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ModernaTX, Inc.

Protocol mRNA-1273-P401

Randomized, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults

Statistical Analysis Plan

SAP Version 2.0

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
bAb	Binding antibody
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
D	Day
DBL	Data base lock
DHHS	Department of Health and Human Services
eCRF	Electronic case report form
EoS	End of study
FAS	Full analysis set
GCP	Good Clinical Practice
GM	Geometric mean
GMFR	Geometric mean fold rise
GMR	Geometric mean ratio
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
LTFU	Lost to follow-up
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum

Abbreviation	Definition
mRNA	Messenger ribonucleic acid
N (or n)	Number of subjects
nAb	Neutralizing antibody
PD	Protocol deviation
PP	Per-Protocol
PPIS	Per-Protocol Immunogenicity Subset
PPIS-Neg	PP Set for Immunogenicity –SARS-CoV-2 negative
PT	Preferred term
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	Standard deviation
SMQ	Standardized MedDRA Query
SoA	Schedule of activities
SOC	System organ class
S protein	Spike protein
SRR	Seroresponse rate
ULOQ	Upper limit of quantification
US	United States
V	Visit
WHODrug	World Health Organization drug dictionary
XBB.1.5	Omicron subvariant strain of SARS-CoV-2

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P401, is based on the approved clinical study protocol (CSP) amendment 2 dated 27-Feb-2024, and the most recent approved electronic case report form (eCRF), dated 20-Mar-2024.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9) which provides the principal features of 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-1273-P401 is a Phase 3b randomized, observer-blind, active-controlled, clinical study to assess the immunogenicity of an investigational mRNA-1273.815 COVID-19 Vaccine in previously vaccinated adults.

NJS Associates Company Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety 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 clinical database lock and treatment unblinding. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail and the difference will be described in Section 7.

In this document, study vaccination, injection of investigational medicinal product (IMP)/ investigational vaccine, and injection are used interchangeably; study arm, treatment arm, vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objectives

The primary objective is the following:

- To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain.

2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the safety of the CCI-µg licensed Spikevax or Investigational mRNA-1273.815.
- To evaluate immune responses elicited by CCI-µg dose of licensed Spikevax or Investigational mRNA-1273.815 against the XBB.1.5 strain.

3. Study Endpoints

3.1. Primary Endpoint

The primary objective will be evaluated by the following endpoint:

- GM value of nAb against XBB.1.5 at Day 15.

3.2. Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

3.2.1. Safety Endpoint

- SAEs, AESIs, and AEs leading to withdrawal from the study on Day 1 through 15 days after injection.

3.2.2. Immunogenicity Endpoints

- SRR of nAb against the XBB.1.5 strain at Day 15, where seroresponse is defined as nAb value change from baseline (preinjection Day 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ;
- GMR of nAb against the XBB.1.5 at Day 15 between the 2 treatment groups.

4. Study Design

4.1. Overall Design

This is a Phase 3b randomized, observer-blind, active-controlled, clinical study to assess descriptively the immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine compared to the licensed Spikevax vaccine, both containing the updated XBB1.5 strain, in previously vaccinated adults. Randomization will be stratified by age (18 to <65 years, and ≥65 years).

The study comprises 3 scheduled in-clinic visits including a Screening Visit (Screening and dosing can be performed on the same day) per Protocol Section 1.2 and Protocol Section 1.3.

This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

In this multisite study, participants will be randomized to either licensed Spikevax or Investigational mRNA-1273.815 with a wider RNA encapsulation lower-limit specification. The percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IMP administered on Day 1 until study end.

With SARS-CoV-2 expected to circulating in the general population during the study, blood samples will be tested at baseline (preinjection Day 1) for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2.

To assess the vaccine-induced immune responses, blood samples will also be collected from all participants on Day 1 (preinjection) and Day 15 for measurement of SARS-CoV-2 specific nAb responses.

In addition, participants will have nasal swab samples collected before the injection on Day 1 as well as on Day 15.

To monitor for safety, safety data will be collected and will include SAEs, and AESIs, and AEs leading to discontinuation from study participation.

Number of Participants:

Approximately 200 adult (≥18 years of age) participants will be enrolled and randomized (1:1) to licensed Spikevax or Investigational mRNA-1273.815.

Study Duration:

Participants will be in the study for approximately 2 weeks which includes 7 days for Screening (Day -7 to Day 1), 1 day of dosing (Day 1), and 2 weeks of follow-up.

Study Treatment:

CCI μg dose of licensed Spikevax or Investigational mRNA-1273.815 injection (administered intramuscularly).

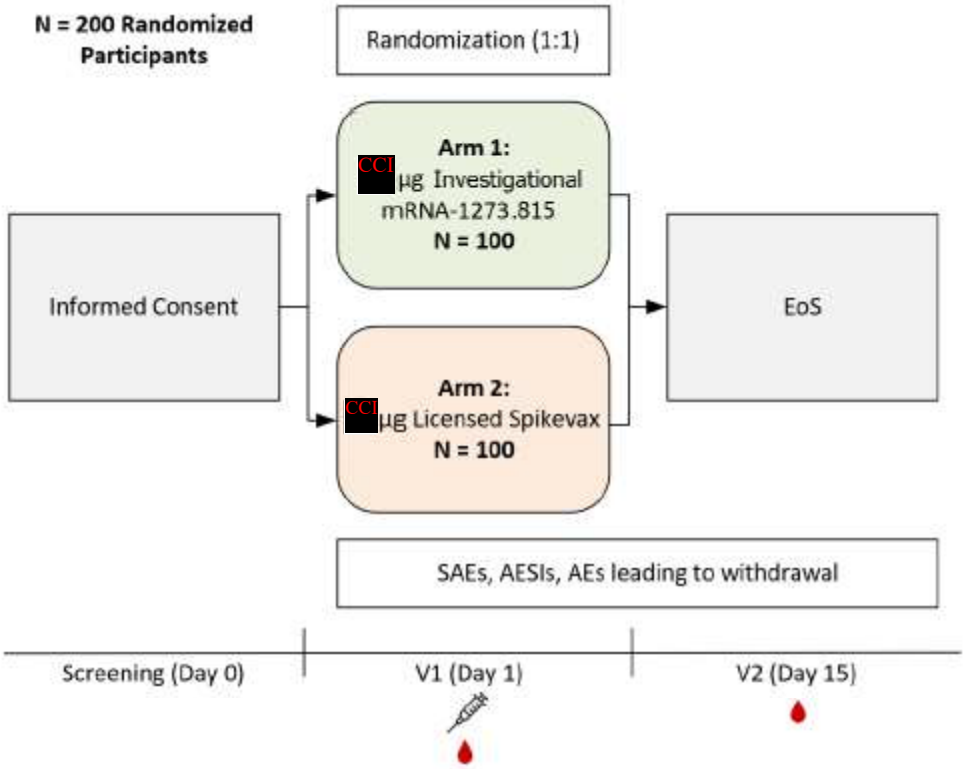
End-of-Study Definition (EoS)

The EoS is defined as the date when last data are available.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Protocol Section 1.3).

The study schema is presented in Figure 1.

Figure 1 Schema of Study Design



Abbreviations: AE = adverse event; AESI = adverse event of special interest; EoS = end-of-study; V = visit; mRNA = messenger ribonucleic acid; N = number of participants; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: the percent RNA encapsulation lower-limit of the Investigational mRNA-1273.815 vaccine is no more than CCI lower than that of the licensed Spikevax vaccine, both of which target the Omicron subvariant XBB.1.5.

Study Injection

Blood for SARS-CoV-2 serology (antinucleocapsid antibody) at Day 1 and for immune response to injection (Day 1 [preinjection] and Day 15).

4.2.Statistical Hypothesis

There is no hypothesis testing in this study.

4.3.Sample Size Determination

A minimum of 200 participants will be randomized in a 1:1 ratio to the 2 treatment groups in this study.

4.4.Randomization

Approximately 200 adult (≥18 years of age) participants will be enrolled and randomized (1:1) to licensed Spikevax or Investigational mRNA-1273.815. Randomization will be stratified by age (18 to <65 years, and ≥65 years).

4.5.Blinding and Unblinding

This study is observer-blind; blinding during the study will be conducted as described in protocol Section 6.4. The Investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IMP administered until study end (the study database is locked and unblinded), with certain exceptions (Protocol Section 6.4.2 and 9.1).

5. Analysis Sets

The following analysis sets are defined: Randomization Set, Full Analysis Set (FAS), Immunogenicity Subset, Per-Protocol Immunogenicity Subset (PPIS), PP Set for Immunogenicity –SARS-CoV-2 negative (PPIS-Neg) and Safety Set.

5.1.Randomization Set

The Randomization Set consists of all participants who are randomized, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2.Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized participants who received the IMP. Participants will be analyzed according to their randomized study arm.

5.3. Immunogenicity Subset

Participants in the FAS who have immunogenicity testing.

5.4.Per-Protocol Immunogenicity Subset (PPIS)

The PP Immunogenicity Subset includes participants who received planned dose of study injection per schedule, complied with immunogenicity testing schedule (visit window in Appendix 2), and have no major protocol deviations that impact key or critical data. The PPIS will be the primary immunogenicity analysis set.

5.5.Per-Protocol Set for Immunogenicity –SARS-CoV-2 negative (PPIS-Neg)

Participants in the PPIS who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline, i.e., who are SARS-CoV-2 negative, defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid.

5.6.Safety Set

All enrolled participants who received IMP. The Safety Set will be used for all analyses of safety. Participants will be analyzed according to the study treatment they actually received.

6. Statistical Analysis

6.1.General Considerations

The Schedule of Activities (SoA) is provided in the protocol Table 2.

General considerations for analyses will be applied to this study, unless otherwise specified. All analyses will be performed by treatment groups, unless otherwise specified. Statistical outputs (tables, figures, listings, and datasets) will refer to study participants as participants and will use vaccination, injection of IMP and injection interchangeably. All analyses will be conducted using SAS Version 9.4. All table data will have a corresponding listing.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix 1 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 participants in that vaccination group within the analysis set of interest, unless otherwise specified.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (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 IMP. For immunogenicity tests, the baseline is defined as the most recent non- missing measurement (scheduled or unscheduled) collected before or on the dose date of IMP.

Age: unless otherwise specified, age is calculated as the age at screening.

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;

If untreated, the randomization date will be used as reference date for study day.

Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline
- In individual participant data listings as appropriate

The analysis visit windows for protocol-defined visits are provided in Appendix 2.

Incomplete/missing Data:

- Imputation rules for missing or partial missing dates of prior/concomitant medications and procedures are provided in Appendix 4.
- Imputation rules for missing or partial missing AE dates are provided in Appendix 5.
- If the immunogenicity results are reported as below the LLOQ (eg, < 0.1), the numeric values will be replaced by 0.5 × LLOQ in the summary. If the immunogenicity results are reported as greater than the upper limit of quantification (ULOQ) (eg, > 3000), the

numeric values will be replaced by ULOQ in the summary if the numeric values are not available (i.e., if numerical values are available, the numerical values are used).

Other incomplete/missing data including immunogenicity will not be imputed, unless otherwise specified.

Treatment Groups

The following vaccination groups will be used for summary purposes:

- CCI µg Investigational mRNA-1273.815
- CCI µg licensed Spikevax
- Overall (optional)

All analyses and data summaries/displays will be provided by vaccination group using appropriate analysis population, unless otherwise specified.

Baseline SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

Positive SARS-CoV-2 status at 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 status is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1.

The baseline SARS-CoV-2 status is defined as missing for participants with both tests missing, or with one test missing and one test negative.

6.2.Background Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following categories will be summarized by treatment group as defined in Section 6.1 based on Randomization Set:

- Full Analysis Set (FAS)
- Immunogenicity Subset
- Per Protocol Immunogenicity Subset (PPIS)

- PP Set for Immunogenicity –SARS-CoV-2 negative (PPIS-Neg)
- Safety Set

The percentage will be based on participants in the Randomization Set. A summary of reasons for participants who are in the Randomization Set but excluded from PPIS will also be provided. A listing of analysis sets will be provided based on the Randomization Set.

For screened failure participants, age (years), as well as sex, race, ethnicity, and reasons for screen failure will be presented in a listing.

The number and percentage of participants in each of the following disposition categories will be summarized by treatment group based on the Randomization Set:

- Received the dose of IMP
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
    - Adverse Event
    - Death
    - Lost to follow-up (LTFU)
    - Physician decision
    - Pregnancy
    - Protocol deviation
    - Study terminated by sponsor
    - Withdrawal of consent by participant
    - Other

A participant disposition listing will be provided, including informed consent, participants who received injection, participants who completed study, participants who discontinued from participation in the study, with reasons for discontinuation.

In addition, randomized participants with any inclusion and exclusion criteria violation will also be provided in a listing.

Study duration will be summarized from the injection, until completed/discontinued the study or the data cutoff date, whichever occurs first, based on the Safety Set.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2). The number and percentage of participants will be provided for categorical variables such as age group (18 to <65, and ≥65 years), sex (female, male), race and race group (White, Black, Asian, other), ethnicity, baseline SARS-CoV-2 status (positive, negative), number of prior doses of COVID-19 vaccines (2, 3, 4, ≥5). Type of prior COVID-19 vaccine may be summarized if data warrants.

The summaries will be presented by treatment group as specified in Section 6.1 based on Safety Set and PPIS.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version used for coding medical history diseases will be included in footnote of analysis output.

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the [CCI] µg Investigational mRNA-1273.815 group and then alphabetically within SOC.

All medical history data will be presented in a listing.

6.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODrug Global). WHODrug Global version used will be included in footnote of analysis output. The summary of concomitant medications will be based on the Safety Set, unless otherwise specified. Imputation rules for missing/partial dates of medications are detailed in Appendix 4. Categorization of prior, concomitant and post medications are defined below:

- A medication taken before the study vaccine injection date is considered a "prior" medication;
- The medication taken on or after study vaccine injection date through end of study follow-up (approximately 2 weeks from study injection) will be considered as "concomitant" medication.

The number and percentage of participants using concomitant medications will be summarized by treatment groups as follows:

- Any concomitant medications throughout the study
- Any non-study vaccination throughout the study

A summary table of all medications that continued or newly received throughout the study will be provided by PT in descending frequency in the Investigational mRNA-1273.815 group.

Prior, concomitant medications will be presented in a listing.

Concomitant procedures will be presented in a listing only.

6.2.4. Study Exposure

Study IMP administration data including reasons for IMP injection not administered will be summarized in disposition table and presented in a listing.

6.2.5. 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 participant's rights, safety, or well-being. Major protocol deviations rules are developed based on the protocol and ongoing data and will be finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by treatment group as defined in Section 6.1 based on the Randomization Set.

Major PDs may impact immune response corresponding to the immunogenicity objective, and participants with such deviations will be excluded from the PPIS for immunogenicity analyses; these major PDs will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from the PPIS will be summarized and listed.

Major protocol deviations will be presented in a listing.

6.3. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PPIS and will be by treatment group unless otherwise specified.

6.3.1. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Protocol Section 1.3). The following analytes will be measured in blood samples for immunogenicity assessments:

- Serum nAb level against SARS-CoV-2 S protein as measured by pseudovirus and/or live virus neutralization assays

6.3.2. Analysis of Immunogenicity Endpoints

The 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 levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity levels within participants. The GMFR 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 participants, v_{ij} and v_{ik} are observed immunogenicity levels for participant i at time points j and k, $j \neq k$ and k is baseline.

For calculation of GM values, missing results will not be imputed. Values reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values reported that are greater than the

ULOQ will be converted to the ULOQ if the numeric values are not available (i.e., if numerical values are available, the numerical values are used).

6.3.2.1. Analysis for Primary Immunogenicity Endpoints

GM level of nAb against the XBB.1.5 strain at Day 15 is the primary endpoint:

The GM level of nAb against the XBB.1.5 strain with corresponding 95% CI will be provided at baseline and Day 15. 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 baseline and Day 15: the number of participants (n), median, minimum and maximum.

6.3.2.2. Analysis for the Secondary Immunogenicity Endpoints

- The GMR of nAb against XBB.1.5 with 95% CI in the Investigational mRNA-1273.815 treatment group to the licensed Spikevax treatment group at Day 15 will be computed based on the t-distribution of mean difference using the log-transformed values and then back transformed to the original scale for presentation.
- GMFR of nAb against XBB.1.5 with corresponding 95% CI will be provided at Day 15 over baseline level. The GMFR and 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 be also provided for fold-rise at each timepoint: the number of participants (n), median, minimum, and maximum.
- The number and percentage of participants with seroresponse (SRR) for nAb value against the XBB.1.5 strain at Day 15 will be provided with 95% CI (using Clopper-Pearson method). Seroresponse is defined as nAb value change from baseline (preinjection) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ.

In addition, a listing of neutralizing antibodies (nAb) targeting XBB.1.5 and figure for geometric mean levels will be provided, along with a box plot (log scale) illustrating the distribution of nAb levels against XBB.1.5.

6.3.2.3. Immunogenicity Subgroup Analysis

To assess consistency of antibody response across various subgroups, antibody response data will be summarized for each subgroup below. Subgroup analysis for the immunogenicity endpoint will be performed using the same methods described in Section 6.3.2.1 and Section 6.3.2.2.

Immunogenicity will be assessed in the following subgroups:

- Age (≥18 to <65 Years, and ≥65 Years)
- Sex (Female, Male)
- Baseline/preinjection SARS-CoV-2 Status (Positive, Negative)
- Race group (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Number of prior doses of COVID-19 vaccines (2, 3, 4, ≥5)
- Type of prior COVID-19 vaccine (if data warrants)

Subgroups may be combined if necessary.

6.4. Safety Analysis

All safety analyses will be summarized by treatment based on the Safety Set. Safety will be assessed by clinical review of all relevant parameters, including SAEs, AESIs, AEs leading to withdrawal, vital sign measurements, and physical examination findings.

6.4.1. Unsolicited Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans whether it is considered drug related or not. SAEs, AESIs (defined in Protocol Table 4), and AEs leading to discontinuation of study participation will be collected throughout the study. All AEs started after the injection will be reported in summary tables.

Unsolicited AEs will be coded by SOC and PT according to MedDRA dictionary.

All summary tables for unsolicited AEs will be presented by SOC and PT for AEs with counts of participants included. Given study duration is approximately 2 weeks, the unsolicited AEs will be summarized throughout the study.

When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE within SOC or PT group will be counted once. Separate listings for corresponding AE tables will also be provided.

In addition, adverse events based on CDC wording cased definition of pericarditis, myocarditis, and myopericarditis occurring after receipt of study vaccines (defined in Protocol Appendix 4) will be listed if data is available.

The number of events and number of participants with occurrences of selected AEs of clinical interests identified by SMQ throughout the study will be summarized for narrow scope, narrow and broad scope, separately.

6.4.1.1.AEs by System Organ Class and Preferred Term

The following summary tables of AEs throughout the study will be provided by MedDRA SOC and PT using frequency counts and percentages:

- All unsolicited AEs leading to discontinuation from participation in the study,
- All unsolicited AESIs.

6.4.1.2.Serious Adverse Events

The summary table of serious AEs throughout the study will be provided by SOC and PT using frequency counts and percentages.

Death events will be provided in a separate listing.

6.4.2. Vital Signs

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria (DHHS 2007) will be flagged in the data listing.

6.5. Planned Analysis

The final analysis of all endpoints will be performed after participants have completed all planned study procedures. Results of the analysis will be presented in a final clinical CSR, including individual listings.

7. Changes from Planned Analyses in Protocol

Not applicable.

8. References

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U. S. Department of Health and Human Services (DHHS). Food and Drug Administration. Center for Biologics Evaluation and Research. September 2007.

9. List of Appendices

9.1. Appendix 1: Standards for 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 more significant figure than the original results; the SD will be presented to two more significant figures 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. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

9.2.Appendix 2: Analysis Visit Windows

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

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 1 below.

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

- If multiple assessments occur for both scheduled visit and unscheduled visit, the assessment collected at scheduled visit will be used.
- If multiple assessments occur for an analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments with equal distance to the target study day, the last assessment will be used.

Table 1 Visit Window

Visit	Target Study Day	Visit Window in Study Day
Immunogenicity		
Day 1	1 (Date of the Injection)	1, Preinjection
Day 15	15	[12, 22]
Vital Signs		
Day 1	1 (Date of the Injection)	1, Preinjection
Day 1	1 (Date of the Injection)	1, Postinjection
Day 15	15	[12, 22]

9.3.Appendix 3: Schedule of Activities

Refer to Table 2: Schedule of Activities (SoA) in the protocol.

9.4. Appendix 4: Imputation Rules for Missing Dates of Prior/Concomitant Medications, Non-Study Vaccinations

Imputation rules for missing or partial start/stop dates of medication 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 on/after the date of injection or is missing/partial AND the start month and year of the medication coincide with the start month and year of the injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of injection.
    - If Day and Month are both missing, use the first day of the year, unless:
        - The medication end date is on/after the date of injection or is missing/partial AND the start year of the medication coincide with the start year of the injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of 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. However, if the medication is known to be not taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is No), the medication will be treated as though it began after the injection for purposes of determining status as prior or concomitant.

2. Missing or partial medication stop date:
    a. If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).

b. 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).

c. 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 categorization of medications is described in the table below. Non-study vaccinations will be considered as prior if start date is before IMP.

Table 2 Prior, Concomitant, and Post Categorization of Medications

Medication Start Date	**Medication Stop Date**	
	< Injection Date of IMP	**≥ Injection Date [2]**
< Injection date of IMP [1]	P	P, C
≥ Injection date	-	C

C: Concomitant; P: Prior

[1] includes medications with completely missing start date

[2] includes medications with completely missing end date

Note: study duration is approximately 2 weeks. All medication taken on or after the dose date of study vaccine are considered concomitant medication.

9.5.Appendix 5: Imputation Rules for Missing Dates of AEs

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

1. Missing or partial start date:
    - If only Day is missing, use the first day of the month, unless:
        - The AE end date is on/after the date of injection or is missing/partial 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 AE time was collected.
    - If Day and Month are both missing, the date will not be imputed, unless:
        - The AE end date is on/after the date of injection or is missing/partial AND the start year of the AE coincides with the start year of the injection. In this case, use the date and time of injection, when time is available.
    - 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 end dates will not be imputed.

9.6.Appendix 6: Severity Grading of Vital Sign Abnormalities

Table 3 Vital Sign Abnormalities

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
For analysis purpose, the grades will be calculated using the numerical portion only.