ModernaTX, Inc.

Protocol mRNA-1283-P201

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

Statistical Analysis Plan

SAP Final Version 2.0
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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CDC	US Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICF	Informed consent form
IP	investigational product
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NP	nasopharyngeal

Abbreviation	Definition
NTD	N-terminal domain
PI	Principal Investigator
PP	Per-Protocol
PPIS	Per-Protocol Immunogenicity Set
PPIS-Neg	Per-Protocol Immunogenicity Subset-Pre-booster SARS-CoV-2 Negative
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcriptase polymerase chain reaction
S	Spike
SAE	serious adverse event
SAP	statistical analysis plan
SAR	solicited adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
SoE	schedule of events
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for study mRNA-1283-P201, is based on the most recently approved clinical study protocol (CSP) amendment, dated 31-Jan-2022 and the most recent electronic case report form (eCRF) Version v2.003, dated 18-Feb-2022.

Summary of Major Changes in SAP, Version 2.0

Section	Brief Description of Changes	Rationale
3.1.1/2	Inclusion of binding antibody variant B1.1.529 to endpoints.	Analysis requirement
3.2.1	Remove the comparison of immune response between Part B treatment arms and Part A mRNA-1273 CCI .	Consistency with protocol
6.4.2	Inclusion of analysis at Day 91. Remove mRNA-1273 CCI from Part B analysis (ANCOVA model). Remove stratified Miettinen-Numinen analysis.	Analysis requirement and consistency with protocol

In addition to the information presented in the statistical analysis plan section of the protocol (Section 8) which provides the main analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1283-P201 is a Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).

The PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment

unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

2. Study Objectives

2.1. Part A Objectives

2.1.1. Primary Objectives

The primary objective is to assess the safety, reactogenicity and immunogenicity of the mRNA-1283 and mRNA-1283.211 vaccines as single booster doses for participants 18 years and older who were previously vaccinated with mRNA-1273 primary series.

2.1.2. Secondary Objectives

The secondary objective is to evaluate the immunogenicity of the mRNA-1283 and mRNA-1283.211 vaccines as single booster doses at all immunogenicity time points (Days 1, 15, 29, 91, 181 and 366).

2.1.3. Exploratory Objectives

The exploratory objectives are the following:

- To characterize cellular immunogenicity
- To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection
- To assess the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence

2.2. Part B Objectives

2.2.1. Primary Objectives

The primary objective is to assess the safety, reactogenicity and immunogenicity of the mRNA-1283.529 vaccine administered as the second booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273 primary series and a mRNA-1273 booster dose.

2.2.2. Secondary Objectives

The secondary objective is to assess the immunogenicity of the mRNA-1283.529 vaccine at all immunogenicity time points (Days 1, 15, 29, 91, 181 and 366).

2.2.3. Exploratory Objectives

The exploratory objectives are the following:

- To characterize cellular immunogenicity
- To conduct active detection of symptomatic and asymptomatic SARS-CoV-2 infection
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence

3. Study Endpoints

3.1. Part A Endpoints

3.1.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- 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)
- Immune response of the mRNA-1283 and mRNA-1283.211- vaccines against the ancestral SARS-CoV-2 and SARS-CoV-2 variants, including B.1.351 and B.1.1.529, at Day 29 by geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroresponse rate (SRR)
- To compare descriptively the immune response elicited by the mRNA-1283 and mRNA-1283.211 - vaccines with that elicited by the mRNA-1273 vaccine when administered as a booster, at Day 29 by GMT, GMFR, and SRR

3.1.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

Immune response of the mRNA-1283 and mRNA-1283.211 vaccines against the ancestral SARS-CoV-2 and SARS-CoV-2 variants, including B.1.351 and B.1.1.529, at all immunogenicity time points (Days 1, 15, 29, 91, 181 and 366) by GMT, GMFR, and SRR.

3.1.3. Exploratory Endpoints

The exploratory objective will be evaluated by the following endpoints:

- Frequency, magnitude, and phenotype of antigen specific B- and T-cells, to include B-cell and T-cell receptor repertoires
- 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
- Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

3.2. Part B Endpoints

3.2.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- 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
- Immune response of the mRNA-1283.529 vaccine by dose level against SARS-CoV-2 Omicron variant (B1.1.529) at Day 29 by GMT, GMFR, and SRR

3.2.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

Immune response of the mRNA-1283.529 vaccine by dose level against the ancestral SARS-CoV-2 and SARS-CoV-2 variants, including B.1.529, at all immunogenicity time points (Days 1, 15, 29, 91, 181 and 366) by GMT, GMFR, and SRR.

3.2.3. Exploratory Endpoints

The exploratory objective will be evaluated by the following endpoints:

- Frequency, magnitude, and phenotype of antigen-specific B- and T-cells, to include B-cell and T-cell receptor repertoires
- 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
- Comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and characterization of immune responses to vaccine breakthrough isolates

4. Study Design

4.1. Overall Study Design

This is a Phase 2a study that consists of two parts: Part A is an observer-blind, stratified, randomized design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283 and mRNA-1283.211 vaccines administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273, respectively. Part B is an open-label design to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283.529 administered as the second booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273 primary series and a single mRNA-1273 booster dose (i.e., three doses of mRNA-1273).

Up to 420 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 (i.e., up to 70 participants per treatment group) to receive a single boost of mRNA-1283 at one of three dose levels CCI, a single boost of mRNA-1283.211 at one of two dose levels CCI, or a single dose of the active comparator, mRNA-1273 at a single dose level CCI (Table 1-1).

Up to 140 participants in Part B who received the primary series of mRNA-1273 CCI and a first booster dose of mRNA-1273 CCI at least 3 months prior will be enrolled in a 1:1 ratio (i.e., up to 70 participants per dose level) to receive a single boost of mRNA-1283.529 as the second booster dose at one of two dose levels CCI (Table 1-2).

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.

Table 1-1: 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.

Table 1-2: Part B Treatment Groups:

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

Participants in both parts will have up to 7 study visits; 6 visits if screening and randomization/enrollment 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, 91, 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 non-study 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, 91, 181, and 366, as well as by nasopharyngeal swab RT-PCR on Days 1, 29, 91, 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 and the case definition from the Phase 3 study (mRNA-1273-P301) 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, 91, 181, and 366) during the study for immunogenicity assessments or other medical concerns according to the investigator's judgment.

4.2. Sample Size and Power

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 (i.e., 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.

4.3. Randomization

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.

4.4. Blinding and Unblinding

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 for Part A is provided in protocol Section 5.3.8. Part B of the study is open-label and therefore unblinded.

At the time of primary analysis (Day 29 for Part A), only pre-identified sponsor and unblinded CRO team members as specified in the study Data Blinding Plan will become unblinded to review treatment level results and individual listings, please also refer to Section 6.7.

5. Analysis Sets

The following analysis sets are defined: Randomization Analysis Set (Part A), Enrolled Analysis Set (Part B), Full Analysis Set (FAS), Per-Protocol (PP) Set for Immunogenicity (PPIS), Per-Protocol Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative (PPIS-Neg), Safety Set, and Solicited Safety Set.

5.1. Randomization Analysis Set (Part A)

The Randomization Analysis Set consists of all participants who are randomized. Participants will be included in the treatment group to which they were randomized. Randomization Analysis Set is applicable to Part A only.

5.2. Enrolled Analysis Set (Part B)

The Enrolled Analysis Set consists of all enrolled participants. Participants will be included in the treatment group to which they were enrolled. Enrolled Analysis Set is applicable to Part B only.

5.3. Full Analysis Set (FAS)

The FAS consists of all randomized/enrolled (Part A: randomized, Part B: enrolled) participants who receive one dose of IP. Participants will be included in the treatment group to which they were randomized/enrolled.

5.4. Per-Protocol (PP) Immunogenicity Set (PPIS)

The PPIS consists of all participants in the FAS who receive the planned dose of IP, have pre-booster and Day 29 neutralizing antibody data against prototype virus strain, have no previous HIV infection and who have no major protocol deviations that impact key or critical data. Participants will be included in the treatment group to which they were randomized/enrolled. The PPIS will be used as the sensitivity analysis set for analyses of immunogenicity.

5.5. Per-Protocol Immunogenicity Set – Pre-booster SARS-CoV-2 Negative (PPIS-Neg)

The PPIS-Neg consists of participants who are in PPIS and are pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before booster, i.e., RT-PCR result is not positive if available at pre-booster and a negative bAb specific to SARS-CoV-2 nucleocapsid on or before booster. The PPIS-Neg will be used as the analysis set for the primary analyses of immunogenicity.

5.6. 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 Analysis 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.

5.7. 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.

6. Statistical Analysis

6.1. General Considerations

Please refer to Table 8 in the protocol for Schedule of Events (SoE).

The following follow-up periods for safety analyses and Concomitant Medications will be used:

- Overall follow-up period (throughout the study): from the day of the IP injection (Day 1) to the earliest date of (study completion, discontinuation from the study, or death)
- Up to 28 days follow-up period: from the day of the IP injection (Day 1) to the earliest date of (the day of the IP injection and 27 subsequent days, discontinuation from the study, or death)
- After 28 days follow-up period: from the 28 days after the IP injection to the earliest date of (study completion, discontinuation from the study, or death)
- 7-day follow-up period: from the day of the IP injection (Day 1) to the earliest date of (Day 7 after the IP injection, discontinuation from the study, or death)

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the dose of IP in this study.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the treatment group within the analysis set of interest, unless otherwise specified.

End of Study (EoS) for the participants is defined as any of completion of the study if the participant has completed all phases of the study including the last scheduled procedure as shown in the SoE (Table 8 in the protocol), discontinuation of study due to any reason, death, and termination of the trial by the Sponsor.

Pre-booster SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1 (pre-booster).

Positive SARS-CoV-2 status at pre-booster baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Negative SARS-CoV-2 status at pre-booster baseline is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Study day relative to the injection will be calculated as below:

a) study day prior to the injection will be calculated as: date of assessment/event – date of the injection

b) study day on or after the date of the injection will be calculated as: date of assessment/event – date of the injection + 1

For calculation regarding antibody levels/titers, antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ if actual values are not available. Missing results will not be imputed.

Unscheduled visits: Unscheduled visit measurements will be included in the analyses as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline/last on-treatment measurements
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses
- In individual subject data listings

Visit window rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C
- Imputation rules for missing AE dates are provided in Appendix D
- If antibody values reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If antibody values reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary if actual values are not available
- Other incomplete/missing data will not be imputed, unless specified otherwise

The following treatment groups will be used for summary purposes:

Part A

- mRNA-1283 vaccine CCI
- mRNA-1283 vaccine CCI
- mRNA-1283 vaccine CCI
- mRNA-1283.211 vaccine CCI
- mRNA-1283.211 vaccine CCI
- mRNA-1273 vaccine CCI

Part B

- mRNA-1283.529 vaccine CCI
- mRNA-1283.529 vaccine CCI

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

The following summary analyses will be similar for Part A and Part B.

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by treatment group as defined in Section 6.1 based on the Randomized/Enrolled Set:

- Randomized Set (Part A only)

- Enrolled Set (Part B only)
- FAS
- PPIS
- PPIS-Neg
- Safety Set
- Solicited Safety Set

Percentages will be based on the number of subjects in the treatment group within the Randomized/Enrolled Set (as randomized/enrolled). For Solicited Safety Set, the percentage will be based on the number of subjects in the treatment group within the Safety Set (as treated).

Summary of reasons for subjects excluded from the PPIS, PPIS-Neg analysis sets will also be provided.

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by treatment group based on the Randomized/Enrolled Set:

- Received IP
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

This study treatment consists of a single booster, thus discontinuation from study treatment is not applicable to this study. A subject is considered to have completed the study if he or she has completed the study including the last scheduled procedure as shown in the SoE (Table 8 in the Protocol).

A subject disposition listing will be provided, including the information about ICF completion, IPs received, Study completion and EoS reasons if discontinuation from the study. A separate listing will be provided for screen failure subjects with reasons for screen failure.

6.2.2. Demographics

Descriptive statistics for demographics and baseline characteristics will be calculated for the following continuous variables: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of subjects will be provided for categorical variables such as age group (18-55, ≥56 years of age), gender, race, ethnicity, pre-booster SARS-CoV-2 infection status, and duration in months from completion of primary series to booster dose. The summaries will be presented by treatment group as defined in Section 6.1 based on the randomization/enrollment set, Safety Set, PPIS and PPIS-Neg.

In addition, randomized/enrolled subjects with any inclusion and exclusion criteria violations will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) when the analyses are performed.

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. Angioedema, anaphylaxis and hypersensitivity will be summarized separately by preferred term. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1273 CCI group for Part A and mRNA-1283.529 10 ug for Part B, and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Concomitant Medications

Concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set. Categorization of concomitant, and post medications is summarized in Appendix C Table 4.

The number and percentage of subjects using concomitant medications and non-study vaccination will be summarized by follow-up period and treatment group as defined in Section 6.1. Antipyretic, or analgesic medication (pain or fever-), along with seasonal influenza and non-study vaccines will be summarized separately. The tables will be sorted by SOC in internationally agreed order and PT in descending frequency based on mRNA-1273 group for Part A, mRNA-1283.529 CCI group for Part B.

Prior, concomitant and post medications and non-study vaccination will be presented in a listing. Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study vaccine administration data will be presented in a listing.

Study duration will be summarized since randomization/enrollment, and- since the study injection based on Safety Set.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by treatment group as defined in Section 6.1 based on the Randomized/Enrolled Set. Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing will be provided for COVID-19 impact on missed or out of window visits or assessments for subjects in Safety Set.

6.3. Safety Analysis

Part A and B:

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 (Table 5 in the protocol). The Toxicity Grading Scale for Healthy Adult and

Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study for solicited ARs.

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.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study vaccine or any event already present that worsens after exposure to study vaccine. [Note: worsening of a pre-existing condition after vaccination will be reported as a new AE.]

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner. All confirmed COVID-19 cases will be recorded as MAAEs.

AEs of special interest (AESI) are defined in Appendix 4 of the protocol.

Unsolicited AEs will be coded by PT and SOC using the latest MedDRA available at the analyses and summarized by treatment group and follow-up period (defined in Section 6.1).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for TEAEs with counts of subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1273 CCI and then alphabetically within SOC. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity in the summaries by severity, if subjects reported multiple events under the same PT.

Percentages will be based upon the number of subjects in the Safety Set within each treatment group.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited TEAEs
- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited MAAEs
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any unsolicited AESIs

The same table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related per PI's assessment in each of the above categories.

The above overall summaries will be done for unsolicited non-serious TEAEs with applicable TEAE categories.

In addition, Unsolicited AEs, unsolicited TEAEs leading to discontinuation from the study, serious AEs, unsolicited MAAEs, and AESIs, will be listed. AESI other than myocarditis and pericarditis; AESI of myocarditis and pericarditis, will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC (in internationally agreed order) and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited TEAEs that are medically-attended
- All unsolicited medically-attended TEAEs that are treatment-related

- All AESIs of myocarditis and/or pericarditis
- All AESIs other than myocarditis and/or pericarditis
- All AESIs that are treatment-related

6.3.2. Solicited Adverse Reactions

An AR is any AE related to the IP injection. Solicited Adverse Reactions, i.e., reactogenicity, refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (the day of injection and 6 subsequent days). The occurrence and intensity of the solicited ARs are recorded by subject in eDiary with some occasions that may be captured in Solicited Adverse Reaction (SAR) eCRF page. If a solicited local or systemic AR continues beyond 7 days after injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution.

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

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, fever, chills, irritability/crying, sleepiness, and loss of appetite.

The number and percentage of participants who reported solicited local AR, solicited systemic AR and any SAR, regardless of local or systemic, during the 7-day follow-up period after the IP injection will be tabulated by treatment group, toxicity grade, age group and day of reporting (Day 1 through Day 7). A two-sided 95% CI using the Clopper-Pearson method will be provided for the percentage of participants. The tables will be generated for all SARs both within or persisting beyond 7 days of injection separately.

The AR with the same selected signs and symptoms occurring 7 days after IP injection is called “delayed SAR”, whose incidence will be also summarized.

The onset of the SAR is defined as the day after the IP injection at which the respective SAR first occurred. The number and percentage of subjects with onset of SAR will be summarized by treatment group, day of reporting (Day 1 through Day 7). The tables will be generated for all SARs both within or persisting beyond 7 days of injection separately.

The SAR duration will be summarized for SARs by treatment group, within the 7 days of the IP injection and those persisting beyond 7 days separately. The duration of SAR in days will be calculated from the first to the last day when the solicited AR occurred within the 7 days of injection including the day of injection.

SARs collected on eDiary, along with those collected on reactogenicity aCRF, will be provided in a listing with the maximum grade from eDiary and aCRF. All SARs that persist beyond 7 days after IP injection will be listed separately.

6.3.3. Clinical Laboratory Evaluations

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, a follicle-stimulating hormone (FSH) test to confirm may be performed at the Screening Visit, as necessary and at the discretion of the investigator.

A by-subject listing will be provided for pregnancy tests with positive results.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PPIS and PPIS-Neg and will be performed by treatment group as defined in Section 6.1.

The geometric mean titer (GMT) and geometric mean (GM) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers or levels within subjects. It will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers or levels for subject i at time points j and k, $j \neq k$

6.4.1. Immunogenicity Assessments

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

- The levels of Serum bAb, against SARS-CoV-2 and its variants, as measured by ligand-binding assay specific to the SARS-CoV-2 S protein, the S protein RBD, Nucleocapsid protein and NTD
- The Titers of Serum nAb, against SARS-CoV-2 and its variants, as measured by pseudo-virus neutralization assays
- Serologic markers for SARS-CoV-2 infection as measured by antinucleocapsid antibodies detected by immunoassay at the baseline (Day 1) and scheduled post-baseline timepoints

6.4.2. Analysis for the Primary Immunogenicity Objective

For Part A and Part B, PPIS-Neg will be used as primary analysis set. Sensitivity analyses may be performed using PPIS and a subset of PPIS-Neg only including subjects with no virologic or serologic evidence of SARS-CoV-2 infection on or before Day 29 or Day 91, i.e., RT-PCR results are not positive up to Day 29 or Day 91 and negative bAb specific to SARS-CoV-2 nucleocapsid on or before Day 29 or Day 91. The comparison of immunogenicity between the different vaccines is descriptive.

Part A:

For the primary immunogenicity endpoints of levels of serum nAb and bAb against SARS-CoV-2 prototype virus strain and its variant strains including B.1.351, immune response of each treatment group will be assessed with respect to mRNA-1273 CCI booster dose.

An analysis of covariance (ANCOVA) model will be employed to compare immune response of each treatment group with that of mRNA-1273 CCI booster dose. Day 29 serum bAb or nAb (against prototype virus strain or the variant strain) will be included in the model as a dependent variable and a treatment group variable (mRNA-1283 at each dose level, mRNA-1283.211 at each dose level, and mRNA-1273 CCI) will be included

as the fixed effect. The model will also adjust for age group (18-55, and ≥56 years of age) and the pre-booster baseline value.

The GMT or GM level will be estimated by the geometric least square mean (GLSM) from the model for each treatment group and its corresponding 95% CI will be provided.

The GMR (ratio of GMTs or GM levels) 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 of the ratio of GLSM will be provided to assess the between-group difference (each treatment group against mRNA-1273 CCI booster dose) in immune response against the prototype strain (or variant strains).

The primary immunogenicity endpoints of Part A will also be assessed by the vaccine seroresponse against SARS-CoV-2 prototype virus strain and against variant strains including B.1.351. Vaccine seroresponse at a time point is defined by an increase of SARS-CoV-2 specific bAb level or nAb titer to at least 4xLLOQ if the baseline is below the lower limit of quantification (<LLOQ), or a 4-fold or greater rise if pre-booster ≥ LLOQ.

Two types of baselines for Part A will be employed to compute the seroresponse:

1) Pre-vaccination (Pre-Dose 1 of the primary series)
2) Pre-booster

Seroresponse based on pre-vaccination is defined as ≥ 4*LLOQ for subjects with negative SARS-CoV-2 status at their pre-vaccination baseline. For this study, subjects SARS-CoV-2 status at pre-booster baseline will be used to impute their SARS-CoV-2 status pre-vaccination baseline. If the participant tests negative at pre-booster, the serum Ab value of the pre-vaccination baseline will be imputed with LLOQ, otherwise, For subjects with positive SARS-CoV-2 status at pre-booster, their seroresponse based on pre-vaccination baseline will be set to missing.

The SRR at Day 29 will be summarized for each treatment group with its 95% CI calculated with the Clopper-Pearson method. The difference of SRRs at Day 29 for mRNA-1283 at each dose level, mRNA-1283.211 at each dose level compared with mRNA-1273 will be provided with its 95% CI with the Miettinen-Nurminen method.

Part B:

Similar analysis methods will be used to analyze immunogenicity data for Part B. An ANCOVA model will be used to compare immune response between treatment group ([redacted] mRNA-1283.529). 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, adjusting for age group (< 56, ≥ 56) and the pre-booster baseline Ab value. 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-group difference in immune response against B.1.1.529.

SRR against B.1.1.529 at Day 29 will be summarized for each mRNA-1283.529 dose level with its 95% CI calculated using the Clopper-Pearson method. The difference of SRRs at Day 29 between two dose levels will also be calculated with 95% CI using the Miettinen-Nurminen method.

For Part B, seroresponse will be based on both pre-vaccination and pre-booster baseline as well. The derivation rule is the same as described in Part A.

6.4.3. Analysis for the Secondary and Exploratory Immunogenicity Objectives

Part A and B:

Immunogenicity, including the SARS-CoV-2–specific bAb and nAb along with seroresponse rate , will be assessed at multiple time points in this study (Days 1, 15, 29, 91, 181 and 366); however, Day 29, 28 days after booster dose, is the time point of primary interest.

The following evaluations will be performed at each time point for immunogenicity.

- In relation to the immune response of each booster arm to SARS-CoV-2 prototype and viral variants, the GMT or level, GMFR and SRR will be calculated at the time points where the immune response is assessed for prototype and viral variants. For each antibody of interest, the GMT or level and GMFR with their corresponding 95% CIs at each time point will be provided. 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. Additionally, reverse cumulative distribution plots and box plots of titers or levels will be generated for each antibody of interest.

- For each antibody of interest, the proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 from baseline at each post-injection time point will be tabulated with its 95% CI calculated using the Clopper-Pearson method.
- The SRR of each treatment group against the prototype strain and variant strains, defined as the percentage of participants achieving seroresponse against the prototype strain and variant strains, respectively, will be provided with their 95% CI calculated with the Clopper-Pearson method.
- For the exploratory objectives, to characterize cellular immunogenicity, frequency, magnitude, and phenotype of antigen-specific B- and T-cells may be analyzed; comparison of the SARS-CoV-2 genetic sequence of viral isolates with the vaccine sequence and immune responses to vaccine breakthrough isolates may be performed to evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.

6.5. Subgroup Analysis

Part A and B:

Selected immunogenicity and safety analyses will be assessed in the following subgroups:

- Age group (18-55, and ≥56 years of age)
- Pre-booster SARS-CoV-2 infection status (negative or positive)

6.6. Efficacy Analysis

Part A and B:

SARS-CoV-2 infection cases, including both symptomatic and asymptomatic cases, and COVID-19 cases, defined with both CDC and Moderna mRNA-1273 P301 study, by treatment group will be summarized.

Pre-booster SARS-CoV-2 status is described in Section 6.1.

6.6.1. Endpoint Definition/Derivation

6.6.1.1. Derivation of SARS-CoV-2 Infection

SARS-CoV-2 infection is considered as either positive status of COVID-19 or asymptomatic SAS-CoV-2 infection for participants with negative pre-booster SARS-CoV-

2 status. It will be counted starting 14 days after the dose of IP SARS-CoV-2 infection will be defined in participants with negative pre-booster SARS-CoV-2 status by either:

- bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive after the IP injection, OR
- Positive RT-PCR after the dose of IP.

The date of documented infection will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of positive post-baseline serology test result

The time to the first SARS-CoV-2 infection will be calculated as:

Time to the first SARS-CoV-2 infection = Date of the first documented infection – Date of the IP injection + 1.

Cases will be counted starting 14 days after the IP injection. They will be summarized by treatment group.

6.6.1.2. Derivation of Asymptomatic SARS-CoV-2 Infection

The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR of nasopharyngeal swabs and/or serology tests obtained at post-baseline visits is counted starting 14 days after the IP injection in participants with negative pre-booster SARS-CoV-2 status.

Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms with positive status per RT-PCR or serology tests at a post-baseline visit, specifically:

- Absent of COVID-19 symptoms AND at least one from below:
- bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive after the IP injection, OR
- Positive RT-PCR test after the IP injection.

The date of the asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid, or positive post-baseline RT-PCR, with absence of symptoms.

The time to the asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of the asymptomatic SARS-CoV-2 infection – Date of the IP injection + 1.

6.6.1.3. Derivation of COVID-19

The incidence of the first occurrence of symptomatic COVID-19 infection cases is recorded starting 14 days after the injection. Surveillance for COVID-19 will be conducted through monthly contact and scheduled blood collection. Subjects reporting COVID-19 symptoms will be arranged an illness visit to collect an NP swab.

Two definitions of the COVID-19 will be evaluated:

1. Primary case definition per the Phase 3 study (mRNA-1273-P301): Cases are defined as participants meeting clinical criteria based on both symptoms for the COVID-19 and positive RT-PCR test results as described in Table 2-1.
2. Secondary case definition based on CDC criteria: The presence of one of the CDC-listed symptoms (Table 2-2) and a positive RT-PCR test on a respiratory sample.

Table 2-1. Derivation of primary case definition of COVID-19

COVID-19 (per the Phase 3 study (mRNA-1273-P301))	
Post-baseline RT-PCR results	Positive, **AND**
Systemic Symptoms	at least **TWO** of the following **systemic symptoms**: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); **OR**
Respiratory Symptoms	at least **ONE** of the following **respiratory signs/symptoms**: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.

Table 2-2. Derivation of secondary case definition of COVID-19

COVID-19 (CDC criteria)	
Post-baseline RT-PCR results	Positive, **AND**
Systemic and Respiratory Symptoms	at least **ONE** of the following **systemic or respiratory symptoms**: Fever (≥ 38ºC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches (not

	related to exercise), headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.

The date of documented COVID-19 will be the later date of the following two dates (date of positive RT-PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

The time to the first occurrence of COVID-19 will be calculated as:

Time to the first occurrence of COVID-19 = Date of documented COVID-19 – Date of the IP injection + 1.

Cases will be counted starting 14 days after the IP injection.

6.6.2. Analysis Method

The number and percentage of subjects who had each type of event (i.e., an asymptomatic or a symptomatic SARS-CoV-2 infection) will be summarized with FAS.

6.7. Primary Analysis

The primary analysis of safety and immunogenicity will be conducted after Part A participants have completed their Day 29 visit assessments. All data relevant to the primary analysis through Day 29 will be cleaned (as clean as possible) and locked. The primary analysis will be performed by a separate team of unblinded programmers and statisticians. The analysis, including any case 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.

6.8. 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.

6.9. 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).

6.10. Data and Safety Monitoring Board

An independent data and safety monitoring board (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 if any pause rule is met or as requested by the safety oversight and/or the internal safety team.

6.11. Cardiac Event Adjudication Committee

An independent cardiac event adjudication committee (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. Changes from Planned Analyses in Protocol

There are no changes from planned analyses in protocol.

8. References

1. 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 preventative vaccine clinical trials. September 2007 [cited 2019 Apr 10] [10 screens]. Available from:https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

9. List of Appendices

9.1. Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis (Part A and Part B)

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 3 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 3 Visit Window

Visit	Target Study Day	Visit Window in Study Day
SARS-CoV-2 Serology		
Baseline	1 (Date of Injection)	≤1
Day 29 (Month 1)	29	[2, 59]

Day 91 (Month 3)	91	[60, 135]
Day 181 (Month 6)	181	[136, 273]
Day 366 (Month 12)	366	≥274
Vital Signs		
Baseline	1 (Date of Injection)	≤1, Pre-dose
Day 1, Post-Dose	1 (Date of Injection)	1, Post-dose
Day 29 (Month 1)	29	[2, 105]
Day 181 (Month 6)	181	[106, 273]
Day 366 (Month 12)	366	≥274
Humoral Immunogenicity		
Baseline	1 (Date of Injection)	≤1
Day 15	15	[2, 22]
Day 29 (Month 1)	29	[23, 59]
Day 91 (Month 3)	91	[60, 135]
Day 181 (Month 6)	181	[136, 273]
Day 366 (Month 12)	366	≥274
Cellular Immunogenicity		
Baseline	1 (Date of Injection)	≤1
Day 29	29	[2, 105]
Day 181 (Month 6)	181	[106, 273]
Day 366 (Month 12)	366	≥274
Nasopharyngeal Swabs for SARS-CoV-2		
Baseline	1 (Date of Injection)	≤1
Day 29 (Month 1)	29	[2, 59]
Day 91 (Month 3)	91	[60, 135]
Day 181 (Month 6)	181	[136, 273]

Day 366 (Month 12)	366	≥274

9.3. Appendix A Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of injection or is missing AND the start month and year of the medication coincide with the start month and year of the injection. In this case, use the date of the injection
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after date of the injection or is missing AND the start year of the medication coincide with the start year of the injection. In this case, use the date of the injection
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 4 below.

Table 4 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< Injection Date**	**≥ Injection Date and ≤ Injection Date + 27 days**	**> 27 Days After Injection [2]**
< Injection Date [1]	P	PC	PCA
≥ Injection date and ≤ 27 days after injection	-	C	CA
> 27 days after injection	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

9.4. Appendix B Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:

- If only DAY is missing, use the first day of the month, unless:
  - The AE end date is after the date of injection or is missing AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date and time of injection, even if time is collected.
- If DAY and Month are both missing, use the first day of the year, unless:
  - The AE end date is after the date of injection or is missing AND the start year of the AE coincides with the start year of the injection. In this case, use the date of injection
- If DAY, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed.

9.5. Appendix E Schedule of Events

Refer to Table 8 in Appendix 1: Schedule of Events in the protocol.