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ModernaTX, Inc.

Protocol mRNA-1073-P101

Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age

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
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CI	confidence interval
CDC	US Centers for Disease Control and Prevention
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
HAI	hemagglutination inhibition
IM	intramuscular
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

Abbreviation	Definition
NP	nasopharyngeal
PP	Per-Protocol
PT	preferred term
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
SOC	system organ class
SoE	schedule of events
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-1073-P101, is based on the most recent approved clinical study protocol (CSP), Amendment 2, dated 16-Aug-2022, and the most recent approved electronic case report form (eCRF), dated 03-August-2022.

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-1073-P101 is a Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age.

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.

In this document, study vaccination, injection of investigational product (IP)/ investigational vaccine, and injection are used interchangeably.

2. Study Objectives

2.1. Primary Objectives

The primary objective is to evaluate the safety and reactogenicity of study vaccines.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 across study vaccine arms at Day 29
- To evaluate the humoral immunogenicity to vaccine-matched strains for influenza and SARS-CoV-2 at all evaluable humoral immunogenicity time points

2.3. Exploratory Objectives

The following exploratory objectives may be performed:

- To evaluate the humoral immunogenicity against vaccine mismatched strains
- To evaluate the humoral immunogenicity against vaccine-matched and mismatched strains using alternative methods (eg, microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2)
- To evaluate cellular immunogenicity in a subset of participants
- To further characterize the immune response across study vaccines
- To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates

3. Study Endpoints

3.1. 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 post vaccination
- Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period post vaccination
- Frequency of any serious adverse events (SAEs), adverse events of special interest (AESIs), medically attended adverse events (MAAEs), and AEs leading to discontinuation from Day 1 to Day 181/EoS

3.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- Geometric mean titer (GMT) and geometric mean fold rise (GMFR) at Day 29 compared with Day 1 (baseline) by hemagglutination inhibition (HAI) assay for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer ≥ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is ≥ 1:10 in anti-HA antibodies measured by HAI assay
- SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥ 4-fold if baseline is ≥ LLOQ or ≥ 4 × LLOQ if baseline titer is < LLOQ in neutralizing antibody (nAb) titers measured by PsVNA (or binding antibody assay).
- GMT and GMFR compared with Day 1 (baseline) by HAI for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2
- Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) as defined above

3.3. Exploratory Endpoints

The exploratory objectives may be evaluated by the following endpoints:

- GMT and GMFR (compared to Day 1) to vaccine mismatched strains
- GMT and GMFR (compared to Day 1) to vaccine-matched and mismatched strains assayed by alternative methods (eg, microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2)
- Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells and T cells after vaccination
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
- Frequency of laboratory-confirmed clinical influenza and COVID-19 and assessment of immune responses to infection and viral isolates

4. Study Design

4.1. Overall Study Design

This is a Phase 1/2, randomized, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 compared to co-administered mRNA-1010 and mRNA-1273 vaccines and to the individual vaccines alone in healthy adults 18 to 75 years of age.

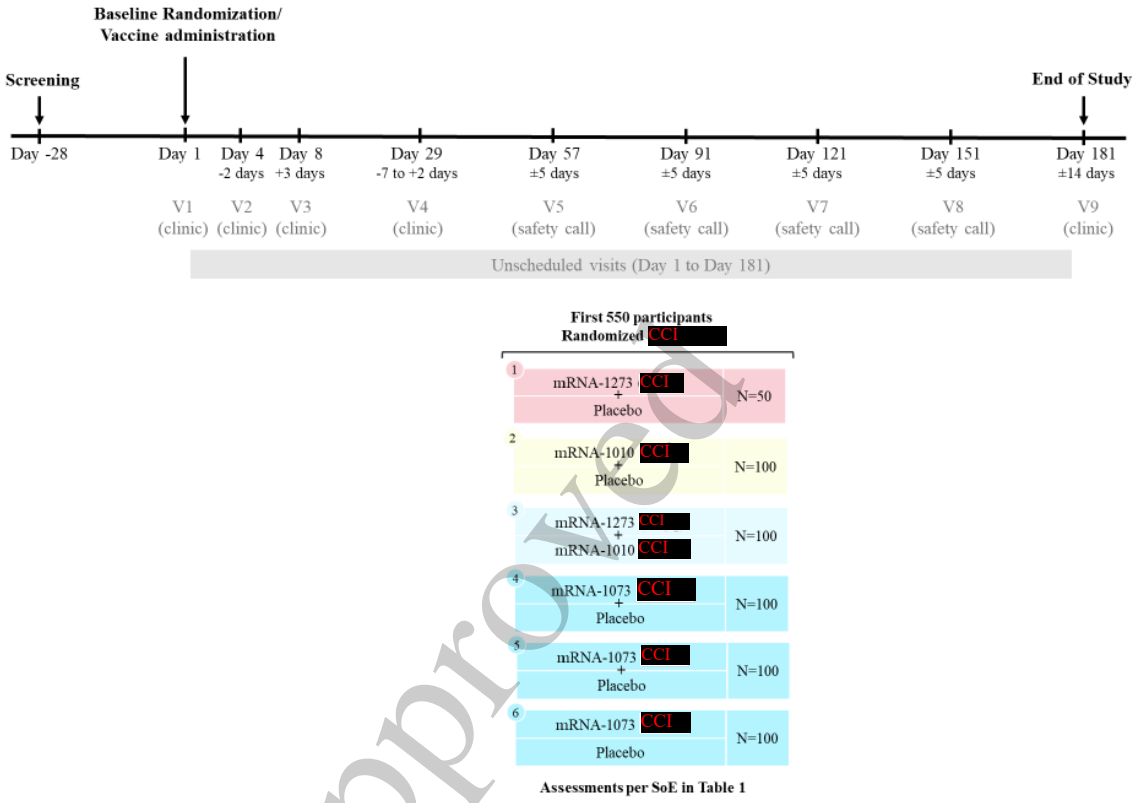
The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine (primary series or booster) must be ≥ 120 days prior (or less per local guidance) to the randomization visit. Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have no known history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening. The numbers of participants and groups are shown in Table 1.

Table 1 Study Arms

#	Group Name	Sample Size (N=550)
1	mRNA-1273 CCI + placebo	50
2	mRNA-1010 CCI + placebo	100
3	mRNA-1010 CCI + mRNA-1273 CCI co-administration	100
4	mRNA-1073 CCI + placebo	100
5	mRNA-1073 CCI + placebo	100
6	mRNA-1073 CCI + placebo	100

All participants of the study will participate in a Screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and a follow-up period (up to 6 months after vaccination). The study schema is presented in Figure 1. Please refer to Table 1 in the protocol for Schedule of Events (SoE).

Figure 1 Study Schema



4.2. Statistical Hypotheses

No formal hypotheses will be tested. All analyses will be descriptive using observed data only, and presented by vaccine group.

4.3. Sample Size and Power

The sample size for this study 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 different study groups.

The study will enroll approximately 550 generally healthy adults 18 to 75 years of age who were previously fully vaccinated for COVID-19 primary series with a locally authorized and approved SARS-CoV-2 vaccine, and their last COVID-19 vaccine must be ≥ 120 days prior to the randomization visit (or less per local guidance). Participants must not have received a licensed influenza vaccine within ≤ 180 days of randomization and have not had known

history of confirmed influenza infection within ≤ 180 days or SARS-CoV-2 infection within ≤ 90 days of Screening. The number of participants and groups are shown in Table 1.

Approximately 550 participants will be enrolled at a CCI [redacted]. A sample size of 100 participants in one group has at least an 85% (or 95%) probability to observe at least 1 participant with an AE at a true 2% (or 3%) AE rate(Table 2).

Table 2 Randomized Sample Size Calculations

Sample Size	True AE Rate	Probability to Observe 0 AEs	Power to Detect at Least 1 AE
50	0.05	7.7%	92.3%
50	0.03	21.8%	78.2%
100	0.03	4.8%	95.2%
100	0.02	13.3%	86.7%

Abbreviation: AE = adverse event.

4.4. Randomization

Randomization will be performed using an interactive response technology (IRT). Participants will be randomized in a CCI [redacted] to receive mRNA-1273 (CCI) + placebo (50 participants), mRNA-1010 (CCI) + placebo (100 participants), mRNA-1010 (CCI + mRNA-1273 (CCI) co-administration (100 participants), mRNA-1073 (CCI) + placebo (100 participants), mRNA-1073 (CCI) + placebo (100 participants), or mRNA-1073 (CCI) + placebo (100 participants). Randomization will be stratified by age (18 to 49 years old and 50 to 75 years old, balanced across the 2 age groups within each vaccination group).

4.5. Blinding and Unblinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with certain exceptions (please refer to Section 9.1 of the protocol for details).

An independent unblinded statistical and programming team will perform the preplanned IA (Section 6.7.1). Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results to the blinded investigators, study site staff, clinical monitors, or participants.

The Data Safety Monitoring Board (DSMB) will review unblinded safety data provided by the independent unblinded statistician to safeguard the interests of clinical study participants and to help ensure the integrity of the study. The DSMB will also review unblinded statistical outputs for ad hoc safety reviews triggered by pause rules, should this occur.

5. Analysis Sets

5.1. Randomization Set

The randomization set consists of all participants who are randomly assigned.

5.2. Full Analysis Set (FAS)

The FAS consists of all randomly assigned participants who receive the IP. Participants will be analyzed according to the group to which they were randomized.

5.3. Per Protocol (PP) Set

The PP set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment and a Day 29 assessment, do not have influenza or SARS-CoV-2 infection at baseline and post-baseline up to Day 29 (as documented by positive RT-PCR testing result), and have no major protocol deviations and/or prohibited concomitant medication use (in the Protocol section 6.5.3) that are prespecified with impacts on the immune response and should be excluded from the PP analysis set. The PP set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.

Subjects with dosing error will be considered as having a protocol deviation. However, the determination of whether to include/exclude subjects from the PP Set due to dosing error will be based on the dosage difference (in µg) between the actual dose received and the randomized dose. The PP Set exclusion criteria for subjects with dosing error are described below in Table 3.

Table 3 PP Set Exclusion Criteria for Dosing Errors

Group Name	Exclusion Conditions
mRNA-1273 CCI + placebo	Any mRNA-1010 received or mRNA-1073 received or mRNA-1273 received CCI or mRNA-1273 received CCI
mRNA-1010 CCI + placebo	Any mRNA-1273 received or mRNA-1073 received or mRNA-1010 received CCI or mRNA-1010 received CCI
mRNA-1010 CCI + mRNA-1273 CCI co-administration	Any mRNA-1073 received or mRNA-1010 received CCI CCI or mRNA-1010 received CCI or mRNA-1273 received CCI or mRNA-1273 received CCI
mRNA-1073 CCI + placebo	Any mRNA-1273 received or mRNA-1010 received or mRNA-1073 received CCI or mRNA-1073 received CCI CCI
mRNA-1073 CCI + placebo	Any mRNA-1273 received or mRNA-1010 received or mRNA-1073 received CCI or mRNA-1073 received CCI
mRNA-1073 CCI + placebo	Any mRNA-1273 received or mRNA-1010 received or mRNA-1073 received CCI or mRNA-1073 received CCI

Note: '≤ x.x µg' includes the missing injection (i.e. 0.0 µg) of the planned vaccination.

5.4. Safety Set

The safety set consists of all randomly assigned participants who receive the IP. The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the vaccination group corresponding to what they actually received according to the rules given below in Table 4:

Table 4 Vaccination Group Corresponding to Dose Received

Group Name	Conditions
mRNA-1273 CCI + placebo	No mRNA-1010 received and No mRNA-1073 received and mRNA-1273 dose CCI
mRNA-1010 CCI + placebo	No mRNA-1273 received and No mRNA-1073 received and mRNA-1010 dose CCI
mRNA-1010 CCI + mRNA-1273 CCI co-administration	No mRNA-1073 received and mRNA-1273 dose CCI and mRNA-1010 dose CCI
mRNA-1073 CCI + placebo	No mRNA-1010 received and No mRNA-1273 received and mRNA-1073 dose CCI
mRNA-1073 CCI + placebo	No mRNA-1010 received and No mRNA-1273 received and mRNA-1073 received CCI and mRNA-1073 received CCI
mRNA-1073 CCI + placebo	No mRNA-1010 received and No mRNA-1273 received and mRNA-1073 received CCI and mRNA-1073 received CCI

5.5. 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 and participants will be included in the vaccination group corresponding to what they actually received.

6. Statistical Analysis

6.1. General Considerations

All analyses will be conducted using SAS Version 9.4 or higher. Statistical outputs (tables, figures, listings, and datasets) will refer study participants as subjects and will use injection of IP and injection interchangeably.

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 immunogenicity tests and nasopharyngeal (NP) swab tests, the baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date (and time, if available) of injection (Day 1).

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.

Symptomatic COVID-19 is defined by the presence of one of the CDC-listed symptoms (CDC 2021c) and a positive RT-PCR test on a respiratory sample.

Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test result at the time of enrollment, with the serologic assay detecting previously resolved SARS-CoV-2 infections that may have occurred between visits, and the RT-PCR to detect active viral infection at the time of a visit.

The following analysis periods of safety analyses will be used:

- Overall period: from the day of vaccination (Day 1) and continues through the earliest date of (study completion, discontinuation from the study, or death).
- 7 days following vaccination: this period includes the day of vaccination and 6 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period will be used for solicited local and systemic AR that occur during this time.
- Up to 28 days following vaccination: starts from the day of vaccination (Day 1) and spans 28 days to include the day of vaccination and 27 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period

will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

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.

Table layouts will be presented according to vaccination group and, separately, randomization stratification factors.

The following vaccination groups will be used for summary purposes:

- mRNA-1273 [redacted] + placebo
- mRNA-1010 [redacted] + placebo
- mRNA-1010 [redacted] + mRNA-1273 [redacted] co-administration
- mRNA-1073 [redacted] + placebo
- mRNA-1073 [redacted] + placebo
- mRNA-1073 [redacted] + placebo
- All (the combined group will be applicable to the disposition and baseline demographic only)

As well, the following groups will be used for summary purposes:

- Overall
- Age: 18 to 49 years old
- Age: 50 to 75 years old

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

6.2. Background Characteristics

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 4 based on the Randomization Set:

- Randomization Set
- FAS
- PP
- Safety Set
- Solicited Safety Set

Percentages will be based on the number of subjects in the treatment group within the Randomization Set. 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 PP 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 Randomization Set:

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

This study treatment only consists of a 1-dose, 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 1 in the Protocol).

A subject disposition listing will be provided, including informed consent, subjects who received IP, subjects who completed study, subjects who discontinued from study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

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), and body mass index (BMI) (kg/m^2). Number and percentage of subjects will be provided for categorical variables such as age group (18 to 49 years old and 50 to 75 years old), gender, race, ethnicity. The summaries will be presented by treatment group as defined in Section 4 based on the FAS.

In addition, randomized subjects with any inclusion and exclusion criteria deviation 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 Medical Dictionary for Regulatory Activities (MedDRA).

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. PT will be displayed in descending order of frequency of mRNA-1073 CCI group and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and 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 prior, concomitant, and post medications is summarized in Appendix C Table 5.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after the injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination group (as defined in Section 6.1) as follows:

- Any concomitant medications and non-study vaccination within 7 days post-injection
- Any concomitant medications and non-study vaccination within 28 days post-injection
- Seasonal influenza or COVID-19 vaccine within 28 days post-injection
- Antipyretic or analgesic medication within 28 days post-injection

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the injection through 28 days will be provided by PT in descending frequency based on mRNA-1073 CCI group.

Medications taken to prevent or treat pain or fever will be collected in the electronic diary (eDiary), and summaries will be provided based on the Solicited Safety Set by vaccination group (and then by age group) as defined in Section 6.1, including within 7 days after injection, beyond 7 days after injection, and any time after injection.

Prior, concomitant and post medications and non-study vaccination will be presented in a listing. Medications taken to prevent or treat pain or fever will also 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. Subjects with any dosing errors will also be presented in a separate listing.

Study duration will be summarized since randomization, 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 Randomization 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. Efficacy analysis

While the study is not powered for efficacy assessments, symptoms of infection with respiratory pathogens will be tracked as an exploratory objective in this study. All participants will provide nasopharyngeal (NP) swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2. Additionally, participants will be instructed to report via Symptom Reporting eDiary or telephone calls whether ILI/COVID-19 symptoms have been experienced (see Section 8.4.5 and Section 8.4.6 in Protocol for symptoms), 2 times weekly from Day 1 through Day 29 and once weekly from Day 30 through Day 181/EoS.

6.3.1. Influenza infection

Influenza infection during the study is an efficacy endpoint, and the analyses of influenza infection by RT-PCR test may be performed using the FAS.

1. A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom, or the occurrence of any 2 or more respiratory symptoms defined below:
    - Sore throat
    - Cough/rhinorrhea/nasal congestion (≥ 1 of the 3 symptoms count as 1 respiratory symptom)
    - Sputum production
    - Wheezing
    - Difficulty breathing
2. A CDC defined ILI is defined as body temperature ≥ 37.8°C (100°F) accompanied by cough and/or sore throat.
3. An RT-PCR confirmed ILI is defined as a positive influenza result by RT-PCR done at any setting during the study period.

The following summaries will be provided for influenza infection:

- RT-PCR test results at baseline will be summarized by vaccination group. Participants with positive influenza results at baseline will be presented in a listing.
- The number and percentage of participants with at least one positive influenza result at post-baseline will be provided by vaccination group. Participants with at least one positive influenza result at post-baseline will be presented in a listing.
- Participants with RT-PCR confirmed ILI will be presented in a listing.

6.3.2. SARS-CoV-2 Infection

- Symptomatic COVID-19 is defined by the presence of one of the below CDC-listed symptoms (CDC 2021c) and a positive RT-PCR test on a respiratory sample. Fever (temperature ≥ 38.0°C [100.4°F]) or chills (of any duration)
- Cough (of any duration)
- Shortness of breath and/or difficulty breathing (of any duration)
- Nausea, vomiting or diarrhea (of any duration)
- Fatigue (lasting ≥ 48 hours)
- Muscle or body aches (lasting ≥ 48 hours)
- Headache (lasting ≥ 48 hours)
- New loss of taste and/or smell (lasting ≥ 48 hours)
- Sore throat, congestion, or runny nose (lasting ≥ 48 hours)

Asymptomatic SARS-CoV-2- infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test result at the time of enrollment, with the serologic assay detecting previously resolved SARS-CoV-2 infections that may have occurred between visits, and the RT-PCR to detect active viral infection at the time of a visit. The following summaries will be provided for SARS-CoV-2- infection:

- RT-PCR test results at baseline will be summarized by test and vaccination group. Participants with positive SARS-CoV-2- results at baseline will be presented in a listing.

- The number and percentage of participants with at least one positive SARS-CoV-2- result at post-baseline will be provided by vaccination group. Participants with at least one positive SARS-CoV-2- result at post-baseline will be presented in a listing.
- Participants with RT-PCR confirmed SARS-CoV-2 infection will be presented in a listing.

6.4. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal from study vaccine and/or study participation, vital signs, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA.

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 vaccination group.

6.4.1. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). An eDiary will solicit daily the participant on the occurrence and intensity of selected signs and symptoms using a pre-defined structured checklist.

The following local ARs will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and underarm gland swelling or tenderness.

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

The solicited ARs will be graded based on the grading scales presented in Table 6 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days post-injection, the subject will be prompted to capture solicited local or systemic AR in the eDiary until resolution, not to exceed 28 days after study injection.

All solicited ARs (local and systemic) will be considered causally related to dosing.

Analyses of solicited ARs will be provided by vaccination group based on the Solicited Safety Set. Summaries of local solicited ARs will be also presented by vaccination group and injection content received in the corresponding side/deltoid.

The number and percentage of participants with any solicited local ARs, solicited systemic ARs, and solicited ARs during the 7-day follow-up period after the injection will be summarized, along with the number of events under each category. A two-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The number and percentage of participants who reported each individual solicited local AR and solicited systemic AR during the 7-day follow-up period after injection will be provided by severity grade.

The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38°C/100.0°F by the oral route) by severity grade and the number and percentage of subjects experiencing a fever of Grade 3 or higher temperature (a temperature greater than or equal to 39.0°C/102.1°F by the oral route) will be provided.

The onset of individual solicited AR is defined as the time point after injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by study day relative to the injection (Day 1 through Day 7). The day of onset of each solicited AR within 7 Days will be summarized.

The duration of local or systemic solicited ARs, along with the specific individual solicited ARs, will be calculated as: reaction end date – reaction start date +1, no matter it is intermittent or continued or if the solicited AR continues beyond 7 days. The duration of each solicited AR within 7 Days will be summarized.

All solicited ARs that continue beyond 7 days post-injection will be summarized.

All delayed ARs with onset day after 7 days post injection will also be summarized.

These summaries may be provided for additional subgroups of selected baseline characteristics.

6.4.2. Unsolicited Treatment-emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not present before exposure to the IP or any event already present that worsens after exposure to IP. 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.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by vaccination group.

Unsolicited AEs will be collected for up to 28 days after IP dose; SAEs, MAAEs, AESIs, and AEs leading to withdrawal will be collected throughout the study. Analyses of unsolicited AE will be provided for up to 28 days after vaccination unless otherwise specified. SAE, AESI, MAAE, and AE leading to discontinuation from the study up to 28 days after vaccination and throughout the study (up to Day 181/End of Study) will be summarized. Up to 28 days after vaccination period will be used as the primary analysis period for Unsolicited AEs.

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT or by PT only for TEAEs with counts of participants included. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1073 CCI group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

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

6.4.2.1. Overview of Unsolicited TEAEs

An overall summary of unsolicited TEAEs up to 28 days after IP injection including the number and percentage of participants, along with the number of events, by vaccination group who experience the following will be presented:

- Any unsolicited TEAEs
- Any unsolicited serious TEAEs
- Any unsolicited AESI
- Any unsolicited TEAEs that are medically-attended
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any unsolicited TEAEs that are fatal

The table will also include number and percentage of participants with unsolicited TEAEs that are treatment-related in each of the above categories.

The overall summary will be also provided considering all reported events up to End of Study.

In addition, separate listings containing individual subject adverse event data for unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, serious treatment-related AEs, and unsolicited treatment-related medically-attended AEs will be provided. Listing of deaths including cause of death, and listing of TEAEs in subjects who died will be provided.

6.4.2.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs up to 28 days after IP injection will be provided by SOC and PT using frequency counts and percentages (i.e. number and percentage of participants with an event) and number of events:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All unsolicited AESI

- All unsolicited AESI that are treatment-related
- All unsolicited serious TEAEs
- All unsolicited 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 AEs that are medically-attended

Summary tables of all unsolicited TEAEs, serious AEs, treatment-related SAEs, MAAEs, and TEAE leading to discontinuation from participation in the study will be also be provided by SOC and PT considering all events reported throughout the study.

6.4.2.3. TEAEs by Preferred Term

Tables of all unsolicited TEAEs will be provided by PT sorted in a descending order according to the frequency of the mRNA-1073 CCI group.

6.4.2.4. TEAEs by Toxicity Grade

The following summary tables of TEAEs will be provided by SOC, PT and the maximum severity or toxicity Grade using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.4.2.5. Subgroup Analysis of TEAEs

The overview of TEAEs and the summary of unsolicited TEAEs by SOC and PT will be provided for the following subgroup:

- Age group (18 to 49 years old and 50 to 75 years old)

6.4.3. Vital Sign Measurements

Vital signs will be collected only at Screening and on the day of vaccination (Day 1), once before and at least 60 minutes after vaccination. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

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 will be flagged in the data listing.

The abnormalities meeting the toxicity grading criteria (Grade 3 or higher) in Appendix F in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 3 or higher abnormality after injection visit, then all results of that specific vital sign for that subject will be presented in the listing.

Observed values and changes from pre-injection to post-injection at Day 1 for all vital sign measurements will be summarized by vaccination group as defined in Section 4. Shift from baseline in the toxicity grades to post-injection result at Day 1 will also be summarized by vaccination group.

6.4.4. Clinical Laboratory Evaluations

Safety laboratory assessments (total white blood cell count, hemoglobin, platelets, ALT, AST, creatinine, alkaline phosphatase, and total bilirubin) will be assessed at Screening and Day 8. Individual results of safety laboratory assessments will be presented in a data listing.

For continuous hematology and serum chemistry parameters, the observed values and changes from baseline will be summarized at each visit by vaccination group as defined in Section 6.1. Hematology and chemistry toxicity grades will be summarized using a shift table from baseline to Day 8 by vaccination group.

A pregnancy test will be performed on all female participants of childbearing potential at the Screening Visit and before vaccine administration on Day 1 via point-of-care urine, and as needed at unscheduled visits (urine or blood pregnancy test based on the investigator's discretion). A follicle stimulating hormone (FSH) test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.

6.4.5. Physical Examinations

A full physical examination, including height and weight, will be performed at the Screening Visit. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities.

Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. Individual results of physical examination will be presented in a data listing.

6.5. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP set. If the number of participants in the FAS and PP set differs (defined as the difference divided by the total number of participants in the PP set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

6.5.1. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE. Immunogenicity assessments will be performed for all participants.

Immune responses to SARS-CoV-2 vaccine antigens will utilize either pseudovirus neutralization (PsVNA) nAb assay or multiplex bAb assay, depending on the timing of data delivery. The following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay
- Influenza: Serum nAb level as measured by microneutralization assay as potential substitution to the HAI assay
- SARS-CoV-2: Serum nAb titers as measured by PsVNA assay and potentially serum binding antibody titers by ELISA or multiplex assay specific to the SARS-CoV-2 proteins
- Cellular immunogenicity in a subset of participants

6.5.2. Immunogenicity Analysis

The following immunogenicity endpoints will be evaluated:

- GMT and GMFR at Day 29 compared with Day 1 (baseline) by HAI assay for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer ≥ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is ≥ 1:10 in anti-HA antibodies measured by HAI assay

- SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥ 4-fold if baseline is ≥ LLOQ or ≥ 4 × LLOQ if baseline titer is < LLOQ in nAb titers measured by PsVNA (or binding antibody assay).
- GMT and GMFR compared with Day 1 (baseline) by HAI for influenza and PsVNA (or binding antibody assay) for SARS-CoV-2
- Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) as defined below

For the immunogenicity endpoints, the geometric mean of specific antibody titers with corresponding 95% CI at each time point and the geometric mean fold rise of specific antibody titers with the corresponding 95% CI at each post-baseline time point over pre-injection baseline at Day 1 will be provided by treatment arm.

Descriptive summary statistics, including median, minimum, and maximum, will also be provided. The geometric mean (GM) will be calculated using the following formula (Nauta, 2011):

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2(t_i)}{n}\right\}}$$

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

The GMFR measures the changes in immunogenicity titers or levels within participants. The GMFR will be calculated using the following formula:

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 2^{\left\{\frac{\sum_{i=1}^{n} log_2(v_{ij}) - log_2(v_{ik})}{n}\right\}}$$

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

The 95% CIs for GMT and GMFR will be calculated based on the t distribution of the log-transformed values then back transformed to the original scale for presentation, unless otherwise specified.

The model-based GM titer will be estimated based on an analysis of covariance (ANCOVA) model. In the ANCOVA model, the log-transformed antibody titer at a post baseline timepoint (Day 29) are treated as a dependent variable, with the treatment group

as an explanatory variable and the log-transformed baseline antibody titer as a covariate, adjusting for the stratification factor(s) as appropriate, that is, age groups (18 to 49 years old, and 50 to 75 years old of age).

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

For each pair of between-group comparison specified in Table 5, the GMR (ratio of GMTs) between the two treatment groups in each pair will be estimated from the ANCOVA model, with 95% CI provided accordingly.

For summarizations of geometric mean titer, antibody titers 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.

For mRNA-1010, seroconversion rate from baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point. Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination HAI titer ≥ 1:40 or a pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer.

For mRNA-1273, seroresponse is defined as either participants with GMFR in nAb or bAb titers of ≥ 4 folds at Day 29 compared to Day 1 in those with baseline titer ≥ LLOQ, or Day 29 titer ≥ 4 × LLOQ if baseline titer is < LLOQ. The immunogenicity of mRNA-1073 will follow the same rules as mRNA-1010 and mRNA-1273.

For each pair of between-group comparison specified in Table 5, the difference of seroresponse/seroconversion rate (SRR/SCR) between the two treatment groups in each pair at Day 29 will be provided, with 95% CI estimated using Miettinen-Nurminen method.

Table 5. Exploratory between-group Immunogenicity comparisons

Influenza					
Treatment Group	Group #4	Group #5	Group #6	Group #3	Group #2
Group #5	#4 v.s. #5	NA	NA	NA	NA
Group #6	#4 v.s. #6	#5 v.s. #6	NA	NA	NA

Group #3	#4 v.s. #3	#5 v.s. #3	#6 v.s. #3	NA	NA
Group #2	#4 v.s. #2	#5 v.s. #2	#6 v.s. #2	#3 v.s. #2	NA
SARS-CoV-2					
Treatment Group	Group #4	Group #5	Group #6	Group #3	Group #1
Group #5	#4 v.s. #5	NA	NA	NA	NA
Group #6	#4 v.s. #6	#5 v.s. #6	NA	NA	NA
Group #3	#4 v.s. #3	#5 v.s. #3	#6 v.s. #3	NA	NA
Group #1	#4 v.s. #1	#5 v.s. #1	#6 v.s. #1	#3 v.s. #1	NA

Note: the 6 treatment groups can be found in Table 1.

6.6. Exploratory Analyses

The below exploratory analyses of immunogenicity may be performed:

- GMT and GMFR (compared to Day 1) to vaccine mismatched strains
- GMT and GMFR (compared to Day 1) to vaccine matched and mismatched strains assayed by alternative methods (eg, microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2)
- Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells and T cells after vaccination
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
- Frequency of laboratory-confirmed clinical influenza and COVID-19 and assessment of immune responses to infection and viral isolates

6.7. Planned Analyses

One IA and final analysis will be conducted in the study.

6.7.1. Interim Analyses

An IA will be performed on the data from 550 participants, after they have completed Day 29 visit, and will include the safety and immunogenicity data collected up to Day 29. Either nAb or bAb assay will be used for assessment of immunogenicity on all participants. The IA will be performed by a separate team of unblinded programmers and statisticians. The analysis will be presented by vaccination groups. Except for a limited number of Sponsor and CRO personnel who will be unblinded to perform the IA, the study site staff, investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis (mRNA-1073-P101 Data Blinding Plan).

6.7.2. Final Analyses

The final analysis of all endpoints will be performed after all participants completed Day 181/EoS. 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 181/EoS. For immunogenicity analysis, either nAb or bAb assays will be used in the study.

7. Changes from Planned Analysis in Protocol

There are no changes in planned analysis.

8. References

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.

Nauta J. Statistics in Clinical Vaccine Trials. Heidelberg: Springer, 2011.

9. Appendices

9.1.1. 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.

9.1.2. Appendix A Analysis Visit Windows

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

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 6 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 6: Analysis Visit Windows for Immunogenicity Assessments

Visit	Visit Window in Study Day
Day 1	1, Pre-vaccination
Day 8	[2, 18]
Day 29	[19, 105]
Day 181	≥106

9.1.3. Appendix C 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 5 below.

Table 5 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

9.1.4. Appendix D 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.

9.1.5. Appendix E Severity Grading of Laboratory Abnormalities

Serum*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****

Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - mg/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - mg/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - mg/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – mg/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

9.1.6. Appendix F Severity Grading of 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.