ModernaTX, Inc.

Protocol mRNA-1975/1982-P101
Amendment 4

A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of Heptavalent mRNA-1975 (SR1-7) and Monovalent mRNA-1982 (SR1) In Parallel Against Lyme Disease in Healthy Participants 18 through 70 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
ATC	anatomic class
bAb	Binding antibody
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
DBP	Data Blinding Plan
DHHS	Department of Health and Human Services
eCRF	Electronic case report form
EDC	Electronic Data Capture
eDiary	Electronic diary
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GLSM	geometric least squares mean
GMC	Geometric mean concentration
GMFR	Geometric mean fold-rise
GMR	Geometric mean ratio
CCI	[redacted]
IA	Interim analysis
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IST	Internal safety team
LA-2	Recombinant monoclonal antibody with known bactericidal activity against Borrelia SR-1
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MMRM	mixed model for repeated measures
MTTT	Modified Two-Tiered Testing for Lyme serology screening
N/A	not applicable
OspA	Outer surface protein A
PCR	Polymerase chain reaction
PD1	Post Dose 1
PD2	Post Dose 2
PD3	Post Dose 3

Abbreviation	Definition
PN	preferred name
PP	Per-protocol
PT	preferred term
PN	preferred name
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBA	Serum bactericidal activity
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SR	Serotype
STTT	Standard Two-Tiered Testing for Lyme serology screening
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-1975/1982-P101 is based on the clinical study Protocol Amendment 4, dated 08 Apr 2025.

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-1975/1982-P101 is a Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety and immunogenicity of heptavalent mRNA-1975 (SR1-7) and monovalent mRNA-1982 (SR1) in parallel against Lyme disease in healthy participants 18 through 70 years of age.

NJSTATS 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 interim analysis (IA) clinical database lock/snapshot. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

2 Study Objectives

2.1 Primary Objective

The primary objective is the following:

- To evaluate the safety and reactogenicity of mRNA-1975 and mRNA-1982.

2.2 Secondary Objective

The secondary objective is the following:

- To evaluate the humoral immunogenicity of mRNA-1975 and mRNA-1982 at Days 1, 29, 85, and 197.

2.3 Exploratory Objectives

The exploratory objectives are the following:

3 Study Endpoints

3.1 Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each study injection.
- Unsolicited adverse events (AEs) through 28 days after each study injection.
- Medically attended adverse events (MAAEs) from Day 1 to 6 months after last study injection.
- Adverse events of special interest (AESIs) from Day 1 to End of Study (EOS).
- Serious adverse events (SAEs) from Day 1 to EOS.
- AEs leading to discontinuation of study injection or study participation from Day 1 to EOS.
- Safety laboratory abnormalities through 7 days after each study injection.

3.2 Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- Geometric mean concentration (GMC) of anti-Outer surface protein A (OspA) binding Immunoglobulin G (IgG) antibodies measured by enzyme-linked immunosorbent assay (ELISA) or a similar method at Days 1, 29, 85, and 197.
- Geometric mean fold-rise (GMFR) of anti-OspA binding IgG Ab concentration at Days 29, 85, and 197 compared to Day 1 (Baseline).

3.3 Exploratory Endpoints

The exploratory endpoints are the following:

4 Study Design

4.1 Overall Study Design

4.1.1 General Design

This is a Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity in parallel of 1) mRNA-1975, containing SR1-7 antigens specific for the 4 major Borrelia species causing disease in United States and Europe (Borrelia burgdorferi (SR1), afzelii (SR2), bavariensis (SR4) and garinii (SR3, 5-7)) and, 2) mRNA-1982, containing SR-1 antigen specific for Borrelia burgdorferi, among healthy participants 18 through 70 years of age.

A total of 800 healthy participants will be enrolled. Those with a history of past treated Lyme infection will represent no more than 20% of all participants. Randomization in the dose expansion groups will be stratified by with or without history of past treated Lyme infection (confirmed by Lyme seropositivity at Screening).

There are approximately 100 participants in each of the 8 groups as shown in Table 1.

Table 1 Randomized Dose Groups

Product	Dose	Schedule	Sample Size
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
Placebo (saline)	N/A	3 doses (0, 2, and 6 months)	100

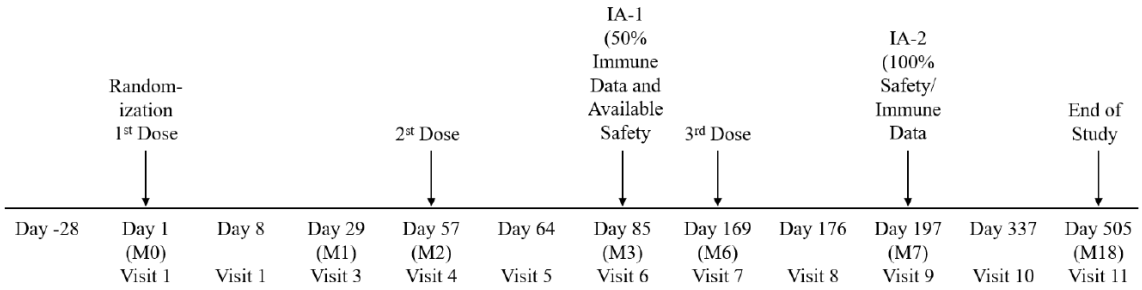
Abbreviation: N/A = not applicable.

Two IAs are planned for this study.

4.1.2 Study Schema

The study schema is displayed in Figure 1.

Figure 1: Study Schema



Abbreviations: IA = interim analysis; M = month.

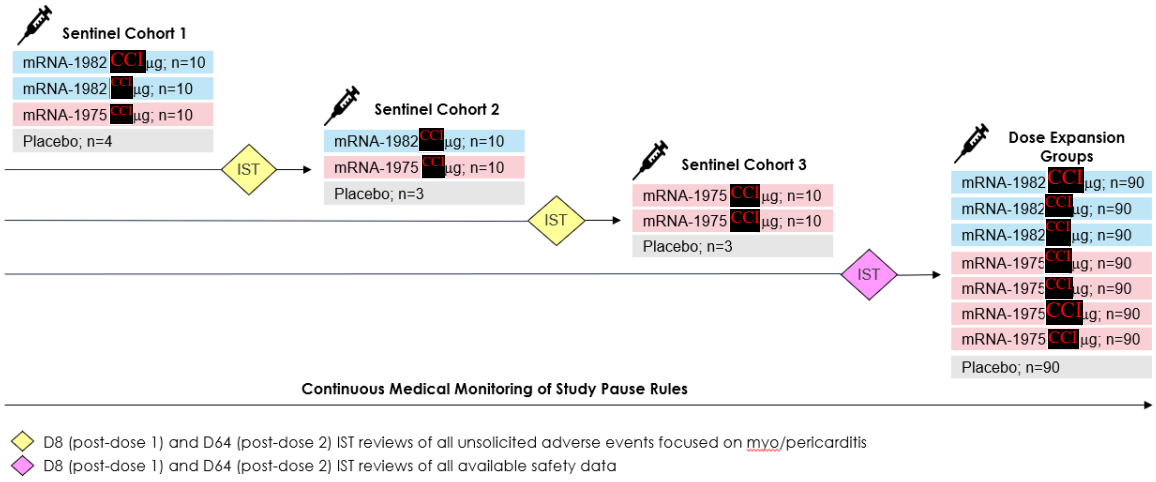
Enrollment Procedure

As shown in Figure 2, study enrollment will begin with an initial sentinel cohort consisting of approximately 10 participants randomized to each of the CCI µg and CCI µg dose groups, plus approximately 4 participants randomized to placebo (N = approximately 34 in total). Study enrollment will then pause for an independent internal safety team (IST) review of unsolicited AEs through Day 8 focused on AEs potentially concerning for myocarditis/pericarditis. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, enrollment will resume with a second sentinel cohort of approximately 10 participants randomized to each of the CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 in total). Study enrollment will then pause again for a second focused IST review of unsolicited AEs reported in the study overall through Day 8 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, study enrollment will resume with a third and final sentinel cohort of 10 approximately participants randomized to each of the CCI µg and CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 in total). Study enrollment will then pause again for a third focused IST review of all available safety data for the study overall through Day 8 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified in the third scheduled IST review, dose expansion with enrollment of the remaining 90 participants in each of the dose groups will proceed in parallel.

Similarly, administration of dose 2 (Day 57) will begin with the initial sentinel cohort. Administration of dose 2 will then pause for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of the initial sentinel cohort. If no AEs

concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of dose 2 will resume with the second sentinel cohort. Administration of dose 2 will then pause again for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of dose 2 will resume with the third and final sentinel cohort. Administration of dose 2 will then pause again for an IST review of all available safety data for the study overall through Day 64 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified, administration of dose 2 to the remaining 90 participants in each of the dose groups will proceed in parallel.

Figure 2: Sentinel Cohort Dose Escalation and IST Reviews for Dose 1 and Dose 2



Abbreviations: µg = microgram; D = day; IST = internal safety team; mRNA = messenger ribonucleic acid; n = number of participants

4.2 Statistical Hypotheses

There is no hypothesis testing in this study.

4.3 Sample Size and Power

The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1975 and mRNA-1982. A total of 800 healthy participants will receive mRNA-1975, mRNA-1982, or placebo. Of these, 100 participants in each dose group and placebo group will be included. With 100 participants in each group, there is approximately 95% probability to observe at least 1 participant with an AE with a true AE rate of 3%.

4.4 Blinding and Unblinding

This study is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product (IP) administered until the study database is locked and unblinded, with certain exceptions; please refer to Data Blinding Plan (DBP) and Blinding Plan for Immunogenicity Data for details.

4.5 Planned Immunogenicity Testing Strategy

The sample testing strategy varies based on different treatment arms.

1. For all the participants in the four heptavalent mRNA-1975 treatment arms (CCI µg, CCI µg, CCI µg, and CCI µg) and 50% of the participants receiving placebo, immunogenicity assessments for antibody for each serotype (SR1-7) will be performed.
2. For all the participants in the three monovalent mRNA-1982 treatment arms (CCI µg, CCI µg, and CCI µg) and the other 50% of participants receiving placebo, immunogenicity assessments for antibody against SR1 will be performed.

The 50% of placebo participants who enrolled first will be included in mRNA-1982/placebo group (Group 2 above); The rest of 50% of placebo participants will be included in mRNA-1975/placebo group (Group 1 above).

The laboratory personnel in charge of immunogenicity testing will be blinded to the actual treatment assignment but need to know which strategy (1 or 2 as above) will be conducted for samples collected from a specific participant.

The unblinded lead biostatistician will access participant level treatment assignment data, generate the partial unblinding listing with the information whether the samples from each specific participant will be conducted using SR1-7 testing or only SR1 testing, and send it to laboratory personnel in charge of immunogenicity testing. The blinded team should not have access to this partial unblinding listing.

5 Analysis Populations

The following analysis sets are defined: Randomized Set, Safety Set, Solicited Full Analysis Set (FAS), and Per-Protocol (PP) Set.

5.1 Randomization Set

The Randomization Set consists of all participants who are randomized.

5.2 Full Analysis Set (FAS)

The FAS consists of all randomized participants who receive the study injection. Participants will be included in the treatment arm to which they were randomized.

5.3 Safety Set

The safety set consists of all randomized participants who receive the study intervention. The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the treatment arm corresponding to what they actually received.

5.4 Solicited Safety Set

The solicited safety set consists of all participants in the safety set who contribute any solicited adverse reaction data. The solicited safety set will be used for the analyses of solicited ARs, and participants will be included in the treatment arm corresponding to what they actually received.

5.5 Per-Protocol (PP) Set

The PP set consists of all participants in the FAS who comply with the injection schedule and the timings of immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment, and have no major protocol deviations that impact the immune response.

For analysis purpose, the participants who received the injections within allowable day windows can be considered compliant with the injection schedule. The allowable day windows are between study days [50 and 85] inclusive for the second injection, and study days [141 and 225] inclusive for the third injection. The allowable dose level is between [75% and 150%] of nominal (assigned) level if a participant takes the same investigational medicinal product (IMP) as planned (assigned).

For analysis purpose, the allowable day windows for immunogenicity blood sampling can be found in immunogenicity visit windows in Appendix B.

Participants who are excluded from the PP set due to major protocol deviations will be determined during the Protocol Deviation Review Meeting.

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.

6 Statistical Analyses

6.1 General Considerations

All analyses will be performed separately by treatment group, unless otherwise specified. Participants from sentinel cohorts and dose expansion groups will be pooled and analyzed by dose group.

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

Categorical variables will be summarized using counts and percentages.

Baseline value for the study, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP. If assessment time is collected, time should be compared as well.

For immunogenicity test, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP.

For safety laboratory tests, the study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP; the period baseline for Day 8 and Day 57 is the same as the study baseline, the period baseline for Day 64 and Day 169 is the non-missing Day 57 measurement collected before the second dose of IP, and the period baseline for Day 176 is the non-missing Day 169 measurement collected before the third dose of IP.

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 participants in that treatment group within the analysis set of interest, unless otherwise specified.

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

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

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

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

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

b) study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;

c) study day on or after the date of the second injection but before the third injection (if applicable) will be calculated as: date of assessment/event – date of the second injection + 1;

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

For calculation regarding antibody concentrations/levels, antibody values reported as below Lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. For IA-1 analyses, any numeric results above ULOQ were used as-is without capping. Values reported as ">yyyy" were imputed as yyyy, where yyyy was not necessarily ULOQ and were not compared with ULOQ column. For the other analyses (including IA-2 analyses and final CSR analyses), numeric results above ULOQ (by comparing results with ULOQ column) or reported as ">zzzz" will be imputed by ULOQ.

The following **analysis periods for safety analyses** will be used in this study:

- Up to 7 days after any vaccination injection: this period starts at the day of each injection and continue through 6 subsequent days. This analysis period will be used for analyses of solicited ARs.
- Up to 28 days after any vaccination injection: this period starts at the day of each injection and continue through 27 subsequent days. This analysis period will be used as the primary analysis period for analyses of unsolicited AEs, unless specified otherwise.
- Throughout the study: this period starts at the first injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death). This analysis period will be used for analyses of unsolicited AEs including

any SAEs, MAAEs, AEs leading to discontinuation of study vaccine and/or study participation, and AESIs.

Unscheduled visits: 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 the derivation of maximum/minimum values and maximum/minimum change from baseline values for safety analyses.
- In individual participant data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B, Table 2.

Incomplete/missing data:

- Imputation rules for missing dates of prior/concomitant medications and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- If the laboratory results are reported as "< X" (e.g., <0.1), the numeric values will be substituted by 0.5 × X in the summary when treating the results as continuous variables. If the laboratory results are reported as "> X" (e.g., >3000), the numeric values will be substituted by X in the summary statistics for continuous variable.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following treatment groups will be used for summary purposes:

- mRNA-1975 CCI µg
- mRNA-1975 CCI µg
- mRNA-1975 CCI µg
- mRNA-1975 CCI µg
- mRNA-1975 Total (optional)

- mRNA-1982 CCI µg
- mRNA-1982 CCI µg
- mRNA-1982 CCI µg
- mRNA-1982 Total (optional)
- Placebo
- Overall (optional)

Total for mRNA-1975 vaccine, total for mRNA-1982 vaccine, and overall treatment group will be applied to disposition, demographics, baseline characteristics, and concomitant medications tables. Total for mRNA-1975 vaccine and total for mRNA-1982 vaccine will be applied to adverse event tables.

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:

- Randomized Set
- Full Analysis Set
- Per-Protocol Set
- Safety Set
- Solicited Safety Set

The percentage will be based on participants in the Randomization Set.

The number of participants in the following categories will be summarized:

- Participants screened
- Screen failure participants
- Individual reasons for screen failure

The percentage of participants who screen failed will be based on the number of participants screened. The percentage of participants reporting each reason for screen failure will be based on the number of participants who screen failed. For screened failure participants, age

(years), as well as sex, race, ethnicity, baseline Lyme seropositivity status, 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 Randomized Set:

- Received each injection (first, second, third) of study vaccine
- Completed three injections of study vaccine
- Discontinuation of study vaccine and the reason for discontinuation
- Received the first injection but did not receive the other two injections and the reason
- Received the first two injections but did not receive the last two injections and the reason
- Completed the study (up to Day 505/Month 18)
- Prematurely discontinued the study and the reason for discontinuation

The number and percentage of the randomized participants will be summarized by site and treatment group.

A participant disposition listing will be provided, including informed consent data, baseline Lyme seropositivity status (seropositive, seronegative), completion of each study injection (first, second, and third), participants who completed study, participants who discontinued from study vaccine or from study 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.

6.2.2 Demographics and Baseline Disease 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 participants will be provided for categorical variables such as age group (≥18 and <50 years, ≥50 and ≤70 years), sex, race, and ethnicity.

The summaries will be presented by treatment group based on Randomized Set, FAS, Safety Set, and PP Set.

Demographics and baseline disease characteristics data will be presented 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, PT, and treatment group based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed alphabetical order. PT will be displayed in descending order of frequency of "Overall" group and then alphabetically within SOC.

Medical history data will also be presented in a listing.

6.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications by treatment group will be based on the Safety Set.

Imputation rules for missing/partial dates of medications are detailed in Appendix C, Table 3. Categorization of prior, concomitant and post medications are defined below:

- A medication taken before the first study vaccine injection date is considered a "prior" medication;
- A medication taken through 28 days after any study vaccine injection (first, second and third injection) is considered a "concomitant" medication;
- A medication taken after 28 days after any study vaccine injection and through the next injection or the last study visit (whichever occurs first), is considered a "post" medication.

An overall summary of concomitant medications including the number and percentage of participants who take the following will be presented by treatment group:

- Any concomitant medications or non-study vaccination within 28 days post each injection
- Any non-study vaccination within 28 days post each injection
- Any concomitant medications or non-study vaccination within 28 days post any injection

- Any non-study vaccination within 28 days post any injection

A summary table of concomitant medications that continued or newly received within 28 days post-injection will be provided by anatomic class (ATC) level 2 and preferred name (PN) in descending frequency in "Overall" group.

A summary table of all medications that continued or newly received throughout the study will be provided by ATC level 2 and PN in descending frequency in "Overall" group.

Medications for pain or fever will be collected on electronic diary (eDiary) and summaries will be provided based on the Solicited Safety Set by treatment group for each injection (first, second, third injection) including within 7 days after injection.

Prior, concomitant and post medications will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5 Study Exposure

The number and percentage of the participants with only one, two, or three injections will be summarized by treatment group based on the Safety Set.

Study duration will be summarized since randomization, since the first injection, since the second injection, and since the third injection until complete/discontinued the study or the data cutoff date, whichever occurs first, based on the Safety Set. The proportion of participants with study duration of at least 168 days (6 months), and at least 336 days (12 months) after the last injection will be summarized.

Study IP administration data including reasons for IP injection not administered will be presented in a listing. Dosing error data will also be presented in a listing.

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 participant's rights, safety, or well-being. Major protocol deviation rules will be developed and finalized before database lock.

The number and percentage of the participants with each major protocol deviation type will be provided by treatment group based on the Randomized Set.

Major protocol deviations may impact immune response corresponding to the immunogenicity objective such as dosing error, etc., and participants with such deviations

will be excluded from the Per-Protocol Set for immunogenicity analyses; these major protocol deviations will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from Per-Protocol Set will be summarized and listed.

6.2.7 COVID-19 Impact

A listing will be provided for Coronavirus Disease 2019 (COVID-19) impact including injections, visits, and assessments avoided/missed due to COVID-19.

6.3 Safety Analyses

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

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 analysis will be summarized by actual treatment group unless otherwise s specified. Participants will be included in the study treatment group corresponding to what they received. Selected Safety endpoints may be summarized by age group (≥18 and <50 years, ≥50 and ≤70 years).

For safety analyses, if a subject has any dosing error, use the highest dose given among the three injections and assign the subject to the closest protocol-specified dose group. If a participant who received both mRNA-1975 and mRNA-1982 and the highest dose levels for each IMP are the same, then:

- if the participant received all the 3 injections, he/she will be assigned to the IMP which the participant received for 2 of the 3 injections;
- if the participant received only 2 injections, he/she will be assigned to IMP administered for Dose 2.

Any special cases will be discussed with decision documented before unblinding.

6.3.1 Unsolicited Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Summaries and analyses of AE newly occurred after study vaccination or any

AE event already present that worsens after exposure to study vaccination will be provided. AEs 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 SOC and PT using MedDRA v28.0 or higher.

Unsolicited AEs will be collected for up to 28 days after any injection (first, second, or third injection). SAEs, MAAEs, AESIs, and AEs leading to discontinuation of study vaccine and/or study participation will be collected throughout the study.

Separate summaries will be provided for unsolicited AEs up to 28 days after any injection and similarly for those throughout the study, unless otherwise specified.

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT with counts of participants included. PT will be displayed in descending frequency in "mRNA-1975 vaccine Total " 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. Participants will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if participants reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of participants in the Safety Set.

In addition, the number of events and number of participants with occurrences of selected AESIs identified by Standardized MedDRA Queries (SMQ) in up to 28 days after injection, and throughout the study will be summarized only for final CSR. SMQ will be summarized by subordinate SMQ, and PT, if applicable. Two sets of summary tables will be provided, one will be based on combined broad and narrow scope of SMQ, the other will be based on narrow scope. SMQ and subordinate SMQ within each SMQ will be displayed in alphabetic order. PTs will be displayed in descending order of frequency in "mRNA-1975 Total " group and then alphabetically within subordinate SMQ or SMQ if no subordinate SMQ.

Detailed descriptions of selected SMQ are presented in Appendix H, Table 7 and Table 8.

6.3.1.1 Overview of Unsolicited AEs

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

- Any unsolicited AEs
- Any unsolicited SAEs
- Any fatal AEs
- Any unsolicited MAAEs
- Any unsolicited AEs leading to discontinuation from study vaccine
- Any unsolicited AEs leading to discontinuation from participation in the study
- Any unsolicited severe AEs
- Any AESI

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

The overall summary will be provided for the unsolicited AEs up to 28 days after any injection and those throughout the study, respectively.

In addition, separate listings containing individual participant adverse event data for unsolicited AEs, unsolicited treatment-related AEs, unsolicited severe AEs, unsolicited treatment-related severe AEs, serious AEs, treatment-related SAEs, unsolicited AEs leading to discontinuation from study vaccine, unsolicited AEs leading to discontinuation from participation in the study, unsolicited MAAEs, and AESI will be provided separately.

6.3.1.2 AEs by System Organ Class and Preferred Term

The following summary tables of AEs will be provided by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited AEs
- All unsolicited AEs that are treatment-related
- All unsolicited SAEs
- All unsolicited SAEs that are treatment-related

- All unsolicited AEs leading to discontinuation from study vaccine
- All unsolicited AEs leading to discontinuation from participation in the study
- All unsolicited severe AEs
- All unsolicited severe AEs that are treatment-related
- All unsolicited MAAEs
- All unsolicited MAAEs that are treatment-related
- All AESI

The above summary tables by SOC and PT will be provided for the period up to 28 days after any injection and then separately throughout the study.

6.3.1.3 AEs by Preferred Term

A summary table by PT will be provided for all unsolicited AEs up to 28 days after any injection and then separately throughout the study. PTs will be sorted in a descending order according to the frequency in the "mRNA-1975 Total" group.

6.3.1.4 AEs by System Organ Class, Preferred Term and Severity

The following summary tables will be provided for all unsolicited AEs up to 28 days after any injection by SOC, PT, and maximum severity (from low to high order: mild (grade 1), moderate (grade 2), severe (grade ≥3)) using frequency counts and percentages:

- All unsolicited AEs
- All unsolicited AEs that are treatment-related

The above summary tables will be also repeated for all unsolicited AEs throughout the study.

6.3.2 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).

The solicited ARs are recorded by the participant in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified

post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist in the eDiary (i.e., solicited ARs).

Any solicited ARs occurring within 7 days after each injection, if not entered in the eDiary in the required input time window, should be reported in the Reactogenicity eCRF. Solicited ARs reported in both the eCRF and eDiary will be included in the evaluation of solicited ARs.

The following local ARs will be solicited: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

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

The solicited ARs will be graded based on the grading scales presented in Protocol Table 10, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Department of Health and Human Services [DHHS] 2007). Investigator will assess Grade 4 events (with exception of fever). Please see Appendix G, Table 6 for severity grading of reactogenicity abnormalities.

If a participant reported a solicited AR during the solicited period and did not record the event in the eDiary, the event should be recorded by the site staff in Electronic Data Capture (EDC) where reactogenicity is collected using the Reactogenicity eCRF.

If a solicited AR starts during the solicited period, but continues beyond 7 days after dosing, the site should collect an end date in the Reactogenicity eCRF from the participant, to close out the event in the EDC.

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

All solicited ARs analyses will be based on Solicited Safety Set. All solicited ARs analyses will be provided by actual treatment group.

An overall summary of solicited ARs including the number and percentage of participants who reported any solicited AR, any solicited local AR, and any solicited systemic AR within 60 minutes and 7 days after each injection, grade 3 or grade 4 Solicited AR after each injection and after any injection will also be summarized.

The number and percentage of participants who reported any solicited AR, any solicited local AR, and any systemic solicited AR within 7 days after each injection and after any injection will be tabulated with a two-sided 95% exact CI using the Clopper-Pearson method.

The number and percentage of participants who reported any solicited AR, any solicited local AR, any systemic solicited AR and individual solicited ARs (has a severity grade of Grade 1 or greater) within 7 days after each injection and after any injection will be tabulated by severity grade.

The number and percentage of participants experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral) by severity grade and the number and percentage of participants 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) in cumulative half-degree (°F) increments will be provided.

The onset day of an individual solicited AR after each injection is defined as the time point at which the solicited AR first occurred. The number and percentage of participants who reported any solicited AR, any solicited local AR, systemic solicited AR and individual solicited ARs (has a severity grade of Grade 1 or greater) within 7 days after each injection will be summarized by onset day.

The duration (days) of each solicited AR after each injection will be summarized. Duration will be calculated as end date of solicited AR – onset date of solicited AR + 1, no matter it is intermittent or continued or if the solicited AR continues beyond 7 days.

Listing of pause rules assessment for grade 3 solicited AR within 7 days of injection will be provided.

6.3.3 Clinical Laboratory Evaluations

Safety laboratory testing will include hematology and serum chemistry.

For hemoglobin, the toxicity grading criteria based on the US Food and Drug Administration (FDA) Guidance for Industry will be presented using period baseline and study baseline respectively. For the other hematology and serum chemistry parameters, the toxicity grading criteria based on the US FDA Guidance for Industry will be presented using period baseline. Please see Appendix E, Table 4 for severity grading of laboratory abnormalities.

All laboratory test results will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the

toxicity grading criteria (Grade 3 or higher) in Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) through 7 days after each injection in any safety laboratory (hematology and serum chemistry) will be listed separately.

The number and percentage of participants for each toxicity grade (based on period baseline) will be tabulated at Baseline, Day 8, Day 57 (predose), Day 64, Day 169 (predose), Day 176. The number and percentage of participants for each maximum toxicity grade will also be provided.

Shift from the period baseline in toxicity grade will be summarized by visit for all the hematology and serum chemistry parameters:

- Day 8 change from baseline,
- Day 57 predose change from baseline,
- Day 64 change from period baseline (period baseline for second injection period),
- Day 169 predose change from period baseline (period baseline for second injection period),
- Day 176 change from period baseline (period baseline for third injection period).

For hemoglobin, shift from the study baseline in toxicity grade will be summarized by visit:

- Day 8 change from study baseline,
- Day 57 change from study baseline,
- Day 64 change from study baseline,
- Day 169 change from study baseline,
- Day 176 change from study baseline,
- Maximum change over study from study baseline.

A point-of-care urine pregnancy test will be performed at the Screening Visit and before each vaccine dose. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator. A by-participant listing will be provided for pregnancy tests.

A follicle stimulating hormone (FSH) test may be performed at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm menopausal status. A by-participant listing will be provided for FSH tests.

6.3.4 Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, pulse, respiratory rate, and oral 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) based on DHHS 2007 in any vital sign measurement will be listed separately. If a participant has a vital sign result with Grade 3 or higher abnormality at any post injection visit, then all results of vital sign measurement for that participant will be presented in the listing. Please see Appendix F, Table 5 for severity grading of vital signs abnormalities.

6.4 Immunogenicity Analyses

The analysis of immunogenicity will be based on the PP Set and will be performed by treatment group unless otherwise specified. Immunogenicity analysis maybe performed by age group.

The GMC 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 concentration or level.

The GMFR measures the changes in immunogenicity concentration or level 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 concentration or level for participant i at time points j and k, $j \neq k$ and k is baseline.

6.4.1 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected and the following analytes will be measured:

6.4.2 Analysis of Secondary Humoral Immunogenicity Endpoints

The secondary immunogenicity endpoints will be analyzed as following:

- GMC of anti-OspA binding IgG antibody against each OspA serotype (SR1-7, when applicable) with corresponding 2-sided 95% confidence interval (CI) will be provided by treatment group at Day 1, 29, 85, and 197 based on PP set. The 2-sided 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at each time point: the number of participants (n), median, minimum and maximum.
- For anti-OspA binding IgG antibodies, the GMC at Days 29, 85, and 197 for each treatment group, will be estimated based on an analysis of covariance (ANCOVA) model that will be carried out using the PP Set. The dependent variables will be the log-transformed immunogenicity concentration or level at Days 29, 85, and 197 respectively with treatment group and age group (≥18 and <50 years, ≥50 and ≤70 years) as factors, and baseline log-transformed immunogenicity concentration or level as covariate. The geometric least square means (GLSMs) for each treatment group at Days 29, 85, and 197 and its corresponding 95% CI on a log-transformed scale estimated from the model will be back-transformed to obtain the estimates in the original scale as an estimate of the GMC.
- Geometric mean ratio (GMR) of anti-OspA binding IgG antibody against each OspA serotype (when applicable) defined as the ratio of GLSM of (1) each mRNA-1975/mRNA-1982 treatment arm vs placebo; (2) mRNA-1975 (CCI µg) vs mRNA-1982 (CCI µg); (3) mRNA-1975 (CCI µg) vs mRNA-1982 (CCI µg). The GMR at Days 29, 85, and 197 for each comparison will be estimated by the ratio of GLSMs. The GMR and its 95% CI will also be provided to assess the difference in antibody response between treatment arms.
- GMFR of postbaseline/baseline (Day 1) concentration or level of anti-OspA binding IgG Ab concentration against each OspA serotype (when applicable) with corresponding

95% CI will be provided at Day 29, 85, and 197. The 95% CIs will be calculated based on the t-distribution of the difference in the log-transformed values (post-baseline time point – Day 1) and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided: the number of participants (n), median, minimum, and maximum.

6.4.3 Exploratory Analyses of Immunogenicity Endpoints

6.4.3.1 CCI

CCI

CCI

[redacted]

6.4.3.2 CCI [redacted]

CCI [redacted]

CCI

6.4.3.3 CCI

CCI

6.4.4 Sensitivity Analysis

If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, immunogenicity endpoints will be conducted using the FAS. Analysis is required if the condition is met at end of study; it is optional for the IA.

For anti-OspA binding IgG antibodies, the GMC at all evaluable postbaseline timepoints for each treatment group, will be estimated using mixed model for repeated measures (MMRM) model for FAS. The model will include treatment group, visit, age group, and treatment group by visit interaction as fixed effects, and baseline log-transformed immunogenicity concentration or level as covariate. An unstructured covariance structure will be used to model the within-subject errors. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence issue due to the unstructured

covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors.

The GLSMs and corresponding 2-sided 95% CI for the anti-body concentration for each treatment group will be provided at each timepoint. The GLSM and corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale.

GMR of anti-OspA binding IgG antibodies will be analyzed by the ratio of GLSM between different treatment groups for comparison at each postbaseline evaluable timepoints based on the method similar to the GMR for anti-OspA binding IgG antibodies (Section 6.4.2).

6.5 Planned Analyses

The following analyses will be conducted:

1. Two IAs will occur. IAs will be performed by a separate team of unblinded programmers and statisticians. Pre-identified Sponsor team members will be unblinded to review treatment level results. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded until the conclusion of the study.

- IA-1 will occur when at least 50% of participants reach Day 85 (PD2).
- IA-2 will occur when 100% of the participants reach Day 197 (PD3).

2. The final CSR will occur when all the eligible participants have completed Day 505 (Month 18) Visit and will include the available safety and immunogenicity data.

7 Biomarker Analyses

Analysis of biomarker data is out of scope of this SAP and will be prepared separately.

8 Changes from Planned Analyses in Protocol

Not applicable.

9 References

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 2020 Oct 28] [10 screens]. Available from:

https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

10 List of Appendices

10.1 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.

10.2 Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity 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 2 below.

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

- If multiple assessments occur within both scheduled visit and unscheduled visit, the assessment collected at scheduled visit 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 with equal distance to the target study day, the last assessment will be used.

Table 2 Visit Window

Visit	Target Study Day	Visit Window in Study Day
Safety Labs		
Baseline	Screening	<= 1 Predose
Day 8 (7 days PD1)	Day 8	[2, 32]
Day 57 (56 days PD1)	minimum(Day 57, Dose 2 date)	[33, Dose 2 day Predose]
Day 64 (7 days PD2)	7 days PD2	[Dose 2 day +1, Dose 2 day + 52]
Day 169 (112 days PD2)	minimum (Dose 2 date + 112, Dose 3 date)	[Dose 2 day + 53, Dose 3 day Predose]
Day 176 (7 Days PD3)	7 days PD3	[Dose 3 day + 1, EOS]
Period Baseline for safety labs: For the first injection period, the period baseline is the same as the study baseline. For the second injection period, the period baseline is the non-missing Day 57 measurement collected before the second dose of IP. For the third injection period, the period baseline is the non-missing Day 169 measurement collected before the third dose of IP.		
Lyme Serodiagnostic Testing		
Baseline	Screening	< 1
Day 85	Day 85	[2, 127]
Day 169	Day 169/Dose 3	[128, 253]
Day 337	Day 337	[254, 421]

Day 505	Day 505	>422
Immunogenicity		
Baseline	Dose 1 date	<=1
Day 29 (28 days PD1)	Day 29	[21, 43]
Day 57 (56 days PD1)	minimum(Day 57, Dose 2 date)	[44, Dose 2 day]
Day 85 (28 days PD2)	28 days PD2	[Dose 2 day + 21, Dose 2 day + 56]
Day 169 (112 days PD2)	minimum(Dose 2 date + 112, Dose 3 date)*	[Dose 2 day + 57, Dose 3 day]
Day 197 (28 days PD 3)	28 days PD3	[Dose 3 day + 21, Dose 3 day + 84]
Day 337 (168 days PD3)	168 days PD3	[Dose 3 day + 85, Dose 3 day + 252]
Day 505 (336 days PD 3)	336 days PD3	[>=Dose 3 day + 253, EOS]

Abbreviation: PD1 = Post Dose 1; PD2 = Post Dose 2; PD3 = Post Dose 3.
* For safety laboratory and Immunogenicity data**,** if Dose 2 day or Dose 3 day are missing ie., no second/third injection, the targeted dates for Dose 2 or Dose 3 day will be used for calculation of visit windows.

10.3 Appendix C Imputation Rules for Missing Dates of Prior/Concomitant Medications

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 first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first 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 eCRF is not Yes). In this case, use the date of first injection
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first 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 eCRF is not Yes). In this case, use the date of first 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 first injection for purposes of determining status as prior or concomitant. 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 eCRF 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:
   - 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 3 below.

	Medication Stop Date		
Medication Start Date	< First Dose Date of IP	≥ Each Dose Date, and ≤ 28 Days After Each Dose	> 28 Days After Each Dose, and < minimum (next dose date if there is any, datadatadatadata cutoff date or end of study date) [2]
< First dose date of IP [1]	P	P, C1/C2/C3	P, C1/C2/C3, A
≥ Each dose date and ≤ 28 days after each dose	-	C1/C2/C3	C1/C2/C3, A
> 28 days after each dose, and < minimum (next dose date if there is any, cutoff date or end of study date)	-	-	A

P: Prior; C1: Concomitant after Dose 1; C2: Concomitant after Dose 2; C3: Concomitant after Dose 3; A: Post.
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

10.4 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 first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if AE start 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 first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date and time of first 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 first 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.

10.5 Appendix E Severity Grading of Laboratory Abnormalities

Table 3 Severity Grading of Laboratory Abnormalities

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 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

* 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).
***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) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value –g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

* 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.

10.6 Appendix F Severity Grading of Vital Signs Abnormalities

Table 4 Severity Grading of Vital Signs 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.

10.7 Appendix G Severity Grading of Reactogenicity Abnormalities

Table 5 Severity Grading of Reactogenicity Abnormalities

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	**Grade 0 (None)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-Threatening)**
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

10.8 Appendix H Definition of AE of Special Interest by SMQ

Table 6 AE of Clinical Interest by SMQ

SMQ/CMQ Name*	Type of MedDRA Query	SMQ Level*	SMQ Code*	Search Criteria
Anaphylactic Reaction	SMQ	1	20000021	Algorithm A or (B and C) or (D and (B or C))
Arthritis	SMQ	1	20000216	Narrow/Broad
Cardiac Arrhythmias	SMQ	1	20000049	Narrow/Broad
Arrhythmia Related Investigations, Signs and Symptoms	SMQ	2	20000051	Narrow/Broad
Cardiac Arrhythmia Terms (including bradyarrhythmias and tachyarrhythmias)	SMQ	2	20000050	Narrow/Broad
Demyelination	SMQ	1	20000154	Narrow/Broad
Guillain-Barre Syndrome	SMQ	1	20000131	Narrow/Broad
Hypersensitivity	SMQ	1	20000214	Narrow/Broad
Immune-mediated/Autoimmune Disorders	SMQ	1	20000236	Narrow/Broad
Noninfectious Myocarditis/Pericarditis	SMQ	1	20000239	Narrow/Broad
Peripheral Neuropathy	SMQ	1	20000034	Narrow/Broad
*Based on MedDRA 28.0.				

Table 7 Algorithmic Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

- A term from Category A
- A term from Category B (Upper Airway/Respiratory) and a term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.
- A term from Category D (Cardiovascular/Hypotension) and at least one of the following:
    - A term from Category B (Upper Airway/Respiratory) that occurred within 24 hours of each other.

- A term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
A	Narrow	Anaphylactic reaction
A	Narrow	Anaphylactic shock
A	Narrow	Anaphylactic transfusion reaction
A	Narrow	Anaphylactoid reaction
A	Narrow	Anaphylactoid shock
A	Narrow	Circulatory collapse
A	Narrow	Dialysis membrane reaction
A	Narrow	Kounis syndrome
A	Narrow	Procedural shock
A	Narrow	Shock
A	Narrow	Shock symptom
A	Narrow	Type I hypersensitivity
B	Broad	Asthma
B	Broad	Bronchial oedema
B	Broad	Bronchospasm
B	Broad	Cardio-respiratory distress
B	Broad	Chest discomfort
B	Broad	Choking
B	Broad	Choking sensation
B	Broad	Circumoral oedema
B	Broad	Cough
B	Broad	Cough variant asthma
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema
B	Broad	Laryngospasm
B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
B	Broad	Nasal obstruction
B	Broad	Oedema mouth
B	Broad	Oropharyngeal oedema
B	Broad	Oropharyngeal spasm
B	Broad	Oropharyngeal swelling
B	Broad	Pharyngeal oedema
B	Broad	Pharyngeal swelling
B	Broad	Respiratory arrest
B	Broad	Respiratory distress
B	Broad	Respiratory failure
B	Broad	Reversible airways obstruction
B	Broad	Sensation of foreign body
B	Broad	Sneezing
B	Broad	Stridor

B	Broad	Swollen tongue
B	Broad	Tachypnoea
B	Broad	Throat tightness
B	Broad	Tongue oedema
B	Broad	Tracheal obstruction
B	Broad	Tracheal oedema
B	Broad	Upper airway obstruction
B	Broad	Vaccine associated enhanced respiratory disease
B	Broad	Wheezing
C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling
C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria
C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest
D	Broad	Cardiovascular insufficiency
D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension