. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 10.2.8).

7.7. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

7.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.9. Biomarkers

Immunogenicity assessments are described in Section 7.1. Biomarkers are not evaluated in this study.

7.10. Health Economics

Health economics are not evaluated in this study.

8. 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. If changes are made to primary and/or key secondary objectives or the related statistical methods after the study has begun, 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.

8.1. Blinding and Responsibility for Analyses

Blinding during the study will be conducted as described in Section 5.2. The Sponsor Biostatistics Department or designee will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented via an IRT.

Participant-level unblinding at the time of the primary analysis will be restricted to an independent unblinded statistician and, as needed, a statistical programmer who will perform the primary analysis, who will have no other responsibilities associated with the study.

The planned study analyses are described in Section 8.6.

8.2. Statistical Hypotheses

No formal hypotheses will be tested.

8.3. Sample Size Determination

The sample size for this trial is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of each treatment group. In Part A, up to 420 participants will be randomized to 6 treatment arms in a 1:1:1:1:1:1 ratio to mRNA-1283 at three dose levels, mRNA-1283.211 at two dose levels, and mRNA-1273 at a single dose level, respectively (ie, up to 70 participants for each treatment group). In Part B, up to 140 participants will be enrolled in a 1:1 ratio to mRNA-1283.529 at two dose levels (ie, up to 70 participants for each treatment group). Enrollment in both parts of this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but not more than 50% of participants 56 years of age or older.

8.4. Analysis Sets

The analysis sets are described in Table 6.

Table 6: Analysis Sets (same definition across part A and B if applicable)

Set	Description
Randomization Analysis Set (Part A)	The Randomization Analysis Set consists of all participants who are randomized. Randomization Analysis Set is applicable to Part A only.
Full Analysis Set (FAS)	The FAS consists of all randomized/enrolled (Part A: randomized, Part B: enrolled) participants who receive one dose of IP.
Per-Protocol (PP) Set for Immunogenicity	The PP Set for Immunogenicity consists of all participants in the FAS who receive the planned dose of IP and who have no major protocol deviations that impact key or critical data. The PP Set for Immunogenicity will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified.
Safety Set	The Safety Set consists of all randomized/enrolled (Part A: randomized, Part B: enrolled) participants who receive one dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the treatment group corresponding to the IP that they actually received.
Solicited Safety Set	The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the treatment group corresponding to the IP that they actually received.

8.5. Statistical Methods

8.5.1. Baseline Characteristics and Demographics

Part A and B:

Demographic variables (eg, age, gender, race, ethnicity, height, weight, and body mass index) and baseline characteristics will be summarized by treatment group and overall. Summary statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables) will be provided.

8.5.2. Efficacy Analysis

Part A and B:

No pre-specified efficacy analysis will be performed. Exploratory analyses of symptomatic and asymptomatic SARS-CoV-2 infection by treatment group may be performed.

8.5.3. Safety Analyses

Part A and B:

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 treatment group. Participants will be included in the treatment group corresponding to the IP that they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs), unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after the single dose, and with Grade 3 or higher solicited AR will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR for each treatment group.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation will be summarized. Unsolicited AEs will be presented by MedDRA system organ class and preferred term. Unsolicited AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

The number of events of solicited ARs, unsolicited AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be reported in summary tables accordingly. Vital signs and physical examination findings will be summarized. Pregnancy outcomes will also be summarized.

Table 7 summarizes the analysis strategy for safety parameters. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Table 7: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI for Each Treatment Group
Any Solicited AR (overall and by local, systemic)	X	X
Any Unsolicited AE	X	—
Any SAE	X	—
Any Unsolicited MAAE	X	—
Any Unsolicited AESI	X	—
Any Unsolicited Treatment-Related AE	X	—
Any Treatment-Related SAE	X	—
Any Unsolicited AE Leading to Withdrawal from Study Participation	X	—
Any Severe Unsolicited AE	X	—
Any Treatment-Related Severe Unsolicited AE	X	—

Abbreviations: AE = adverse event; AESI = adverse event of special interest; 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.

8.5.4. Immunogenicity Analyses

Immunogenicity analyses will be performed based on the PP Set for Immunogenicity and provided by treatment group.

8.5.4.1. Analysis for the Primary Immunogenicity Objective

Part A:

For the primary immunogenicity endpoints of levels of SARS-CoV-2–specific nAb and SARS-CoV-2–specific bAb against the SARS-CoV-2 prototype virus strain and against the variant strains including B.1.351, immune response of each treatment group will be assessed with respect to the mRNA-1273 CCI booster dose. An analysis of covariance (ANCOVA) model will be employed to compare immune response between each treatment group against the mRNA-1273 CCI booster dose. Day 29 antibody titers (against prototype virus strain or the variant strain) will be included in the model as a dependent variable and treatment group variable (mRNA-1283 at each dose level, mRNA-1283.211 at each dose level, and mRNA-1273 CCI) will be included as fixed effect. The model will also adjust for age group (< 56, ≥ 56). The geometric mean titer (GMT) will be estimated by the geometric least square mean (GLSM) from the model for each group and corresponding 95% CI will be provided. The ratio of GMTs for each treatment group with respect to the mRNA-1273 CCI booster dose will be estimated by the ratio of GLSM from the model. The 95% CI for the ratio of GLSM will be provided to assess

the between-groups difference (each treatment group against mRNA-1273 CCI booster dose) in immune response against the prototype strain (or variant strain).

The primary immunogenicity endpoints of the study will also be assessed by the vaccine seroresponse (definition to be provided in the SAP) against the SARS-CoV-2 prototype virus strain and against variant strains including B.1.351. The seroresponse rate (SRR) with 95% CI at Day 29 will be summarized for each treatment group. The difference of SRRs and 95% CI at Day 29 will be calculated for mRNA-1283 at each dose level and mRNA-1283.211 at each dose level compared with mRNA-1273.

Part B:

The same analysis methods will be used to analyzed immunogenicity data for Part B. An ANCOVA model will be used to compare immune response between treatment group (CCI mRNA-1283.529) in Part B. Day 29 antibody titers against B.1.1.529 will be included in the model as a dependent variable and treatment group variable (mRNA-1283.529 at each dose level) will be included as fixed effect. The model will also adjust for age group (< 56, ≥ 56). The GMT will be estimated by the GLSM from the model for each group and corresponding 95% CI will be provided. The ratio of GMTs for CCI mRNA-1283.529 with respect to CCI mRNA-1283.529 booster dose will be estimated by the ratio of GLSM from the model. The 95% CI for the ratio of GLSM will be provided to assess the between-groups difference in immune response against B.1.1.529.

SRR against B.1.1.529 with 95% CI at Day 29 will be summarized for each mRNA-1283.529 dose level The difference of SRRs and 95% CI at Day 29 between two dose levels will also be calculated.

8.5.4.2. Analysis for the Secondary and Exploratory Immunogenicity Objectives

Part A and B:

Immunogenicity, SARS-CoV-2–specific bAb and nAb, will be assessed at multiple time points in this study; however, Day 29, 28 days after booster dose, is the time point of primary interest.

For each of the antibodies of interest, eg, levels of SARS-CoV-2–specific bAb and SARS-CoV-2–specific nAb, the GMT or level with corresponding 95% CI at each time point and geometric mean fold rise (GMFR) of post-baseline/baseline titers or levels with corresponding 95% CI at each post-baseline time point will be provided by treatment group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values, then back-transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: number of participants (n), median, minimum, and maximum.

The SRR of each treatment group against the prototype strain and variant strain, defined as the percentage of participants achieving seroresponse against the prototype strain and variant strain, respectively, will be provided for each treatment group with the 95% CI calculated using the Clopper-Pearson method at each post-baseline time point.

8.5.5. Subgroup Analyses

Part A and B:

Subgroup analyses may include age and SARS-CoV-2 infection status at baseline depending on the sample size in a subgroup. Details will be provided in the SAP.

8.6. Planned Analyses

8.6.1. Primary Analysis

The primary analysis of safety and immunogenicity will be conducted after Part A participants have completed their Day 29 visit assessments. The primary analysis will be performed by a separate team of unblinded programmers and statisticians. The analysis, including any cases of COVID-19, will be presented by treatment group. With the exception of appropriately delegated unblinded study staff, vaccine administrators, and monitors, all personnel involved in the conduct of the trial will remain blinded to individual treatment assignment until unblinding. Investigators will be blinded until after the final database lock for final analysis. The protocol may be amended to further assess or confirm dose selection based on results of this analysis.

8.6.2. Interim Analysis

The interim analysis of safety and immunogenicity will be conducted after Part B participants have completed their Day 29 visit assessments. The interim analysis will be performed by study team programmers and statisticians.

8.6.3. Final Analysis

The final analysis of all endpoints will be performed after all participants (Part A and Part B) have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings. The final CSR will include full analyses of all safety and immunogenicity data through Day 366 (Month 12).

9. REFERENCES

Abdool Karim SS, de Oliveira T. New SARS-CoV-2 variants – clinical, public health, and vaccine implications. N Engl J Med. 2021 May 13;384(19):1866-8.

Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants [correspondence]. N Engl J Med. 2021 Jul 8;385(2):187-9.

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015 Nov 7;36(42):2921-64.

Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol. 1987 Jun;18(6):619-24.

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021 Feb 4;384(5):403-16.

Brouwer PJM, Caniels TG, van der Straten K, Snitselaar JL, Aldon Y, Bangaru S, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. Science. 2020 Aug 7;369(6504):643-50.

Centers for Disease Control and Prevention (CDCa). Coronavirus Disease 2019 (COVID-19): Contact Tracing [Internet]. Atlanta (GA): CDC [cited 2021 Aug 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/contact-tracing-plan/appendix.html

Centers for Disease Control and Prevention (CDCb). Coronavirus Disease 2019 (COVID-19) 2021 Case Definition [Internet]. Atlanta (GA): CDC [cited 2021 Aug 20]. Available from: https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/

Chen WH, Tao X, Agrawal AS, Algaissi A, Peng B-H, Pollet J, et al. Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with aluminum hydroxide induces protective immunity and reduces immune enhancement. Vaccine. 2020 Nov 3;38(47):7533-41.

Choi A, Koch M, Wu K, Dixon G, Oestreicher J, Legault H, et al. Serum neutralizing activity of mRNA-1273 against SARS-CoV-2 variants. bioRxiv [Preprint]. 2021 June 28 doi: https://doi.org/10.1101/2021.06.28.449914.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for Industry, Investigators, and Institutional

Review Boards: Conduct of clinical trials of medical products during the COVID-19 public health emergency. January 27, 2021 [cited 2021 Aug 20] [38 screens]. Available from: https://www.fda.gov/media/136238/download.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for Industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 2020 Oct 28] [10 screens]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018 Dec 18;72(24):3158-76.

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021 Jul 9;70(27):977-82.

Greaney AJ, Loes AN, Crawford KHD, Starr TN, Malone KD, Chu HY, et al. Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe. 2021 Mar 10;29(3):463-76.e6.

Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature. 2020 Aug;584(7821):450-6.

Lv Z, Deng Y-Q, Ye Q, Cao L, Sun C-Y, Fan C, et al. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Science. 2020 Sep 18;369(6510):1505-9.

Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al; NGS-SA Group; Wits–VIDA COVID Group. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021 May;384(20):1885-98.

Martin MA, VanInsberghe D, Koelle K. Insights from SARS-CoV-2 sequences. Science. 2021 Jan 29;371(6528):466-7.

Rüggeberg JU, Gold MS, Bayas J-M, Blum MD, Bonhoeffer J, Friedlander S, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84.

Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al; 2019nCoV-501 Study Group. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021 May 20;384(20):1899-1909.

Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. bioRxiv [Preprint]. 2021; doi: https://doi.org/10.1101/2021.01.15.426911.

World Health Organization (WHO). Weekly epidemiological update on COVID-19 [Internet]. Geneva, Switzerland: WHO; 2021 Aug 10 [cited 2021 Aug 20]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---10-august-2021.\

Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, et al. Serum neutralizing activity elicited by mRNA-1273 vaccine. N Engl J Med. 2021 Apr 15;384(15):1468-70.

Yang J, Wang W, Chen Z, Lu S, Yang F, Bi Z, et al. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. Nature. 2020 Oct;586(7830):572-7.

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations – a postmarketing surveillance review. Eur J Pediatr. 2002 Jan;161(1):21-5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Events

Table 8: Schedule of Events for Part A and Part B

Visit Number	Screening[1]	V1[1]		V2	V3	V4			V5			V6	UNS
Type of Visit	C	C	SC	C	C	C	SFU	SFU	C	SFU	SFU	C	C
Month Time Point	M0	M0			M1	M3	eDiary	SC	M6	eDiary	SC	M12	--
Study Visit Day	Screening[1]	D1[1]	D8	D15	D29	D90	Every 2 weeks D36-D162[2]	Every 2 weeks D43-D169	D181	Every 2 weeks D202-D342[2]	Every 2 weeks D209-D349	D366	
Window Allowance (Days)	-7	0	+3	±3	-7 to +3	±7	±2	±3	±14	±2	±3	±14	--
Days Since Most Recent Injection		0	7	14	28	89	--		180	--		365	--
Informed consent form, demographics, concomitant medications, medical history	X												
Study injection (including 30-minute post-vaccination observation period)		X											
Confirm participant meets inclusion and exclusion criteria	X	X											
Physical examination including vital signs[3]	X	X			X				X			X	X
Pregnancy testing		X											

Visit Number	Screening[1]	V1[1]		V2	V3	V4			V5			V6	UNS
Type of Visit	C	C	SC	C	C	C	SFU	SFU	C	SFU	SFU	C	C
Month Time Point	M0	M0			M1	M3	eDiary	SC	M6	eDiary	SC	M12	--
Study Visit Day	Screening[1]	D1[1]	D8	D15	D29	D90	Every 2 weeks D36-D162[2]	Every 2 weeks D43-D169	D181	Every 2 weeks D202-D342[2]	Every 2 weeks D209-D349	D366	
Window Allowance (Days)	-7	0	+3	±3	-7 to +3	±7	±2	±3	±14	±2	±3	±14	--
Days Since Most Recent Injection		0	7	14	28	89	--		180	--		365	--
Blood for SARS-CoV-2 serology (anti-nucleocapsid antibody)		X			X	X			X			X	X
Blood for humoral immunogenicity[4]		X		X	X	X			X			X	X
Blood (PBMCs) for cellular immunogenicity		X			X				X			X	
Nasopharyngeal swab sample for SARS-CoV-2[5]		X			X	X			X			X	X
eDiary activation for recording solicited adverse reactions (7 days)		X											
Review of eDiary			X				X			X			
Follow-up safety calls[6]			X					X			X		

Visit Number	Screening[1]	V1[1]		V2	V3	V4			V5			V6	UNS
Type of Visit	C	C	SC	C	C	C	SFU	SFU	C	SFU	SFU	C	C
Month Time Point	M0	M0			M1	M3	eDiary	SC	M6	eDiary	SC	M12	--
Study Visit Day	Screening[1]	D1[1]	D8	D15	D29	D90	Every 2 weeks D36-D162[2]	Every 2 weeks D43-D169	D181	Every 2 weeks D202-D342[2]	Every 2 weeks D209-D349	D366	
Window Allowance (Days)	-7	0	+3	±3	-7 to +3	±7	±2	±3	±14	±2	±3	±14	--
Days Since Most Recent Injection		0	7	14	28	89	--		180	--		365	--
Recording of unsolicited AEs		X	X	X	X								
Recording of MAAEs, SAEs, and AESIs and concomitant medications relevant to or for the treatment of these AEs[7]		X	X	X	X		X	X	X	X	X	X	
Recording of concomitant medications and nonstudy vaccinations[8]		X	X	X	X								
Study completion												X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; EoS = end of study; FDA = US Food and Drug Administration; M = month; MAAE = medically attended adverse event; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SFU = Safety Follow-Up; UNS = unscheduled visit; V = visit.

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 Screening Visit and Day 1 (vaccination) visit can be combined and occur on the same day.

2. Safety follow-up via eDiary questionnaire will be performed every 2 weeks from Day 36 to Day 162, and from Day 202 to Day 342. These study days are relative to Day 1 vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
3. Physical examination: A full physical examination, including height and weight, will be performed on Day 1. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be collected pre- and post-vaccination on the day of injection (Day 1) only. When applicable, vital sign measurements should be performed before blood collection. For participants who are febrile (body temperature ≥ 38.0°C [100.4°F]) before injection on Day 1, the visit must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses may be vaccinated at the discretion of the investigator.
4. Sample must be collected prior to vaccination on Day 1.
5. The nasopharyngeal swab sample, collected prior to vaccination on Day 1, will be used to ascertain the presence of SARS-CoV-2 via RT-PCR. The nasopharyngeal swab sample will also be collected within 24 hours if participant experience signs and symptoms of SARS-CoV-2 infection. It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs, that are expected after vaccination with mRNA-1283, mRNA-1283.211, or mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgment to decide if an NP swab should be collected. The collection of an NP swab prior to the Day 1 vaccination can help ensure that cases of COVID-19 are not overlooked. Any study participant reporting respiratory symptoms during the 7-day period after vaccination should be evaluated for COVID-19.
6. Trained site personnel will call all participants to collect information relating to any AEs, MAAEs, AEs leading to withdrawal, SAEs, information on concomitant medications associated with those events, and any nonstudy vaccinations temporally associated with these events. 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 eDiary days only if eDiary responses indicate the need for follow-up via telephone.
7. All concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the EoS Visit (Day 366).
8. All concomitant medications and nonstudy vaccinations will be recorded through 28 days following injection.

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.2.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor, the designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data and/or documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory

authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. Financial Disclosure

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 the Sponsor with 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.

The Sponsor, the CRO, and the study site are not 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, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

10.2.5. Recruitment Procedures

Advertisements to be used for the recruitment of study participants and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

10.2.6. Informed Consent/Assent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center. All consent documents will be approved by the appropriate IRB. The actual ICF used at each center may differ, depending on local regulations and IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the form being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate.

The participant must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant should also be informed that he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial screening period).

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 CoVs.

10.2.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study or the potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed to by the investigator(s), and approved by the relevant IRB(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s) must be provided to the Sponsor before the study is initiated.

Administrative changes to the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed to by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

Noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations to the Sponsor or its designee. All deviations must be addressed in study source documents and reported to the study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being.

Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his/her participation in this study.

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, the 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 confidential information to other parties.

10.2.10. Sample Retention and Future Biomedical Research

The Sponsor may store samples for the time frame specified in the ICF to achieve study objectives. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity to SARS-CoV-2 to include humoral and cellular immune assay methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of the mRNA-1283 vaccines as well as to determine how changes in biomarkers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.2.11. Safety Oversight

Safety monitoring for this study will include an unblinded DSMB.

Blinded safety monitoring for this study will include study team members, inclusive of, at a minimum, the Sponsor medical monitor, Sponsor safety physician (from Pharmacovigilance), and CRO medical monitor. The study team will conduct ongoing safety reviews during the study and will be responsible for monitoring of safety concerns during the study, as described in the Safety Management Plan.

An independent DSMB, composed of external and independent subject matter experts and an unblinded statistician, will conduct unblinded reviews of safety data on an ad hoc basis as requested by the study team members.

Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in their respective charters.

An independent CEAC that includes pediatric and adult cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity.

10.2.12. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), as well as some national registries.

10.2.13. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from the Sponsor or qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include onsite inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

10.2.14. Data Collection and Management

This study will be conducted in compliance with ICH GCP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the study site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHO – Drug Reference List.

10.2.15. Source Documents

Source documents are original documents or certified copies and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the case report form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents, such as any hospital, clinic, or office charts, and the signed ICFs are to be included in the investigator's files with the participant's study records.

10.2.16. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

10.2.17. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the study site, discontinue enrollment, or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants
- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further mRNA-1283 development

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

10.2.18. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

10.3. APPENDIX 3: Contraceptive Guidance

Definitions: Woman of Childbearing Potential

Women of childbearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before vaccination at Day 1, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential:

1. Premenarchal
2. Premenopausal, surgically sterile female with 1 of the following:
   a. Documented complete hysterectomy
   b. Documented surgical sterilization

   For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. The following age-specific requirements apply:
     - Women < 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and FSH levels in the postmenopausal range for the institution.
     - Women ≥ 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago.
   - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to

continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an 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 that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

10.4. APPENDIX 4: Adverse Events of Special Interest Terms for mRNA-1273

Investigators should report all events that fall into the following categories as AESIs for mRNA-1273 per the reporting processes specified in Section 7.4.5. The following AESIs are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID-associated or idiopathic events without other etiology excluding congenital etiologies or trauma.
Subacute thyroiditis	• Including but not limited to events of atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis, and thyroiditis.
Acute pancreatitis	• Including but not limited to events of autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis. • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures).
Appendicitis	• Include any event of appendicitis.
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma.
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis.
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction.
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies. • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast agents, etc). • Include all cases that meet the following criteria: o Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; OR o Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days; OR o Urine volume ≤ 0.5 mL/kg/hour for 6 hours.

Medical Concept	Additional Notes
Acute liver injury	• Include events with idiopathic or autoimmune etiologies. • Exclude events with clear alternate etiology (trauma, infection, tumor, etc). • Include all cases that meet the following criteria: o > 3-fold elevation above the upper normal limit for ALT or AST OR o > 2-fold elevation above the upper normal limit for total serum bilirubin or gamma glutamyl transferase or alkaline phosphatase.
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous ARs including but not limited to: Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, and fixed drug eruptions.
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults. • Multisystem inflammatory syndrome in children. • Kawasaki's disease.
Thrombocytopenia	• Platelet counts < 150×10^9 per mm^3. • Including but not limited to: immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome.
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma).
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barre syndrome o Acute disseminated encephalomyelitis (ADEM) o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy

Medical Concept	Additional Notes
Anaphylaxis	• Anaphylaxis as defined per Section 7.4.4. • Follow reporting procedures per Section 7.4.11.
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (includes myalgic encephalomyelitis and postviral fatigue syndrome) • Myasthenia gravis

10.5. APPENDIX 5: Protocol Amendment History

Amendment 1, 22 Oct 2021: Current Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment

1. To change the dose levels of mRNA-1283 to CCI [redacted] and of mRNA-1283.211 to CCI [redacted], and to remove the mRNA-1283.351 arm. In order to accomplish this, an additional arm of mRNA-1283 was added. The dose modification and removal of mRNA-1283.351 arm was in response to a review of topline results from the interim analysis of the Phase 1 Study mRNA-1283-P101.
2. The study was changed to Phase 2a to reflect that the study is continuing dose-ranging for mRNA-1283 to identify the appropriate dose levels for continued clinical development.
3. The size of each of the arms of the study were increased from 35 to 70 participants to improve the precision in the descriptive summary statistics.
4. Minor changes have been made throughout the protocol to provide additional clarity and correct grammatical or spelling errors.

Summary of Major Changes from Original Protocol to Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature Page, Protocol Amendment Summary of Changes, and Header	• Updated the protocol version and date. • Added Protocol Amendment Summary of Changes for Amendment 1.	Updated to reflect the new version and date.
Throughout the protocol	• Minor updates to language	Updates for improved clarity and to correct grammatical or spelling mistakes.
Title Page, Signature Page, Declaration of Investigator, Protocol Synopsis	• Changed the protocol title to remove the mention of specific variants of mRNA-1283	To avoid future changes in the protocol title if additional variants are added to the study.
Title Page, Signature Page, Declaration of Investigator, Protocol Synopsis, Section 1.1 (Study Rationale), Section 3.1 (General Design)	• Changed study phase to Phase 2a	Updated to reflect the new dose-ranging nature of the study.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis, Section 3.1 (General Design), Section 5.3.1 (Study Vaccine Preparation)	• Changed the dose levels of the mRNA-1283 arms of the study to CCI [redacted] (added an arm to the mRNA-1283 portion of the study). • Changed the dose levels of the mRNA-1283.211 arms to CCI [redacted].	Analysis of topline results from the interim analysis of Study mRNA-1283-P101 support a lower dose profile for mRNA-1283. The mRNA-1283-P101 results are currently blinded and interim analysis results of the study will be summarized after study unblinding.
Title Page, Signature Page, Declaration of Investigator, Protocol Synopsis, Section 1.1 (Study Rationale), Section 1.2.3 (mRNA-1283.351), Section 1.2.4 (now Section 1.2.3 Nonclinical Studies), Section 3.1 (General Design), Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population), Section 4 (Study Population), Section 5.1 (Investigational Products Administered), Section 5.3.1 (Study Vaccine Preparation), Section 5.3.4 (Study Vaccine Packaging and Labeling), Section 5.3.5 (Study Vaccine Storage), Section 8.3 (Sample Size Determination), Section 8.5.4.1 (Analysis for the Primary Immunogenicity Objective), Section 10.1 (Appendix 1: Schedule of Events)	1. Removed the mRNA-1283.351 arm of the study	The multivalent vaccine mRNA-1283.211 contains the B.1.351 variant mRNA and so mRNA-1283.351 will not be evaluated separately.
Protocol Synopsis, Section 3.1 (General Design), Section 4 (Study Population), Section 8.3 (Sample Size Determination)	2. Changed the number of participants per arm from 35 to 70	To improve the descriptive summary value of each of the arms of the study.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis	3. Changed projected date of first participant enrolled 4. Changed projected date of first participant completed	To reflect updated projected study timelines.
Protocol Synopsis	5. Increased number of planned sites to 13	To reflect the planned increase in the number of sites in the study.
Protocol Synopsis, Section 2 (Objectives and Endpoints)	6. Updated language for the Objectives and Endpoints	To improve clarity in the language surrounding the mRNA-1283 booster vaccines.
Protocol Synopsis, Section 4.2 (Exclusion Criteria)	7. Updated Exclusion Criteria	To improve clarity and align protocol language with other booster study protocols.
Protocol Synopsis, Section 8.6.1 (Primary Analysis)	8. Added statement that the protocol may be amended based on the results of the primary analysis.	Clarifying statement.
Section 1.2.5 (now 1.2.4 Clinical Studies)	9. Removed language stating that no clinical studies with mRNA-1283 have been completed	Study mRNA-1283-P101 has completed enrollment and topline results have been prepared.
Section 1.3.2 (Risks from Study Participation and Their Mitigation	10. Removed discussion of the potential for vaccine associated enhanced disease	Based on the mRNA-1273-P301 results, there are no data suggestive of vaccine associated enhanced disease.