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Protocol mRNA-1083-P201

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of Age**

Statistical Analysis Plan

SAP Version 2.0

Version Date of SAP: 27-MAR-2025

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	06DEC2024	Original version per the study protocol dated on 10MAY2024
2.0	27MAR2025	Amendment 1 (Version 2.0) - Updated section 1, 4.1, 4.3, 4.4, 6.1, 6.2.2, 6.5 and Appendix A to reflect the addition of a new study part (Part 2) per Protocol Amendment 1 - Updated subgroup definition in Section 6.1

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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
BMI	body mass index
CEAC	cardiac event adjudication committee
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
EDC	electronic data capture
EoS	end of study
eDiary	electronic diary
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
HAI	hemagglutination inhibition
HCP	healthcare professional
IA	interim analysis
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
PP	Per-Protocol
PPIS	Per Protocol Immunogenicity Set
PsVNA	pseudovirus neutralization assay
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SCR	seroconversion rate
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
SoA	schedule of activities
SRR	seroresponse rate
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-1083-P201, is based on the most recent approved clinical study protocol (CSP), dated 04-Feb-2025, and the most recent approved electronic case report form (eCRF), dated 24-Feb-2025.

In addition to the principal features of analyses for this study described in Section 9 of the protocol, 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-1083-P201 is a Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in adults ≥ 50 to < 65 years of age.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, 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, intervention administration, injection of investigational product (IP)/ investigational vaccine, dosing, and injection are used interchangeably. Treatment group and intervention group are used interchangeably.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are:

- To evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.
- To evaluate the safety and reactogenicity in relation to the product attributes of mRNA-1083.

2.2 Secondary Objectives

The secondary objective is to further evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.

2.3 Exploratory Objectives

The following exploratory objectives may be performed:

- To evaluate the humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083 at all evaluable humoral immunogenicity timepoints.
- To further characterize immunogenicity in relation to the product attributes of mRNA-1083.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary objectives will be evaluated by the following endpoints:

- Immunogenicity endpoints:
 - Geometric mean (GM) value at Day 29 in antibody measured by hemagglutination inhibition (HAI) assay for influenza and by pseudovirus neutralization assay (PsVNA) for SARS-CoV-2.
- Reactogenicity and safety endpoints:
 - Solicited local and systemic adverse reactions (ARs) through 7 days after study injection.
 - Unsolicited adverse events (AEs) through 28 days after study injection.
 - Medically attended AEs (MAAEs) from Day 1 through Day 181 (Month 6) or End of Study (EoS).
 - Adverse events of special interest (AESIs) from Day 1 through Day 181 (Month 6) or EoS.
 - Serious AEs (SAEs) from the time of informed consent through Day 181 (Month 6) or EoS.
 - AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.

3.2 Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

- Geometric mean fold rise (GMFR) at Day 29 relative to Day 1 in antibody measured by HAI assay for influenza and by PsVNA for SARS-CoV-2.
- Seroconversion rate (SCR) at Day 29 in anti-HA antibody values measured by HAI assay for influenza.
- Seroresponse rate (SRR) at Day 29 in nAb values measured by PsVNA for SARS-CoV-2.

3.3 Exploratory Endpoints

The following exploratory endpoints may be performed:

- GM values and GMFR at all evaluable timepoints by HAI assay for influenza and by PsVNA for SARS-CoV-2.
- SCR of influenza at all evaluable timepoints.
- SRR of SARS-CoV-2 at all evaluable timepoints.
- Frequency, levels, and specificities of immune responses, or other endpoints to be determined for the further characterization of immunogenicity.

4 STUDY DESIGN

4.1 Overall Study Design

This study is a Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in adults ≥ 50 to < 65 years of age.

The study includes a Screening period (up to 28 days before Day 1), study intervention administration on Day 1 (Baseline), and a Follow-up period (through Day 181 [Month 6] after the study intervention). The study duration for each participant will be approximately 6 months.

The study will be comprised of 2 parts, Parts 1 and 2. In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups (Lots A, B, C, and D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups (Lots A and E) in Part 2. The study intervention groups are shown in [Table 1](#).

Table 1 Study Intervention Groups

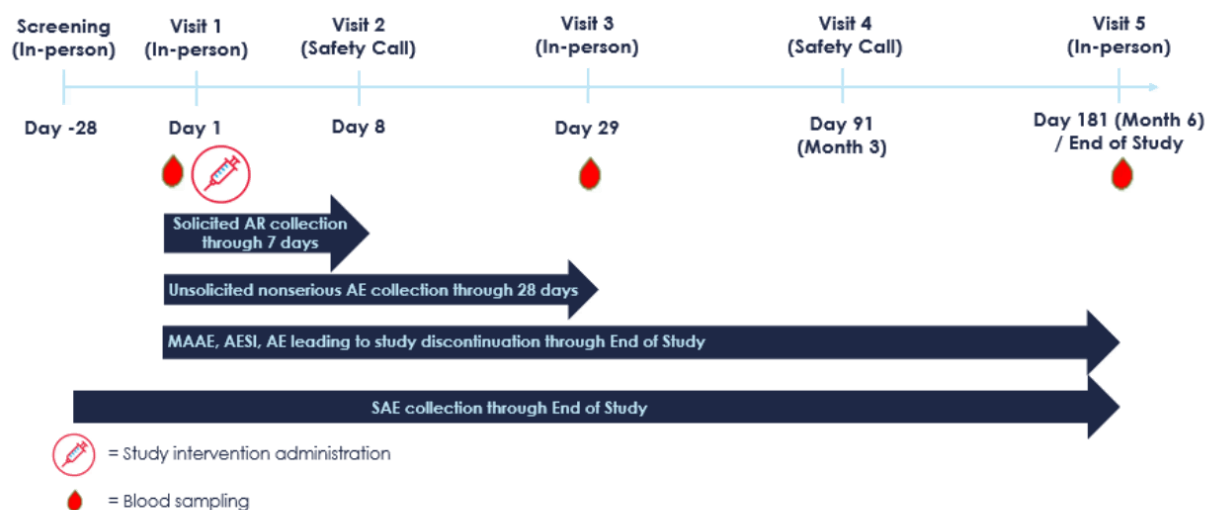
Group Name	Vaccine Administered	Approximate Sample Size	Dose (μ g)
Part 1			
Group 1	mRNA-1083 Lot A ^a	150	40
Group 2	mRNA-1083 Lot B ^a	150	40
Group 3	mRNA-1083 Lot C ^a	150	40
Group 4	mRNA-1083 Lot D ^a	150	40
Part 2			
Group 5	mRNA-1083 Lot A ^a	150	40
Group 6	mRNA-1083 Lot E ^a	150	40

Abbreviation: mRNA = messenger ribonucleic acid.

^a Lot numbers will be assigned and reflected on the label.

Participants will have up to 4 scheduled in-person visits (Screening, Day 1, Day 29, and Day 181 [Month 6]), unscheduled visits if required, and 2 safety telephone calls (Day 8 and Day 91 [Month 3]). For a more detailed presentation of the study, please refer to the Schedule of Activities (SoA) available in [Appendix A](#). The study schema is presented in [Figure 1](#).

Figure 1 Study Schematic and Participant Disposition



	Study Intervention Group	Vaccine Administered	Approximate Sample Size
Part 1			
	Group 1	mRNA-1083 40 µg: Lot A	150
	Group 2	mRNA-1083 40 µg: Lot B	150
	Group 3	mRNA-1083 40 µg: Lot C	150
	Group 4	mRNA-1083 40 µg: Lot D	150
Part 2			
	Group 5	mRNA-1083 40 µg: Lot A	150
	Group 6	mRNA-1083 40 µg: Lot E	150

Abbreviations: AE = adverse event; AR = adverse reaction; AESI = adverse event of special interest; MAAE= medically attended adverse event; SAE = serious adverse event.

4.2 Statistical Hypotheses

This study does not have formal statistical hypothesis testing planned for the study objectives (safety, reactogenicity, and immunogenicity). Descriptive analysis will be conducted for safety, reactogenicity and immunogenicity endpoints.

4.3 Sample Size and Power

Approximately 600 participants and 300 participants will be randomized in Part 1 and Part 2 of this study, respectively. With approximately 150 participants randomized into each study intervention group, there is approximately 90% probability of observing at least 1 participant in each study intervention group reporting an AE if the true rate of AEs is 1.5%.

4.4 Randomization

In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups to receive a single injection of mRNA-1083 (Lot A, Lot B, Lot C, or Lot D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups to receive a single injection of mRNA-1083 (Lot A or E) in Part 2.

Randomization will be performed using an interactive response technology (IRT) by a 3rd party vendor.

4.5 Blinding and Unblinding

This is an observer-blind clinical study. The Investigator, study site staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until the end of the study, with certain exceptions to facilitate IA and safety monitoring or in the case of an emergency, please refer to Section 9.1 of the protocol for details.

5 ANALYSIS SETS

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

5.1 Randomization Set

The randomization set consists of all participants who are randomly assigned. Participants will be included in the intervention group to which they are randomized.

5.2 Full Analysis Set

The FAS consists of all participants who are randomly assigned and receive the study intervention. Participants will be analyzed according to the intervention group to which they are randomized.

5.3 Per Protocol Immunogenicity Set

The PPIS consists of all the participants in the FAS who comply with the timing of immunogenicity blood sample collections to have both Baseline (see Section 6.1) and Day 29 assessments, and have no major protocol deviations or conditions/medications that affect the immune response.

Participants whose Day 29 immunogenicity blood sample was collected out of window [-7, +14] days will be excluded from the PPIS.

The PPIS will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the intervention group to which they are randomized.

5.4 Safety Set

The Safety Set consists of all participants who are randomly assigned and 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 intervention group corresponding to what they actually received.

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 intervention group corresponding to what they actually received.

6 STATISTICAL ANALYSIS

6.1 General Considerations

The SoA is provided in [Appendix A](#).

Analysis for Part 1 and Part 2 of this study will be performed separately.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, Q1 and Q3 (only for summaries specified below), as well as minimum (min), and maximum (max). For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please refer to [Appendix B](#).

Summaries that require Q1 and Q3 for descriptive statistics:

- Demographic and baseline characteristics
- Study duration
- Characteristics of solicited adverse reactions after injection
- Descriptive summaries of antibody levels

Categorical variables will be summarized using counts and percentages. 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 the intervention group within the analysis set of interest, unless otherwise specified.

Baseline value, unless specified otherwise, is defined as the most recent non missing measurement (scheduled or unscheduled) collected before the dose/time of IP in this study. For immunogenicity tests, the baseline is defined as the most recent non missing result/measurement (scheduled or unscheduled) collected before or on the date of injection (Day 1). If there are multiple valid results on the same 1st injection date/time or date (if time is not available) the largest value will be considered in the immunogenicity baseline derivation.

Analysis periods of safety analyses will be used:

- Within 7 days after injection, 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 unsolicited AE that occur during this time.
- Up to 28 days after injection, 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.
- Throughout the Study, from the day of vaccination (Day 1) and continues through the earliest date of (study completion, discontinuation from the study, or death).

Visit window rules: The analysis visit windows for the immunogenicity protocol-defined visits are provided in [Appendix C](#).

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

- In scheduled visit windows per specified visit windowing rules ([Appendix C](#)).
- In the derivation of baseline/last post-baseline measurements.
- In the derivation of maximum/minimum post-baseline values and maximum/minimum change from baseline values for safety analyses.
- In individual participant data listings.

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

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

- study day prior to the injection will be calculated as: date of assessment/event – date of the injection (resulting in negative study day);
- study day on or after the date of the injection will be calculated as: date of assessment/event – date of the injection + 1;

Duration of an event will be calculated as (Event end date – Event start date +1).

Incomplete/missing data: Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations and procedures are provided in [Appendix D](#). Imputation rules for missing AE dates are provided in [Appendix E](#). Other incomplete/missing data will not be imputed, unless specified otherwise.

For calculation regarding antibody levels/titers, values reported as below the lower limit of quantification (LLOQ) will be replaced by $0.5 \times \text{LLOQ}$. Values reported as above the upper limit of quantification (ULOQ) will be converted to the ULOQ, regardless if numeric values exist. Missing results will not be imputed.

Intervention group will be presented according to the analysis set of interest, unless otherwise specified. The following intervention group labels will be used for summary purposes:

Part 1:

- mRNA-1083 40 µg Lot A
- mRNA-1083 40 µg Lot B
- mRNA-1083 40 µg Lot C
- mRNA-1083 40 µg Lot D
- Overall (Lots A, B, C, and D combined)

Part 2:

- mRNA-1083 40 µg Lot A
- mRNA-1083 40 µg Lot E
- Overall (Lots A and E combined)

All analyses and data summaries/displays for disposition, demographics and baseline characteristics and safety will be provided by all of the above intervention groups. Immunogenicity analyses will be provided by the above intervention groups except overall.

Subgroups: Where indicated in this SAP, the following subgroups, detailed in [Table 2](#), will be used for summary purposes. Unless otherwise specified, all subgroups are based on eCRF.

Table 2 Subgroups Definition

Subgroup Variables	Categories
Sex	Male Female
Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Multiple Other Unknown/ Not Reported
Ethnicity	Hispanic or Latino Not Hispanic or Latino Unknown/ Not Reported
COVID-19 vaccination status since Sept. 2023 for Part 1 and since Sept. 2024 for Part 2 (only for SARS-CoV-2 related immunogenicity analyses)	Received Not Received
Number of prior COVID-19 vaccines (only for SARS-CoV-2 related immunogenicity analyses)	No Dose ≥ 1 Dose 1 - 2 Doses 3 Doses 4 Doses ≥ 5 Doses

6.2 Background Characteristics

6.2.1 Participant Disposition

The number and percentage of participants in each of the following disposition categories will be summarized by intervention group (as defined in Section 6.1) based on the Randomization Set and Safety Set (as defined in Section 5):

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

A Participant is considered to have completed the study if he or she has completed the last Day 181 scheduled procedure.

Participant randomization and disposition listings will be provided, including randomization information such as randomization date, number, planned and actual intervention group, informed consent, participants who received study injection, participants who completed study, participants who discontinued from study, with reasons for discontinuation. In addition, participants in Randomization Set with any inclusion and exclusion criteria deviation will also be provided in a listing.

The number of participants in the following categories will be summarized based on Participants Screened:

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

The percentage of participants who screen failed will be based on the number of participants screened. The reason for screen failure will be based on the number of participants who screen failed. A screen failure listing will be provided including information on the screen failed participants and the reasons for screen failure.

The number and percentage of participants in the following analysis sets (see Section 5) will be summarized by intervention group based on the Randomization Set:

- Randomization Set,
- Full Analysis Set,
- Per Protocol Immunogenicity Set,
- Safety Set,
- Solicited Safety Set.

For Solicited Safety Set, the percentage will be based on the number of participants in the intervention group within the Safety Set (as treated).

A summary of reasons for participants excluded from the Per Protocol Immunogenicity Set will also be provided.

A listing, including information related to the different analysis sets of the randomized participants as well as the reason for exclusion from analysis set will be provided.

The number and percentage of participants randomized by country and site will be provided as well.

6.2.2 Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics:

- Age (years)
- Weight (kg)

- Height (cm)
- Body mass index (BMI) (kg/m^2)

The number and percentage of participants will be provided for the following categorical variables:

- BMI group ($< 30 \text{ kg}/\text{m}^2$, $\geq 30 \text{ kg}/\text{m}^2$)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Other, Unknown, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Influenza vaccine status in the most recent influenza season (received or not received since Sept. 2023 for Part 1 and since Sept. 2024 for Part 2)
- COVID-19 vaccine status (received or not received since Sept. 2023 for Part 1 and since Sept. 2024 for Part 2)
- Number of COVID-19 vaccinations (No Dose, ≥ 1 Dose, 1-2 Doses, 3 Doses, 4 Doses, ≥ 5 Doses)
- Childbearing Potential for female participants (Yes/No) and reason if “No”
- Baseline Elecsys Anti-SARS-CoV-2 Results (positive, negative, or missing)

The summaries will be provided separately for Randomization Set, Safety Set and PPIS defined in Section 5, by intervention group.

Descriptive statistics of time interval from the last influenza and COVID-19 vaccine to the study vaccine will also be presented. The time interval will be calculated as: date of study vaccine – date of last flu/COVID-19 vaccine.

Demographic and baseline characteristics will also be provided in a listing for randomized participants.

6.2.3 Medical History

Medical history data will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class (SOC) and preferred term (PT).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set, by intervention group. 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 the “overall” 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 and imputation rules for missing/partial dates is summarized in [Appendix D](#).

An overall summary with the number and percentage of participants using concomitant medications and non-study vaccination will be provided by intervention group 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
- Any seasonal influenza or COVID-19 vaccine within 28 days post-injection

The number and percentage of participants with at least one concomitant medications and non-study vaccination will be provided by PT in descending frequency based on “overall” group.

Medications taken to prevent or treat pain or fever will be collected in the electronic diary (eDiary). A summary table of medications taken to prevent or treat pain or fever within 7 days post injection will be provided based on the Solicited Safety Set by intervention group.

Prior and concomitant 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. Procedures will be presented in a listing.

6.2.5 Protocol Deviations

The study protocol deviations will be reviewed on a regular basis and categorized in “Significant” and “Non-significant” based on the impacts on study results. Significant protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Significant protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each significant protocol deviation type will be provided by intervention group, based on the Randomization Set.

Selected significant protocol deviations might impact critical or key study data such as the immune response. Participants with such deviations will be excluded from the PPIS. Such significant protocol deviations will be determined and documented by Sponsor prior to database lock and unblinding. Reasons of exclusion from the PPIS will be summarized.

Significant protocol deviations will also be presented in a listing.

6.2.6 Study Exposure

Study duration will be summarized by intervention group since randomization, and since the study injection based on Safety Set. Study vaccine administration data will be presented in a listing. Participants with any dosing errors will also be presented in a separate listing.

The duration of the study will be calculated for the participants included in the safety set:

- Since randomization: date of last visit (as recorded on EoS eCRF) – date of randomization + 1,
- Since study injection: date of last visit (as recorded on EoS eCRF) – date of injection + 1.

If the last visit date on the EoS eCRF page is missing, then the latest of either the cut-off date or the last available visit date will be employed.

6.3 Immunogenicity Analyses

The primary analysis population for immunogenicity will be the Per Protocol Immunogenicity Set (PPIS), unless otherwise specified.

For humoral immunogenicity on Day 1 (prior to study intervention administration), Day 29, and Day 181 (Month 6) or EoS, samples will be collected and analyzed for all participants. Plasma and serum from humoral immunogenicity samples will be stored for potential future use.

The following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay.
- SARS-CoV-2: Serum nAb levels as measured by PsVNA assay by enzyme linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.

The GM value will be calculated using the following formula:

$$X \left\{ \frac{\sum_{i=1}^n \log_X(v_i)}{n} \right\}$$

where, $X=2$ for influenza and $X=10$ for SARS-CoV-2, for n participants, v_i is the immunogenicity level measurement for participant i .

GMFR measures the changes in immunogenicity levels within participants. The GMFR of immunogenicity levels at time point j relative to time point k will be calculated using the following formula:

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

where, $X=2$ for influenza and $X=10$ for SARS-CoV-2, for n participants, v_{ij} and v_{ik} are observed immunogenicity levels for participant i at time points j and k , $j \neq k$.

Please refer to [Appendix C](#) for details regarding the analysis visit window or in case of multiple postbaseline assessment available.

6.3.1 Primary Immunogenicity Endpoints Analysis

The primary endpoints include the following:

- GM value at Day 29 in antibody measured by HAI assay for influenza
- GM value at Day 29 in antibody measured by PsVNA for SARS-CoV-2

An ANCOVA model will be carried out including the log-transformed HAI or PsVNA values at Day 29 as the dependent variable, the treatment group as the fixed variable and log transformed baseline HAI or PsVNA values as a fixed covariate. The GLSM and its corresponding 95% CI in log-transformed scale will be back-transformed to the original scale to obtain an estimate of the GM value and its corresponding 95% CI.

The primary immunogenicity endpoints may be analyzed by subgroup categories available in [Table 2](#).

6.3.2 Secondary and Exploratory Immunogenicity Endpoints Analysis

The observed GM values of HAI, PsVNA with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The following descriptive statistics will be also provided by intervention group (available in Section 6.1) at each time point: the number of subjects (n), median, minimum and maximum. GM value will be plotted at all evaluable timepoints.

GMFR of HAI, PsVNA with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GMFR will be plotted at all evaluable timepoints.

SCR, defined as proportion of participants with seroconversion (influenza) and SRR, defined as proportion of participants with seroresponse (SARS-CoV-2), will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline time point for each study intervention group. Seroconversion of antibodies for an influenza strain at participant level is defined as a post-vaccination value $\geq 1:40$ if baseline is $< 1:10$ or a ≥ 4 -fold rise in post-vaccination value if baseline is $\geq 1:10$. Seroresponse of SARS-CoV-2 antibodies at participant level is defined as a post-vaccination value $\geq 4 \times \text{LLOQ}$ if baseline is $< \text{LLOQ}$, or a ≥ 4 -fold rise in post-vaccination value if baseline is $\geq \text{LLOQ}$.

In addition, percentage of participants with antibody values below ($<$) LLOQ and above ($\geq$) LLOQ values at baseline will be provided.

For SARS-CoV-2 antibody value: Percentage of participants with ≥ 2 -fold rise from baseline values with the corresponding 2-sided 95% Clopper Pearson CI at each post-baseline time point will be provided. Percentage of participants with SRR among participants with values above ($\geq$) LLOQ and below ($<$) LLOQ values at baseline will be provided.

6.3.3 Other Immunogenicity Exploratory Endpoints

The exploratory analyses of immunogenicity may be performed on frequency, levels, and specificities of immune responses, or other endpoints to be determined for the further characterization of immunogenicity.

6.4 Safety Analyses

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

Participants will be included in the intervention group corresponding to what they actually received and will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set, unless otherwise specified. When summarizing the number and percentage of participants with an event, participants will be presented according to the highest severity/toxicity. Imputation rules for missing/partial dates is detailed in [Appendix E](#).

6.4.1 Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term “reactogenicity” refers to the occurrence of transient adverse effects associated with vaccine administration. The eDiary will solicit daily participant reporting of ARs using a structured checklist. Participants will record such occurrences in the eDiary on the day of study injection (Day 1) and the 6 subsequent days, for a total of 7 days (Day 1 through Day 7).

If a participant inaccurately reports an AR in the eDiary, the event should be recorded in the EDC with correct assessment. If the event starts during the solicited period, but continues beyond 7 days after injection, the participants should notify the site to record in the EDC. If the event is determined to be not related to IP, it should be recorded in the EDC. For each event and timepoint, assessment from EDC will be used for analyses if it is recorded on both eDiary and EDC, regardless which one is more severe.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS, 2007) available in [Appendix F](#) will be used to categorize local and systemic solicited ARs. All solicited ARs will be considered causally related to study intervention, unless it is determined as not related to IP and recorded in the EDC.

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

6.4.1.1 Overview of Solicited ARs

An overall summary of solicited ARs after injection (with a toxicity grade of Grade 1 or greater) including the number and percentage of participants, will be presented by intervention group. The number and percentage of participants experiencing any solicited local ARs and solicited systemic ARs of Grade 3 or higher will be provided as well.

Solicited local and systemic ARs will be provided in listings. Medications taken to prevent or treat pain or fever will also be presented.

6.4.1.2 Solicited ARs by Toxicity Grade

A summary of solicited ARs after injection (with a toxicity grade of Grade 1 or greater) by toxicity grade, including the number and percentage of participants, will be provided by intervention group. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR (overall, local, and systemic).

The same summary will be conducted for subgroups as defined in [Table 2](#) of Section 6.1.

A summary figure will be produced for local and systemic event rates by toxicity grade.

6.4.1.3 Solicited ARs by Onset Day

A summary of solicited ARs after study injection (with a toxicity grade of Grade 1 or greater) by onset day (from Day 1 through Day 7), including the number and percentage of participants, will be provided by intervention group.

The onset of individual solicited AR is defined as the time point after injection at which the respective solicited AR first occurred.

6.4.1.4 Characteristics of Solicited ARs

A descriptive summary of the day of onset and the duration of solicited ARs after study injection (with a toxicity grade of Grade 1 or greater), will be provided by intervention group.

The duration of solicited ARs will be calculated as: reaction end date – reaction start date +1, regardless of whether the AR is intermittent or continued or if the solicited AR continues beyond 7 days.

The same analysis will be conducted for subgroups as defined in [Table 2](#) of Section 6.1.

6.4.1.5 Solicited ARs Persisting beyond 7 Days Post-injection

A summary of solicited ARs persisting beyond 7 days after study injection (with a toxicity grade of Grade 1 or greater) by grades, including the number and percentage of participants, will be provided by intervention group.

All solicited ARs that continue beyond 7 days post-injection will be provided in a listing.

6.4.2 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.

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (e.g., rash assessment, abnormal laboratory follow-up) and visits to HCPs external to the study site (eg, urgent care, primary care physician). AESI for this study are pre-defined in the protocol Section 10.3.

All unsolicited AEs reported or observed during the clinical trial will be collected from start of study intervention through 28 days after injection. All AEs leading to study discontinuation, MAAE, and AESIs will be collected from the study intervention administration until through Day 181 (Month 6) or EoS Visit at the timepoints specified in the SoA ([Appendix A](#)). All SAEs

will be collected from the signing of the ICF until Day 181 (Month 6) or EoS at the timepoints specified in the SoA.

Unsolicited AEs will be coded according to MedDRA and presented by MedDRA system organ class (SOC) and preferred term (PT).

For analysis and reporting purpose, unsolicited AEs will include the following:

- AEs that are reported by participants and recorded on the AE eCRF
- Solicited ARs that meet SAE criteria and are recorded on the Serious Reactogenicity eCRF

Unsolicited AEs will be summarized up to 28 days after vaccine injection. MAAEs, AESIs, SAEs, and AEs leading to discontinuation from study participation will be summarized throughout the study (up to Day 181/EoS). All summaries will be based on AEs started after vaccine injection.

SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of the “overall” treatment group and then alphabetically within each 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/toxicity level will be presented in the severity/toxicity summaries, and the strongest relationship level will be presented in the relationship summaries.

For the by severity summaries, the toxicity grade of a solicited AR meeting SAE criteria will be mapped to a severity level of Mild/Grade 1, Moderate/Grade 2, or Severe/ $\geq$ Grade 3, and the maximum severity level in the case of multiple events will be presented.

The following listings containing individual participant AEs data will be provided:

- Any unsolicited AEs,
- Unsolicited serious AEs,
- Unsolicited severe AEs,
- Unsolicited AEs leading to discontinuation from the study,
- Unsolicited MAAEs,
- Unsolicited AESIs.

All AEs will be included in the listings.

In addition, number of participants with occurrences of selected AEs of clinical interests identified by SMQ will be summarized. SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in [Table 7](#). A listing of unsolicited AEs by SMQ will be provided.

6.4.2.1 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 serious AEs,
- Any unsolicited AESI,
- Any unsolicited AEs that are medically attended,
- Any unsolicited AEs leading to study discontinuation,
- Any unsolicited severe AEs,
- Any unsolicited AEs that are fatal,
- Any unsolicited non-serious AEs.

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

6.4.2.2 AEs by System Organ Class and Preferred Term

Summary of the following unsolicited AEs 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 by intervention group (as defined in Section 6.1):

- All unsolicited AEs,
- All unsolicited AEs that are treatment-related,
- All unsolicited serious AEs,
- All unsolicited serious AEs that are treatment-related,
- All unsolicited AESI,
- All unsolicited AESI that are treatment-related,
- All unsolicited AEs that are medically attended,
- All unsolicited AEs that are medically attended that are treatment-related,
- All unsolicited severe AEs,
- All unsolicited severe AEs that are treatment-related,
- All unsolicited AEs leading to study discontinuation,
- All unsolicited non-serious AEs,
- All unsolicited non-serious severe AEs.

All summary tables by SOC and PT will be provided for up to 28 days after vaccine injection. In addition, all unsolicited AEs and SAEs summary tables will be provided for up to 7 Days after injection.

For all SAEs, AESIs, MAAEs, AE leading to discontinuation from the study, AE leading to death summary tables will also be provided through Day 181/EoS as well.

All unsolicited AEs and unsolicited treatment-related AEs up to 28 days after vaccine injection with occurrence in $\geq 1\%$ of participants in any intervention group based on PT will be summarized by SOC and PT.

6.4.2.3 AEs by Preferred Term

The following summary tables of unsolicited AEs will be provided by PT sorting by descending frequency on the “overall”:

- All unsolicited AEs,
- SMQ

All summary tables by PT will be provided up to 28 days after vaccine injection. In addition, all SMQ summary tables by PT will be provided through Day 181/EoS as well.

6.4.2.4 AEs by Severity

The following summary tables of AEs up to 28 days after vaccine injection will be provided by SOC, PT and the maximum severity or toxicity Grade:

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

6.4.2.5 Independent Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for “probable” or “confirmed” events. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

A summary table will be provided based on the data adjudicated by the CEAC, as the primary analysis of cardiac events.

6.4.2.6 Subgroup Analysis

Summary of unsolicited AEs will be conducted for subgroups as defined in [Table 2](#) of Section 6.1 for the following summaries:

- Overall summary of the unsolicited AEs,
- All unsolicited AEs up to 28 days after injection,
- All unsolicited AEs up to 28 days after injection that are treatment-related,
- All unsolicited AEs up to 28 days after injection by severity,
- All serious unsolicited AEs up to 28 days after injection and throughout the study,
- All serious unsolicited AEs that are treatment-related up to 28 days after injection and throughout the study.

6.4.3 Death

Total number of deaths due to any cause and time of death from injection (numeric and by time point window) may be summarized in a table. A listing of deaths including cause of death will be provided.

6.4.4 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). On the day of study injection, vital sign measurements will be collected once before and at least 30 minutes after study injection. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical (DHHS, 2007) available in [Appendix G](#) will be used to categorize vital sign measurements observed during this clinical trial.

Observed values and changes from pre-injection (Baseline) to post-injection (at Day 1, 30 minutes after study intervention) for all vital sign measurements will be summarized by intervention group. A toxicity grade shift table of the vital signs from pre-injection to post-injection will be provided as well.

A listing containing individual participant vital sign measurement data will be provided. Additionally, participant with any abnormal post-baseline vital sign measurement where toxicity grade is Grade 3 or higher will be listed separately.

6.4.5 Pregnancy Testing

For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before injection. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. For participants assigned female at birth and of nonchildbearing potential, the FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.

A listing containing individual participant pregnancy test results and FSH blood levels (if tested) for those participants who have at least one positive pregnancy test result will be provided.

6.5 Planned Analyses

6.5.1 Interim Analysis

For each study part, an interim analyses of safety and immunogenicity will be performed after all participants who receive the study vaccine have completed the Day 29 assessment.

6.5.2 Final Analysis

For each study part, the final analyses of all safety and immunogenicity data will be performed once all participants have completed all planned study procedures or discontinued from the study. Results of the final analysis will be presented in a final CSR.

6.6 Multiplicity Control

No multiplicity adjustment will be implemented because there will not be formal statistical hypothesis testing planned for the study objectives (safety, reactogenicity, and immunogenicity).

7 CHANGES FROM PLANNED ANALYSIS IN PROTOCOL

Not applicable.

8 REFERENCES

DHHS, Department of Health and Human Services, FDA, Food and Drug Administration, Center for Biologics Evaluation and Research (US). 2007. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. [Online] September 2007.

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

9 APPENDICES

Appendix A Schedule of Activities (SoA) (Part 1 and Part 2)

Visit Number	Screening	1	2	3	4	5	USV
Timepoint	Screening ^a	Day 1 (Baseline) ^a	Day 8	Day 29	Day 91/Month 3	Day 181 /Month 6 (EoS) ^b	Up to Month 6/ USV
Window Allowance (Days)	Up to -28	N/A	-1 to +3	-7 to +3	±5	±14	N/A
Type of Visit	C	C	SC	C	SC	C	C
Informed consent, demographics, concomitant medications, medical history ^c	X						
Inclusion and exclusion criteria	X	X					
Full Physical examination ^d	X						
Symptom directed physical examination ^d		X		X		X	X
Injection site and corresponding draining lymph nodes assessment		X					
Vital sign measurements ^e	X	X					
Pregnancy testing ^f	X	X					
Randomization		X					
Blood collection for humoral immunogenicity ^g		X ^h		X		X	
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X ^h					
Study injection (including 30-minute postdosing observation period) ⁱ		X					
eDiary activation for recording solicited ARs (7 days) ^j		X					
Review of solicited AR eDiary			X				
Follow-up safety call ^k			X		X		

Visit Number	Screening	1	2	3	4	5	USV
Timepoint	Screening ^a	Day 1 (Baseline) ^a	Day 8	Day 29	Day 91/Month 3	Day 181 /Month 6 (EoS) ^b	Up to Month 6/ USV
Window Allowance (Days)	Up to -28	N/A	-1 to +3	-7 to +3	±5	±14	N/A
Type of Visit	C	C	SC	C	SC	C	C
Recording of unsolicited AEs		X	X	X			
Recording of AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications/procedures relevant to or for their treatment		X	X	X	X	X	X
Recording of SAEs ^l and concomitant medications/procedures relevant to or for their treatment	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations ^m	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = in-person visit; eDiary = electronic diary; EoS = end-of-study; FSH = follicle stimulating hormone; HCP = healthcare professional; IM = intramuscular;; MAAE = medically attended adverse event; N/A = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety telephone call; SoA = schedule of activities; USV = unscheduled visit.

- a Screening and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day Screening window.
- b EoS is defined as completion of the last visit of the last participant in the clinical study or last scheduled procedure as shown in the SoA for the last participant in the clinical study globally. If a participant discontinues from the clinical study, an EoS Visit should be conducted if possible.
- c Verbal history is acceptable.
- d A full physical examination, including height and weight for calculation of body mass index, will be performed at the Screening Visit. If the participant reports symptoms, symptom-directed physical examinations will be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant findings identified by an HCP during postinjection study visits should be reported as an AE.
- e Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs will only be collected at Screening and on the day of injection (Day 1), once before and at least 30 minutes after injection. Vital signs may be collected at other clinical visits only in conjunction with a symptom-directed physical examination. For all vital sign measurements, participant must be seated for 5 minutes before any measurements are taken.
- f For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injection on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The FSH level may be measured for participants of nonchildbearing potential at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
- g Blood samples on Day 1, Day 29, and Day 181 (Month 6) will be collected in all participants. Serum from humoral immunogenicity samples will be stored for potential future use.
- h All Baseline samples must be collected prior to the study intervention administration on Day 1.
- i All participants will be randomized to receive a single IM injection of study intervention in a deltoid muscle.

- j The eDiary will be activated and entries will be recorded by the participant at approximately 30 minutes after injection while at the clinic with instruction provided by study site staff. Study participants will continue to record in the eDiary after they leave the clinic preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection, for a total of 7 days.
- k Trained study site staff will call all participants to collect information related to any AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation from study participation, information on concomitant medications/procedures associated with those events, and any nonstudy vaccinations.
- l SAEs will be collected from the time of informed consent through Day 181 (Month 6) or EoS.
- m All concomitant medications will be recorded through 28 days after injection. Additionally, nonstudy vaccinations and certain concomitant medications will be recorded through Day 181 (Month 6) or EoS.

Appendix B Standards for Variable Display in TLF

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. For model-based estimates, the results may be presented up to three decimal points, unless otherwise specified.

Categorical Variables

Percentages will be presented to one decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

Appendix C Analysis Visit Windows for Immunogenicity Analysis

Analysis visit windows will be utilized for immunogenicity assessments only. Data will be mapped using the following approach:

Step 1:

If the immunogenicity assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2:

If the immunogenicity assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in [Table 3](#) below.

Table 3 Analysis Visit Windows for Immunogenicity Assessments

Visit	Target Study Day	Visit Window in Study Day
Baseline	1 (Date of Injection)	≤ 1 (Pre-vaccination)
Day 29	29	[2, 105]
Day 181	181	≥ 106

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

- If multiple assessments occur within a given 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.

Appendix D Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations Dates

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

Missing or partially missing medication start date:

If only Day is missing, use the first day of the month, unless the start month and year of the medication coincide with the start month and year of the study treatment administration.

- If not marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “No”), then use the date of the study treatment administration.
- If marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “Yes”), then use the first day of the month.
- If the mark on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?”) is missing and the medication end date is on/after the date of the study treatment administration or is missing, then use the date of the study treatment administration.

If Day and Month are both missing, use the first day of the year, unless the start year of the medication coincide with the start year of the study treatment administration.

- If not marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “No”), then use the date of the study treatment administration.
- If marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “Yes”), then use the first day of the year.
- If the mark on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?”) is missing and the medication end date is on/after the date of the study treatment administration or is missing, then use the date of the study treatment administration.

If Day, Month and Year are all missing, the date will not be imputed, but will use the following rules for purposes of determining the status as prior and/or concomitant.

- If not marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “No”), then the medication will be treated as having begun after study treatment administration.
- If marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to first study treatment administration?” = “Yes”), or if the mark is missing, then the medication will be treated as a prior medication (and as a concomitant medication unless the stop date indicates the medication was stopped prior to study treatment administration).

Missing or partial medication stop date:

- If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
- If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
- If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in [Table 4](#) below.

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

Medication Start Date	Medication Stop 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

Appendix E Imputation Rules for Missing AE Dates

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

Missing or partial AE start date:

- If only Day is missing, use the first day of the month, unless 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 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.

Missing or partial AE end dates will not be imputed.

Appendix F Solicited Adverse Reactions and Grades

Table 5 Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life- threatening)
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/ induration (hardness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 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	Emergency room visit or hospitalization
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 to 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 to 38.4°C 100.4 to 101.1°F	38.5 to 38.9°C 101.2 to 102.0°F	39.0 to 40.0°C 102.1 to 104.0°F	>40.0°C >104.0°F

Appendix G Toxicity Grading of Vital Sign Abnormalities

Table 6 Toxicity 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 athlete

Appendix H Adverse Events of Special Interest by SMQ

Table 7 Adverse Events of Special Interest by SMQ

SMQ/CMQ Name*	Type of MedDRA Query	SMQ Level	SMQ Code	Broad or Narrow Search
Anaphylactic Reaction	SMQ	1	20000021	Algorithm A or (B and C) or (D and (B or C))
Angioedema	SMQ	1	20000024	Narrow
Arthritis	SMQ	1	20000216	Narrow
Cardiac Arrhythmias	SMQ	1	20000049	Narrow
Arrhythmia Related Investigations, Signs and Symptoms	SMQ	2	20000051	Narrow
Cardiac Arrhythmia Terms (including bradyarrhythmias and tachyarrhythmias)	SMQ	2	20000050	Narrow
Cardiac Failure	SMQ	1	20000004	Narrow
Cardiomyopathy	SMQ	1	20000150	Narrow
Central Nervous System Vascular Disorders	SMQ	1	20000060	Narrow
Central Nervous System Haemorrhages and Cerebrovascular Conditions	SMQ	2	20000061	Narrow
Central Nervous System Vascular Disorders, not Specified as Haemorrhagic or Ischaemic	SMQ	2	20000165	Narrow
Convulsions	SMQ	1	20000079	Narrow
Demyelination	SMQ	1	20000154	Narrow
Embolic and Thrombotic Events	SMQ	1	20000081	Narrow
Embolic and Thrombotic Events, Arterial	SMQ	2	20000082	Narrow
Embolic and Thrombotic Events, Venous	SMQ	2	20000084	Narrow
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous	SMQ	2	20000083	Narrow
Guillain-Barre Syndrome	SMQ	1	20000131	Narrow
Haematopoietic Cytopenias	SMQ	1	20000027	Narrow
Haematopoietic Cytopenias Affecting More Than One Type Of Blood Cell	SMQ	2	20000028	Narrow
Haematopoietic Erythropenia	SMQ	2	20000029	Narrow
Haematopoietic Leukopenia	SMQ	2	20000030	Narrow
Haematopoietic Thrombocytopenia	SMQ	2	20000031	Narrow
Hearing and Vestibular Disorders	SMQ	1	20000170	Narrow
Hearing Impairment	SMQ	2	20000171	Narrow
Vestibular Disorders	SMQ	2	20000172	Narrow
Hypersensitivity	SMQ	1	20000214	Narrow
Immune-mediated/Autoimmune Disorders	SMQ	1	20000236	Narrow
Ischaemic Heart Disease	SMQ	1	20000043	Narrow
Myocardial Infarction	SMQ	2	20000047	Narrow

Other Ischaemic Heart Disease	SMQ	2	20000168	Narrow
Noninfectious Myocarditis/Pericarditis	SMQ	1	20000239	Narrow
Peripheral Neuropathy	SMQ	1	20000034	Narrow
Thrombophlebitis	SMQ	1	20000115	Narrow
Vasculitis	SMQ	1	20000174	Narrow

The following criteria will be used to determine anaphylactic reaction:

- A term from Category A or
- 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 or
- 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.

Table 8 Algorithmic Approach for 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

Category	Scope	PT Search Term
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

Category	Scope	PT Search Term
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

Category	Scope	PT Search Term
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

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