ModernaTX, Inc.

Protocol mRNA-1083-P101

A Phase 1/2, Randomized, Observer-blind, Active-Control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-based Influenza and SARS-CoV-2 Multi-component Vaccines in Healthy Adults

Statistical Analysis Plan

SAP Version 5.0

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CI	confidence interval
CDC	US Centers for Disease Control and Prevention
CMQ	Customized MedDRA Query
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
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
IA	Interim analysis
ILI	influenza-like illness
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
NP	nasopharyngeal
PP	Per-Protocol
PsVNA	pseudovirus neutralization assay
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SCR	seroconversion rate
SD	standard deviation

Abbreviation	Definition
SMQ	Standardized MedDRA Query
SOC	system organ class
SoA	schedule of activities
SRR	seroresponse rate
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

SUMMARY OF MAJOR CHANGES IN SAP VERSION

SAP Version	Section # and Name	Description of Change
V2.0	5.3 Per Protocol (PP) Set	Clarified existing language for conditions/medications that affect the immune response.
V2.0	6.1 General Considerations	Clarified that all subgroups are based on eCRF entries unless otherwise stated. Added definition for Baseline SARS-CoV-2 Status and added this Baseline SARS-CoV-2 Status to Table 5, as a subgrouping factor to be used in table summaries.
V2.0	6.2.2 Demographics and Baseline Characteristics	Added 3 categorical baseline variables: Baseline SARS-CoV-2 RT-PCR Results, Elecsys Anti-SARS-CoV-2 Results, and Baseline SARS-CoV-2 Status.
V2.0	6.3.2 Unsolicited Treatment-Emergent Adverse Events	Updated to reflect only Solicited ARs that meet SAE criteria are recorded on the Reactogenicity eCRF.
V2.0	6.4.2 Immunogenicity Analysis	Updated wording in 6.4.2.2 Analytical summaries, and added a new Table 6 to clarify the covariates used in the ANCOVA analyses. Renumbered later tables and added clarifying language to Table 7. Removed bar-plot of ANCOVA-based GMT.
V3.0	6.2.4 Prior and Concomitant Medications	"Antipyretic or analgesic medication within 28 days postinjection" item removed
V3.0	6.4.2.1. Analysis of Secondary Immunogenicity Endpoints	For GMFR, values below LLOQ imputed to LLOQ
V3.0	6.4.2.2 Analytical summaries	Added D181 GMT/GMR; added figure for D181 GMFR, SCR, SRR, and GMR
V3.0	6.5.1.2 SARS-CoV-2 Infection	Asymptomatic SARS CoV 2 infection language removed
V3.0	Appendix H TEAE of Specifical Interest by SMQ	SMQ table updated
V4.0	Global update	Part 2 added to the SAP per protocol amendment 1 dated 16-Jan-2024 and protocol amendment 2 dated 14 Mar 2024
V5.0	3.6.4.1. Primary Immunogenicity Endpoints	Updated the "Covariate(s)" column in Table 14, by adding "Log-transformed baseline antibody value" for all rows.

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1083-P101, is based on the most recent approved clinical study protocol amendment (CSP), dated 14-MAR-2024, and the most recent approved electronic case report form (eCRF), dated 31-MAY-2024.

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-P101 is a phase 1/2, randomized, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-based Influenza and SARS-CoV-2 multi-component vaccines in healthy adults.

The study is divided into 2 parts: Part 1 and Part 2. Part 1 (Phase 1/2) includes adults who are 18 to <80 years and Part 2 (Phase 2 Extension) includes adults who are 18 to <50 years. Approximately 1744 participants will be enrolled in the overall clinical trial.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, study vaccination, intervention administration, injection of investigational product (IP)/investigational vaccine, dosing, and injection are used interchangeably. Treatment group, investigational treatment arm, vaccination group are used interchangeably.

2. Part 1

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to evaluate the safety and reactogenicity of study intervention administration across study treatment arms.

2.1.2. Secondary Objectives

The secondary objectives are:

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

2.1.3. Exploratory Objectives

The following exploratory objectives may be assessed:

- To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms
- To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms
- To evaluate the cellular immune responses against influenza and SARS-CoV-2 in a subset of participants
- To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms
- To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after injection
- Unsolicited AEs through 28 days after injection
- Unsolicited severe adverse events through 28 days after injection
- Unsolicited medically attended adverse events (MAAEs) from Day 1 to Day 181/End of Study (EoS)
- Unsolicited adverse events of special interest (AESIs) from Day 1 to Day 181/EoS
- Serious adverse events (SAEs) from Day 1 to Day 181/EoS
- Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS

2.2.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

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

2.2.3. Exploratory Endpoints

The exploratory objectives may be evaluated by the following endpoints:

- GMT and GMFR at all evaluable timepoints compared with Day 1 by HAI for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion to vaccine mismatched strains at all evaluable timepoints
- SARS-CoV-2: Percentage of participants with seroresponse to vaccine mismatched strains at all evaluable timepoints
- GMT and GMFR at all evaluable timepoints compared with Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
- Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods
- Perform targeted repertoire analysis of B-cells and T-cells after vaccination
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
- Frequency of RT-PCR-confirmed clinical influenza and COVID-19
- Assessment of immune responses to infection and viral isolates

2.3. Study Design

2.3.1. Overall Study Design

Part 1 of the study is a Phase 1/2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.222, mRNA-1273.222, and licensed active-control vaccines, Fluarix® and Fluzone® HD (Cohort A only) in healthy adults ≥18 to <80 years of age (Cohort A is in adults ≥65 to <80 years of age and Cohort B is in adults ≥18 to <65 years of age).

Approximately 1224 participants will be enrolled into 1 of 2 age cohorts: Cohort A for adults ≥65 to <80 years of age or Cohort B for adults ≥18 to <65 year of age. In Cohort A,

approximately 600 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since September 2022). In Cohort B, approximately 624 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by 2 age groups: ≥18 to <50 years and ≥50 to <65 years of age and by influenza vaccine status in the most recent influenza season (received or not received since September 2022). Approximately 50% of the participants in Cohort B will be ≥50 to <65 years of age. Table 1 lists the details of study cohorts and dose levels for study vaccine administration. All participants will receive a single intramuscular (IM) injection of study intervention administered in a deltoid muscle on Day 1.

Table 1 Study Arm(s) and Interventions (Part 1)

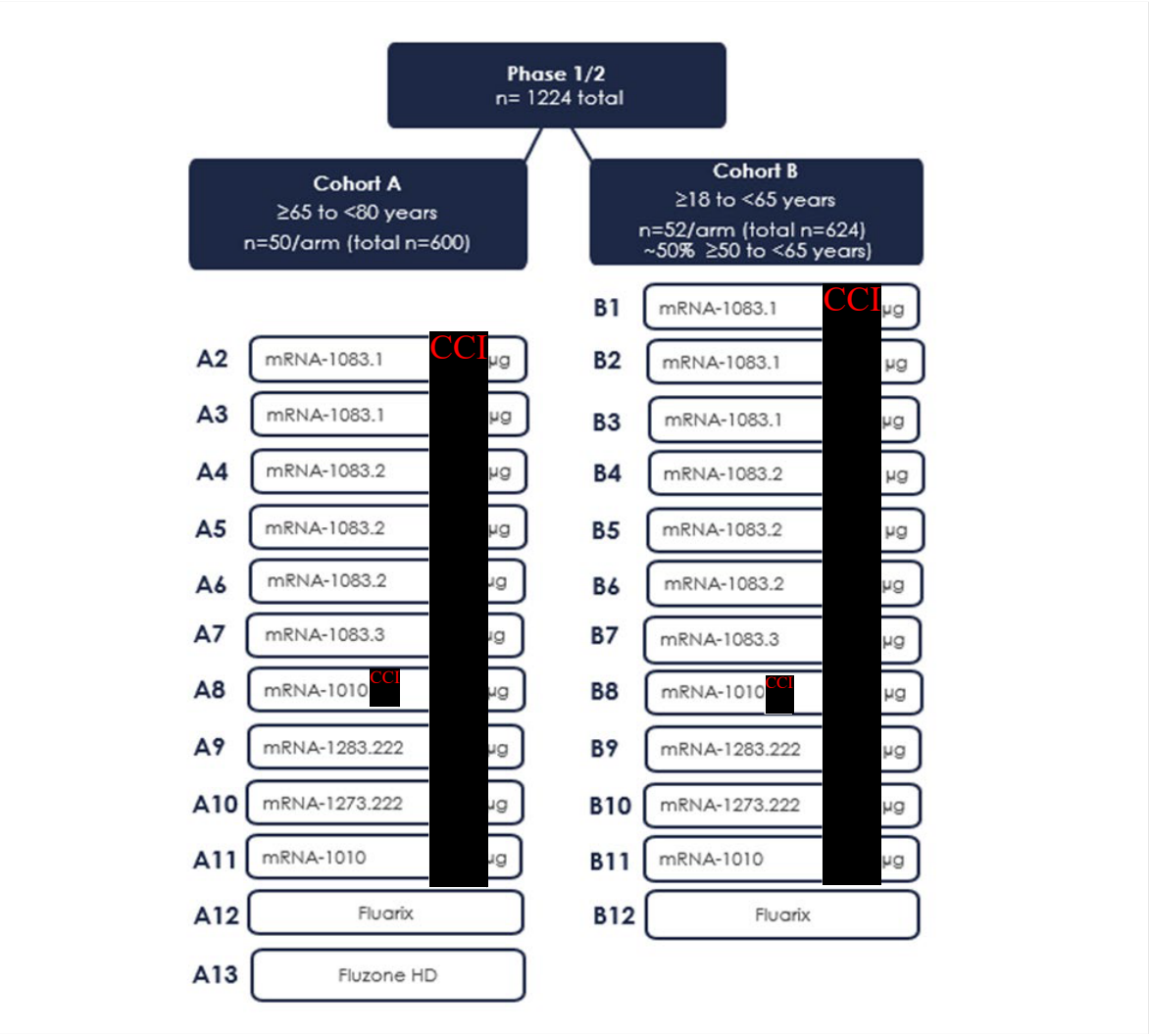
Cohort A Arms: (≥65 to <80 years), n=50/arm, 600 total	Cohort B Arms: (≥18 to <65 years), n=52/arm, 624 total	Intervention	Total mRNA Dose (µg)[1] CCI	Intervention Type
NA	B1	mRNA-1083.1	CCI	IP
A2	B2	mRNA-1083.1		IP
A3	B3	mRNA-1083.1		IP
A4	B4	mRNA-1083.2		IP
A5	B5	mRNA-1083.2		IP
A6	B6	mRNA-1083.2		IP
A7	B7	mRNA-1083.3		IP
A8	B8	mRNA-1010[2]		Non-IP experimental comparator
A9	B9	mRNA-1283.222		Non-IP experimental comparator
A10	B10	mRNA-1273.222		Non-IP experimental comparator
A11	B11	mRNA-1010		Non-IP experimental comparator
A12	B12	Fluarix		Licensed vaccine comparator
A13	NA	Fluzone HD		Licensed vaccine comparator

Abbreviations: HD=high dose; IP=investigational product; mRNA=messenger ribonucleic acid; NA=not applicable; SARS-Cov-2=severe acute respiratory syndrome coronavirus 2.
Total mRNA dose is rounded to the nearest CCI µg
CCI

All participants of the study will participate in a Screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and a follow-up period (up to 6 months after

vaccination). The study schema is presented in Figure 1. Please refer to the Schedule of Activities (SoA) available in Appendix A.

Figure 1 Study Schema (Part 1)



Abbreviations: HD=high dose; mRNA=messenger ribonucleic acid

2.3.2. Statistical Hypotheses

This clinical trial does not have formal statistical hypothesis testing planned for the primary objective (safety and reactogenicity). The total sample sizes planned are considered sufficient to provide descriptive summary of the safety and reactogenicity across study treatment arms within each age Cohort for respective parts.

2.3.3. Sample Size and Power

The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. Approximately 1224 participants will be enrolled at an evenly allocated ratio across the 12 treatment arms in Cohort A for adults ≥65 to <80 years of age and 12 treatment arms in Cohort B for adults ≥18 to <65 years of aged, with 50 participants planned for each arm in Cohort A (600 participants in total) and 52 participants planned for each arm in Cohort B (624 participants in total) (Table 2). Approximately 50 participants in each group receiving an investigational injection have approximately 87% (or 92%) probability to observe at least 1 participant with an AE given the true underlying incidence rate of AE is 4% (or 5%).

Table 2 Sample Size Determination (Part 1)

Sample Size	True AE Rate	Probability of 0 AEs	Power to Detect at Least 1 AE
50	2.0%	36.4%	63.6%
50	3.0%	21.8%	78.2%
50	4.0%	13.0%	87.0%
50	5.0%	7.7%	92.3%

Abbreviation: AE = adverse event.

2.3.4. Randomization

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

- In Cohort A, approximately 600 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since September 2022).
- In Cohort B, approximately 624 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by 2 age groups: ≥18 to <50 years and ≥50 to <65 years of age and by influenza vaccine status in the most recent influenza season (received or not received since September 2022). Approximately 50% of the participants in Cohort B will be ≥50 to <65 years of age.

2.4. Blinding and Unblinding

The planned analyses including a potential Day 8 interim analysis and the Day 29 interim analysis are described in Section 2.6.7 of this SAP. For further details on preidentified sponsor

and CRO team members (identified by role), and the level of unblinding (treatment group level unblinding and/or subject level unblinding) at the IAs and the Final analysis, please refer to the study Data Blinding Plan.

2.5. Analysis Sets

2.5.1. Randomization Set

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

2.5.2. Full Analysis Set (FAS)

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

2.5.3. Per Protocol (PP) Set

The PP Set in Part 1 consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a Baseline and at least 1 post-injection assessment at Day 29 (-7 to +14 days), have no documented infection (confirmed by RT-PCR test) of either influenza or SARS-CoV-2 on Day 1 and up to Day 29 (Day 29 immunogenicity assessment + 7 days), have no major dosing error, and have no major protocol deviations or conditions/medications that affect the immune response. The PP Set will be used as the primary analysis set for analyses of immunogenicity in Cohort A or B unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.

The major dosing error ranges, available in Table 3,will be used to determine participant exclusion from the PP analysis populations:

Table 3 Exclusion Condition for Dosing Errors (Part 1)

Randomized Group	Exclusion Conditions
mRNA-1083.1 ([redacted] µg)	Any of the following received: mRNA-1083.1 ≤ [redacted] µg OR mRNA-1083.1 > [redacted] µg OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.1 ([redacted] µg)	Any of the following received: mRNA-1083.1 ≤ [redacted] µg OR mRNA-1083.1 > [redacted] µg OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.1 ([redacted] µg)	Any of the following received: mRNA-1083.1 ≤ [redacted] µg OR mRNA-1083.1 > [redacted] µg OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.2 ([redacted] µg)	Any of the following received: mRNA-1083.2 ≤ [redacted] µg OR mRNA-1083.2 > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.2 ([redacted] µg)	Any of the following received: mRNA-1083.2 ≤ [redacted] µg OR mRNA-1083.2 > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.2 ([redacted] µg)	Any of the following received: mRNA-1083.2 ≤ [redacted] µg OR mRNA-1083.2 > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1083.3 ([redacted] µg)	Any of the following received: mRNA-1083.3 ≤ [redacted] µg OR mRNA-1083.3 > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1010[redacted] ([redacted] µg)	Any of the following received: mRNA-1010[redacted] ≤ [redacted] µg OR mRNA-1010[redacted] > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1283.222 ([redacted] µg)	Any of the following received: mRNA-1283.222 ≤ [redacted] µg OR mRNA-1283.222 > [redacted] µg OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1273.222 OR Fluarix OR Fluzone HD
mRNA-1273.222 ([redacted] µg)	Any of the following received: mRNA-1273.222 ≤ [redacted] µg OR mRNA-1273.222 > [redacted] OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010[redacted] OR mRNA-1283.222 OR Fluarix OR Fluzone HD
mRNA-1010 ([redacted] µg)	Any of the following received: mRNA-1010 ≤ [redacted] µg OR mRNA-1010 > [redacted] OR

Randomized Group	Exclusion Conditions
	mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010.[CCI] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix OR Fluzone HD
Fluarix	Any of the following received: Fluarix ≤ 30 µg OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010.[CCI] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluzone HD
Fluzone HD	Any of the following received: Fluzone HD ≤ 120 µg OR mRNA-1083.1 OR mRNA-1083.2 OR mRNA-1083.3 OR mRNA-1010 OR mRNA-1010.[CCI] OR mRNA-1283.222 OR mRNA-1273.222 OR Fluarix

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

2.5.4. 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 vaccination group corresponding to what they actually received according to the as treated scheme given below in Table 4.

Table 4 As Treated Grouping Scheme (Part 1)

Group Name	Inclusion condition
mRNA-1083.1 ([CCI] µg)	Any dose of mRNA-1083.1 ≤ [CCI] µg
mRNA-1083.1 ([CCI] µg)	Any dose of mRNA-1083.1 > [CCI] µg and ≤ [CCI] µg
mRNA-1083.1 ([CCI] µg)	Any dose of mRNA-1083.1 > [CCI] µg and ≤ [CCI] µg
mRNA-1083.2 ([CCI] µg)	Any dose of mRNA-1083.2 ≤ [CCI] µg
mRNA-1083.2 ([CCI] µg)	Any dose of mRNA-1083.2 > [CCI] µg and ≤ [CCI] µg
mRNA-1083.2 ([CCI] µg)	Any dose of mRNA-1083.2 > [CCI] µg
mRNA-1083.3 ([CCI] µg)	Any dose of mRNA-1083.3
mRNA-1010.[CCI] ([CCI] µg)	Any dose of mRNA-1010.[CCI]
mRNA-1283.222 ([CCI] µg)	Any dose of mRNA-1283.222
mRNA-1273.222 ([CCI] µg)	Any dose of mRNA-1273.222
mRNA-1010 ([CCI] µg)	Any dose of mRNA-1010
Fluarix	Any dose of Fluarix
Fluzone HD	Any dose of Fluzone HD

2.5.5. Solicited Safety Set

The solicited safety set consists of all participants in the safety set who contribute any solicited AR data. The solicited safety set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to what they actually received (as treated).

2.6. Statistical Analysis

The SoA is provided in the Appendix A.

2.6.1. General Considerations

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

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.

Summaries that require Q1 and Q3 for descriptive statistics:

- Demographic and baseline characteristics
- Study duration
- Characteristics of solicited adverse reactions within 7 days 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 treatment 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 and nasal swab 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 date, the largest value will be considered in the immunogenicity baseline derivation.

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

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

The following analysis periods of safety analyses will be used:

- 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).
- 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 solicited local and systemic AR 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.

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

a) study day prior to the injection will be calculated as: date of assessment/event – date of the injection (resulting in negative study day);
b) 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). 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 End of Study [EoS] eCRF) – date of randomization + 1,

- Since study injection: date of last visit (as recorded on End of Study [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. The durations 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.

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

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

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

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

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Table layouts will be presented according to vaccination group. First for the overall participants, then by subgroups as given in Table 5.

For Part 1, all the statistical analyses will be performed and presented by Cohort A and Cohort B, separately. The following vaccination groups will be used for summary purposes for Cohort A and for Cohort B tables and figures outputs, respectively:

Cohort A:

- Fluarix
- Fluzone HD
- mRNA-1010 [redacted] µg
- mRNA-1010 [redacted] µg
- mRNA-1273.222 [redacted] µg
- mRNA-1283.222 [redacted] µg
- mRNA-1083.1 [redacted] µg
- mRNA-1083.1 [redacted] µg
- mRNA-1083.2 [redacted] µg
- mRNA-1083.2 [redacted] µg
- mRNA-1083.2 [redacted] µg
- mRNA-1083.3 [redacted] µg
- All mRNA-1083.1 (all mRNA-1083.1 vaccination groups combined; applicable to safety and reactogenicity analyses only)
- All mRNA-1083.2 (all mRNA-1083.2 vaccination groups combined; applicable to safety and reactogenicity analyses only)
- Overall (All vaccination groups combined; details are available below)

Cohort B:

- Fluarix
- mRNA-1010 [redacted] µg
- mRNA-1010 [redacted] µg
- mRNA-1273.222 [redacted] µg
- mRNA-1283.222 [redacted] µg
- mRNA-1083.1 [redacted] µg
- mRNA-1083.1 [redacted] µg

- mRNA-1083.1 CCI µg
- mRNA-1083.2 CCI µg
- mRNA-1083.2 CCI µg
- mRNA-1083.2 CCI µg
- mRNA-1083.3 CCI µg
- All mRNA-1083.1 (all mRNA-1083.1 vaccination groups combined; applicable to safety and reactogenicity analyses only)
- All mRNA-1083.2 (all mRNA-1083.2 vaccination groups combined; applicable to safety and reactogenicity analyses only)
- Overall (All vaccination groups combined; details are available below)

The "Overall" combined group will be presented for baseline summaries such as participant disposition, demographic summaries, concordance of randomization stratum, etc. as well as major protocol deviation, medical history, concomitant medication and study duration summaries.

Subgroups by Cohort A and B: For Part 1, the following subgroups will be used for summary purposes, where indicated in this SAP. Unless otherwise specified, all subgroups are based on eCRF.

Table 5 Definition for Subgroups by Cohort A and B (Part 1)

Cohort Applicable	Subgroup Variable	Categories
Cohort B only	Age Group	≥18 to <50 years ≥ 50 to <65 years
Cohort A and B	Influenza vaccine status since Sept 2022	Received previous season flu vaccine Did not receive previous season flu vaccine
Cohort A and B	Prior bivalent Covid vaccine status	Received prior bivalent Covid vaccine Did not receive prior bivalent Covid vaccine
Cohort A and B	Baseline SARS-CoV-2 Status	Positive Negative

2.6.2. Background Characteristics

2.6.2.1. Participant Disposition

The number and percentage of participants in each of the following disposition categories will be summarized by treatment group (as defined in Section 2.6.1) based on the Randomization Set:

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

This study treatment only consists of a 1-dose, thus discontinuation from study treatment is not applicable to this study. A Participant is considered to have completed the study if he or she has completed the study including the last Day 181 scheduled procedure (SoA).

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

In addition, randomized participants 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 0) will be summarized by treatment group (as defined in Section 2.6.1) based on the Randomization Set:

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

For Solicited Safety Set, the percentage will be based on the number of participants in the treatment group within the Safety Set (as treated). A summary of reasons for participants excluded from PP will also be provided.

A Randomization listing will be provided including randomization information such as randomization date, number, planned and actual treatment group and stratification used.

An additional 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 added.

A separate summary table will include the number and percentage of randomized participants by vaccination group with respect to each combined stratification factor at randomization by IRT (i.e. >18 to <50 years and Received, >18 to <50 years and Not Received, ≥50 to <65 years and Received, ≥50 to <65 years and Not Received) and by each of the two stratification factors at randomization separately (>18 to <50 vs. ≥50 to <65 years; Received vs. Not received).

If IRT and eCRF stratum are not concordant, then a concordance table will be presented, by vaccination group based on the Randomization Set, with the number and percentage of patients in IRT randomization stratum and actual stratum derived from eCRF.

2.6.2.2. 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:

- Age group (≥ 18 to <50 years old, ≥ 50 to < 65 years old for Cohort B, ≥ 65 to <80 years old for Cohort A, separately) per age reported on the eCRF
- Sex (Male, Female)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Other, Not Reported, Unknown)
- 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 2022) per eCRF
- Prior bivalent Covid vaccine status (received or not received) per eCRF
- Childbearing Potential for female participants (Yes/No) and reason if "No"
- Baseline SARS-CoV-2 RT-PCR Results (positive, negative, or missing)
- Baseline Elecsys Anti-SARS-CoV2 Results (positive, negative, or missing)
- Baseline SARS-CoV-2 Status (positive, negative, or missing)

The summaries will be provided separately for all analysis sets (except Randomization Set and Solicited Safety Set) defined in the Section 0. The number and percentage of participants randomized by country and site will be provided as well.

2.6.2.3. Medical History

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

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of the "Overall" group and then alphabetically within SOC.

Medical history data will be presented in a listing.

2.6.2.4. 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 C.

An overall summary with the number and percentage of participants using concomitant medications and non-study vaccination that continued or newly received at or after the injection, during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28 day follow-up period after the injection (i.e., on the day of injection and the 27 subsequent days) will be provided by vaccination group (as defined in Section 2.6.1) as follows:

- Any concomitant medications and non-study vaccination within 7 days postinjection
- Any concomitant medications and non-study vaccination within 28 days post-injection
- Any seasonal influenza or COVID-19 vaccine within 28 days post-injection

An additional summary table of concomitant medications and non-study vaccination that continued or newly received at or after the injection through 28 days will be provided by PT in descending frequency based on “Overall” group.

Medications taken to prevent or treat pain or fever will be collected in the electronic diary (eDiary). A summary table will be provided based on the Solicited Safety Set by vaccination group (as defined in Section 2.6.1), including within 7 days after injection, beyond 7 days after injection, and any time after injection.

Prior, concomitant and post medications and non-study vaccination will be presented in a listing. Medications taken to prevent or treat pain or fever will be presented as well (see Section 2.6.3.1 on solicited ARs listings).

Concomitant Procedures will be presented in a listing.

2.6.2.5. Study Exposure

Study vaccine administration data will be presented in a listing. Participants with any dosing errors will also be presented in a separate listing.

Study duration (the study duration calculation is available in Section 2.6.1) will be summarized since randomization, and since the study injection based on Safety Set.

2.6.2.6. 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 deviations 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 (as defined in Section 2.6.1), based on the Randomization Set.

Selected major protocol deviations might impact critical or key study data such as the immune response. Participants with such deviations will be excluded from the PP set. Such major protocol deviations will be determined and documented by Sponsor prior to database lock and unblinding. Reasons of exclusion from PP set will be summarized (see section 2.6.2.1).

Major protocol deviations will be presented in a listing.

2.6.2.7. COVID-19 Impact

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

2.6.3. Safety Analysis

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 withdrawal from study participation.

All safety analyses will be provided by treatment group available in the Section 2.6.1. Participants will be included in the treatment 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. Imputation rules for missing/partial dates is detailed in Appendix D.

2.6.3.1. Solicited Adverse Reactions

Solicited ARs are predefined local (at the injection site) and systemic events/symptoms that participants are specifically asked, and which are noted by the participant in their eDiary. The eDiary will solicit daily participant reporting of ARs using a structured checklist from the day of vaccination (Day 1) and for the 6 days after the day of dosing (through Day 7). Solicited ARs include selected signs and symptoms that are typically associated with vaccine reactogenicity.

Local ARs are expected after intramuscular study intervention administration. These are typically mild, transient, and self-limited and may include pain, erythema (redness), swelling/induration (hardness) at the injection site and/or ipsilateral underarm swelling/tenderness. Systemic ARs may also occur after study intervention administration, the majority of which are of mild to moderate in severity. Systemic ARs reported with other mRNA vaccines may include fatigue, headache, myalgia, fever, chills, arthralgia, vomiting and/or nausea.

Reactogenicity refers to the occurrence and intensity of local and systemic ARs commonly following vaccination. Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Appendix G modified from the Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS, 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded in the participant's Reactogenicity eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare professional (MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the clinical trial or the participant being withdrawn from the clinical trial by the Investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days post-injection
- Solicited local or systemic AR that otherwise meets the definition of an SAE

Additionally:

- 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 on the Reactogenicity page of the eCRF.
- If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant should notify the site to provide an end date to close out the event on the Reactogenicity page of the eCRF.

- If the participant reported an event after the solicited period (i.e., after Day 7), it should be recorded as an AE on the AE page of the eCRF.

When summarizing the number and percentage of participants with an event, participants will be presented according to the highest severity/toxicity in the summaries by severity/toxicity.

2.6.3.1.1 Overview of Solicited ARs

An overall summary of solicited ARs up to 7 days after study injection (with a toxicity grade of Grade 1 or greater) including the number and percentage of participants, along with the number of events, by vaccination group (as defined in Section 2.6.1) will be presented.

The number and percentage of subjects experiencing any solicited local ARs and solicited systemic ARs of Grade 3 or higher will be provided.

2.6.3.1.2 Solicited ARs by Toxicity Grade

An summary of solicited ARs up to 7 days after study injection (with a toxicity grade of Grade 1 or greater) by toxicity grade, including the number and percentage of participants, by vaccination group (as defined in Section 2.6.1) who experience the following will be presented:

- Any solicited ARs,
- Any solicited systemic AR,
- Any solicited local AR,
- Each individual solicited systemic and local AR,

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 and local, systemic). An additional description for Grade 3 or Above (Grade >=3) will be provided for all above categories.

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

2.6.3.1.3 Solicited ARs by Onset Day

An summary of solicited ARs up to 7 days 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, by vaccination group (as defined in Section 2.6.1) who experience the following will be presented:

- Any solicited ARs,
- Any solicited systemic AR,
- Any solicited local AR,
- Each individual solicited systemic and local AR,

The onset of individual solicited AR is defined as the time point after injection (Section 2.6.1) at which the respective solicited AR first occurred.

2.6.3.1.4 Characteristics of Solicited ARs

A descriptive summary of the day of onset and the duration of solicited ARs up to 7 days after study injection (with a toxicity grade of Grade 1 or greater), by vaccination group (as defined in Section 2.6.1) who experience the following will be presented:

- Any solicited ARs,
- Any solicited systemic AR,
- Any solicited local AR,
- Each individual solicited systemic and local AR

The onset of individual solicited AR is defined as the time point after injection (Section 2.6.1) at which the respective solicited AR first occurred. The duration calculation method is available in the Section 2.6.1 as well.

2.6.3.1.5 Other solicited ARs summaries

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, by vaccination group (as defined in Section 2.6.1) who experience the following will be presented:

- Any solicited ARs,
- Any solicited systemic AR,
- Any solicited local AR,
- Each individual solicited systemic and local AR.

Solicited local and systemic ARs (with a toxicity grade of Grade 1 or greater) will be provided in listings. Medications taken to prevent or treat pain or fever will also be presented. All solicited ARs that continue beyond 7 days post-injection (with a toxicity grade of Grade 1 or greater) will be listed as well.

2.6.3.2. Unsolicited Treatment-Emergent Adverse Events

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

An unsolicited TEAE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (i.e., 7 days after study vaccine administration). For analysis and reporting purposes, unsolicited TEAEs will include the following:

- TEAEs that are reported by participants and recorded on the AE eCRF
- Solicited ARs that meet SAE criteria after injection are recorded on the Reactogenicity eCRF

Unsolicited AEs include serious (SAE) and nonserious AEs. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

A MAAE is an AE that leads to an unscheduled visit to a healthcare professional (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. An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required and documentation is in the form of a case narrative. Such events may require further investigation to characterize and understand them.

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, SAEs, and AESIs will be collected from the start of study intervention administration until through EoS or discontinuation from the clinical trial.

Unsolicited AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher and presented by MedDRA system organ class (SOC) and preferred term (PT).

Analyses of unsolicited TEAEs will be provided (1) for up to 28 days after vaccination and (2) until EoS visit unless otherwise specified (as defined in Section 2.6.1). SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of the combined:

- 1083.2 treatment group (mRNA-1083.2 CCI µg, mRNA-1083.2 CCI µg, and mRNA-1083.2 CCI µg), 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 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/≥ 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,
- Any treatment-related unsolicited AEs,
- Unsolicited serious AEs,
- Unsolicited serious treatment-related AEs,
- Unsolicited severe AEs
- Unsolicited AEs leading to discontinued from the study,
- Unsolicited MAAEs,
- Unsolicited AESIs,

Treatment-emergent AEs will be flagged in all data listings.

In addition, number of participants with occurrences of selected TEAEs of clinical interests identified by SMQ will be summarized up to 28 days after injection and throughout the study.

SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in Appendix H. A listing of unsolicited AEs by SMQ will be provided.

2.6.3.2.1 Overview of Unsolicited TEAEs

An overall summary of unsolicited TEAEs, including the number and percentage of participants, by vaccination group (as defined in Section 2.6.1) 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 (/≥ grade 3) AEs,
- Any unsolicited AEs that are fatal.

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

2.6.3.2.2 TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs 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 vaccination group (as defined in Section 2.6.1):

- 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 (grade ≥ 3) AEs,

- All unsolicited severe (grade ≥ 3) AEs that are treatment-related,
- All unsolicited AEs leading to study discontinuation,

2.6.3.2.3 TEAEs by Preferred Term

Tables of all unsolicited TEAEs will be provided by PT sorted in a descending order starting with the frequency of the combined 1083.2 group (mRNA-1083.2 CCI µg, mRNA-1083.2 CCI µg, and mRNA-1083.2 CCI µg).

2.6.3.2.4 TEAEs by Severity

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

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

Summary tables will also be provided by SOC and PT for unsolicited TEAEs that are treatment-related in each of the above categories.

2.6.3.3. Death

Total number of deaths due to any cause and time of death from injection (numeric and by time point window) will be summarized in a table. In addition, number of participants with occurrences of Unsolicited TEAE Leading to Death will be summarized by SOC and PT using frequency counts and percentages. A listing of deaths including cause of death, and a listing of unsolicited AEs in participants who died will be provided.

2.6.3.4. Clinical Safety Laboratory Tests

Safety laboratory tests will consist of white blood cell count, hemoglobin, hematocrit, platelets, AST, ALT, creatinine, alkaline phosphatase, and total bilirubin will be assessed at Screening and Day 8. The Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS, 2007) available in Appendix E will be used to categorize clinical laboratory test results.

Observed values and changes from baseline to post-baseline visit (at Day 8) for continuous hematology and serum chemistry parameters will be summarized by vaccination group. A toxicity grade shift table of the hematology and chemistry parameters from baseline to post-baseline visit will be provided as well.

Listing containing individual participant clinical laboratory tests measurements data will be provided for hematology and serum chemistry. Additionally, participant with any abnormal post-baseline laboratory tests measurements where toxicity grade (Grade 2 or higher) will be listed separately: if a participant has a laboratory result with Grade 2 or higher abnormality after injection visit, then all results for that participant will be presented in the listing. The values that are outside the reference ranges will be flagged in a data listing.

If multiple values are collected within a post-baseline visit/timepoint, the last assessment will be used in the by-visit summary tables. Unscheduled visits (including early termination) will not be summarized in by-visit summaries of data but may contribute to either baseline or post-baseline worst-case (maximum, minimum, etc.) values when applicable. All values will be listed.

2.6.3.5. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral) and will be assessed at Screening and Day 1. On the day of study intervention administration, vital sign measurements will be collected once before and at least 60 minutes after study intervention. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

Following injection, any abnormal vital sign measurement should be assessed by the Investigator to determine if it meets AE reporting criteria per protocol and reported as an AE in EDC, if appropriate.

The Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical (DHHS, 2007) available in Appendix F 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, 60 minutes after study intervention) for all vital sign measurements will be summarized by

vaccination 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 (Grade 3 or higher) will be listed separately: if a participant has a vital sign result with Grade 3 or higher abnormality after injection visit, then all results for that participant will be presented in the listing.

If multiple values are collected within a post-baseline visit/timepoint, the last assessment will be used in the by-visit summary tables. Unscheduled visits (including early termination) will not be summarized in by-visit summaries of data but may contribute to either baseline or post-baseline worst-case (maximum, minimum, etc.) values when applicable.

2.6.3.6. 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 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. For participants 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 will be provided for the pregnancy tests and FSH blood levels.

2.6.3.7. Other Safety Data

2.6.3.7.1 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information.

A listing containing individual participant safety call information will be provided.

2.6.3.7.2 Assessment for Respiratory Viral Infection

For Part 1, during the clinical trial, participants might experience symptoms consistent with ILI or SARS-CoV-2 infection. All participants will provide nasal swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments. Throughout the clinical trial, the participant will be instructed to contact the study site if they have symptoms suggestive of ILI or SARS-CoV-2. An unscheduled visit for symptom assessment and nasal swab for viral respiratory pathogens will be conducted within 7 days of the onset of any potential ILI or SARS-CoV-2 symptoms.

The Assessment for Respiratory Viral Infection is available in protocol Section 8.3.7 corresponding to the Efficacy Analysis. A listing presenting for each participants the symptoms of ILI/COVID-19 will be provided as well.

2.6.3.7.3 Physical examination

A complete physical examination will include, at a minimum, assessments of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. Height and weight will also be measured and recorded.

2.6.3.7.4 Electrocardiograms

For participants aged ≥18 to <51 only, a 12-lead ECG will be obtained at Day 1, after 10 minutes of supine rest. The purpose of the ECG is to serve as a Baseline comparison, should it be necessary, for subsequent clinical evaluation of suspected myocarditis and/or pericarditis. Clinically significant abnormal ECG findings, if incidentally observed by the Investigator, may contribute to Investigator's assessment of eligibility, at his or her discretion.

2.6.4. Immunogenicity Analysis

The primary analysis population for immunogenicity will be the PP Set. Planned timepoints for all immunogenicity assessments are provided in the SoA available in Appendix A.

For Part 1, the following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay and potentially serum neutralizing antibody (nAb) level as measured by microneutralization assay.
- SARS-CoV-2: Serum nAb titers as measured by pseudovirus neutralization assay (PsVNA) assay and potentially serum binding antibody titers by enzyme-linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.
- Cellular immunogenicity in a subset of participants.

For secondary and exploratory endpoints, the Geometric Mean Titer (GMT) will be calculated using the following formula (Nauta, 2011):

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

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

The Geometric Mean Fold Rise (GMFR) measures the changes in immunogenicity titers or levels within participants. The GMFR will be calculated using the following formula:

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

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity titers or levels for participant i at time points j and k, $j \neq k$. For GMFR calculation, antibody values reported as below LLOQ will be replaced by LLOQ.

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

2.6.4.1. Secondary Immunogenicity Endpoints

- GMT and GMFR at Day 29 compared with Day 1 by HAI assay for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay

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

For the secondary immunogenicity endpoints, descriptive summaries statistics, including median, Q1, Q3, minimum, and maximum along with the number and percentage values above (>=) LLOQ and below (<) LLOQ will be provided for the antibody titer values by treatment arm (available in Section 2.6.1) for the influenza and SARS-CoV-2 endpoints. In addition, the following endpoints summaries will be provided:

- Geometric mean of specific antibody titers (GMT) with corresponding 2-sided 95% CI at each time point
- Geometric mean fold rise (GMFR) of specific antibody titers with the corresponding 2-sided 95% CI at each post-Baseline time point over pre-injection Baseline at Day 1,

Listing presenting the antibody level, for each specific strain of influenza and SARS-CoV-2 will be provided. The ratio of post-Baseline/Baseline, LLOQ and ULOQ will be presented as well. An additional listing will be provided for participants with Influenza or SARS-CoV-2 infections.

Reverse Cumulative Distribution Function for each specific strain of influenza and SARS-CoV-2 will be provided. The box plot for GMT and GMFR will be provided at all evaluable timepoints. The bar plot for GMFR at Day 29 will also be provided.

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

Additional descriptions will be provided by treatment arm (available in Section 2.6.1) for the following influenza and SARS-CoV-2 endpoints:

- Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) with the corresponding 2-sided 95% CI at each post-Baseline time point,

- Percentages of participants with a GMFR results >=2, and >=4 with the corresponding 2-sided 95% CI at each post-Baseline time point.

For participants in the groups receiving mRNA-1083, mRNA-1010 or influenza injections, seroconversion rate from Baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-Baseline time point. Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer CCI and a post-vaccination HAI titer CCI or a pre-vaccination HAI titer CCI and a minimum 4-fold rise in post-vaccination HAI antibody titer.

For participants in the groups receiving mRNA-1083, mRNA-1283.222 or mRNA-1273.222, seroresponse rate will be summarized for planned post-Baseline visits, including the 2-sided 95% CI using the Clopper-Pearson method. Rate of Seroreponse for SARS-Cov-2 is defined as a ≥ 4 fold rise in nAb titer from Baseline in those with Baseline titer $\geq$ LLOQ, or a post-Baseline titer $\geq 4 \times$ LLOQ if Baseline titer is < LLOQ.

In addition, the following analysis statistics will be provided by treatment arm (available in Table 7) at Day 29 and D181 for the following influenza and SARS-CoV-2 endpoints:

- Within Treatment Group, Model-based geometric mean titer (GMT) with the corresponding 95% CI,
- Between Treatment Group, Pair-wise geometric mean ratios (GMR) with the corresponding 95% CI

The model-based GM titer will be estimated based on an analysis of covariance (ANCOVA) model, and it will be modelled separately for Cohort A and Cohort B. In the ANCOVA model, the log-transformed antibody titer at a post-Baseline timepoint (Day 29 or Day 181) are treated as a dependent variable, with the treatment group as an explanatory variable and covariates listed in Table 6 below for different assays, Cohorts and subgroups:

Table 6 Covariates Included in Different ANCOVA Models (Part 1)

Assay	Cohort	Subgroup	Covariate(s)
PsVNA	A	Overall	Influenza vaccine status since Sept 2022 (IRT)
		Overall	None
		Prior bivalent Covid vaccine status: Received	None
		Prior bivalent Covid vaccine status: Not Received	None
		Baseline SARS-CoV2 Status: Positive	None
		Baseline SARS-CoV2 Status: Negative	None
	B	Overall	Age Group (IRT), Influenza vaccine status since Sept 2022 (IRT)
		Overall	Age Group (EDC)
		Age Group (EDC): ≥ 18 to <50 years	None
		Age Group (EDC): ≥ 50 to <65 years	None
		Prior bivalent Covid vaccine status: Received	Age Group (IRT)
		Prior bivalent Covid vaccine status: Not Received	Age Group (IRT)
		Baseline SARS-CoV2 Status: Positive	Age Group (IRT)
		Baseline SARS-CoV2 Status: Negative	Age Group (IRT)
HAI	A	Overall	Influenza vaccine status since Sept 2022 (IRT)
		Overall	Influenza vaccine status since Sept 2022 (EDC)
		Influenza vaccine status since Sept 2022 (EDC): Received	None
		Influenza vaccine status since Sept 2022 (EDC): Not Received	None
	B	Overall	Age Group (IRT), Influenza vaccine status since Sept 2022 (IRT)
		Overall	Age Group (EDC), Influenza vaccine status since Sept 2022 (EDC)
		Age Group (EDC): ≥ 18 to <50 years	Influenza vaccine status since Sept 2022 (IRT)
		Age Group (EDC): ≥ 50 to <65 years	Influenza vaccine status since Sept 2022 (IRT)
		Influenza vaccine status since Sept 2022 (EDC)=Y	Age Group (IRT)
		Influenza vaccine status since Sept 2022 (EDC)=N	Age Group (IRT)

The GMT will be estimated by the geometric least square mean (GLSM) from the ANCOVA model for each treatment group and corresponding 2-sided 95% CI will be provided.

For each pair of between-group comparison specified in Table 7, the GMR (ratio of GMTs) between the two treatment groups in each pair will be estimated from the ANCOVA model, with 2-sided 95% CI provided accordingly.

Additional comparisons or analysis statistics will be provided by treatment arm (available in Table 7) at Day 29 for the following influenza and SARS-CoV-2 endpoints:

- Pair-wise seroconversion rate (SCR) difference (influenza) and pair-wise seroresponse rate (SRR) difference (SARS-CoV-2) with the corresponding 95% CI

For each pair of between-group comparison specified in Table 7, the difference of seroresponse/seroconversion rate (SRR/SCR) between the two treatment groups in each pair at Day 29 will be provided, with 2-sided 95% CI estimated using Miettinen-Nurminen method.

A bar plot for GMR and GMFR at Day 29 and at D181, as well as a bar plot of SCR (influenza)/SRR (SARS-CoV-2) at Day 29 and D181 will be provided.

Table 7 Exploratory between-group Immunogenicity comparisons (Part 1)

Influenza Cohort A								
	Treatment Arm							
Control Arm	**mRNA-1010 [redacted] µg**	**mRNA-1010 [redacted] µg**	**mRNA-1083.1 [redacted] µg**	**mRNA-1083.1 [redacted] µg**	**mRNA-1083.2 [redacted] µg**	**mRNA-1083.2 [redacted] µg**	**mRNA-1083.2 [redacted] µg**	**mRNA-1083.3 [redacted] µg**
Fluarix	X	X	X	X	X	X	X	X
Fluzone HD	X	X	X	X	X	X	X	X
mRNA-1010 [redacted] µg	NA	X	X	X	X	X	X	X
mRNA-1010 [redacted] µg	NA	NA	X	X	X	X	X	X

Influenza Cohort B									
	Treatment Arm								
Control Arm	mRNA-1010 CCI µg	mRNA-1010 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.3 CCI µg
Fluarix	X	X	X	X	X	X	X	X	X
mRNA-1010 CCI µg	NA	X	X	X	X	X	X	X	X
mRNA-1010 CCI µg	NA	NA	X	X	X	X	X	X	X

SARS-CoV-2 Cohort A							
	Treatment Arm						
Control Arm	mRNA-1283.222 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.3 CCI µg
mRNA-1273.222 CCI µg	X	X	X	X	X	X	X
mRNA-1283.222 CCI µg	NA	X	X	X	X	X	X

SARS-CoV-2 Cohort B							
	Treatment Arm						
Control Arm	mRNA-1283.222 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.1 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.2 CCI µg	mRNA-1083.3 CCI µg
mRNA-1273.222 CCI µg	X	X	X	X	X	X	X	X
mRNA-1283.222 CCI µg	NA	X	X	X	X	X	X	X

2.6.4.2. Exploratory Immunogenicity Endpoints

The below exploratory analyses of immunogenicity may be performed:

- GMT and GMFR (compared to Day 1) to vaccine mismatched strains at all evaluable time points

- GMT and GMFR (compared to Day 1) to vaccine matched and mismatched strains assayed by alternative methods (including but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2) at all evaluable time points
- Frequency, magnitude, and phenotype of virus specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells and T cells after vaccination
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

2.6.5. Exploratory Analysis

2.6.5.1. Efficacy Analysis

While the study will not be powered for efficacy assessments, symptoms of infection with respiratory pathogens will be tracked as an exploratory objective in this study (Part 1 only). Efficacy analyses will be performed on the FAS. Frequency of RT-PCR-confirmed protocol-defined influenza-like illness (ILI) and RT-PCR-confirmed symptomatic SARS-CoV-2 observed among the participants in the FAS will be summarized according to the vaccination groups as randomized.

2.6.5.2. Influenza Infection

A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom, or the occurrence of any 2 or more respiratory symptoms, as shown in Table 8.

An RT-PCR confirmed protocol-defined ILI is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local certified laboratory within 7 days of onset of protocol-defined ILI at any time during the study period.

Table 8 Respiratory and Systemic Symptoms for Protocol-defined ILI (Part 1)

Respiratory symptoms	Systemic symptoms
Sore throat Cough/rhinorrhea/nasal congestion (≥1 of the 3 symptoms count as 1 respiratory symptom) Sputum production Wheezing Difficulty breathing	Body temperature ≥37.5°C [≥99.5°F] Chills Tiredness Headache Myalgia Nausea/vomiting Diarrhea

Derivation of PT-PCR confirmed protocol-defined ILI:

The eligible protocol-defined ILI symptoms will be documented on the ILI symptom assessment eCRF. The following derivation steps will be performed on each participant to determine whether protocol-defined ILI occurred within the specified window based on positive RT-PCR results:

Step 1: The time window for protocol-defined ILI to be considered as RT-PCR confirmed will be calculated based on each positive RT-PCR collection date +/- 7 days (ex: positive RT-PCR collection date – 7 days through positive RT-PCR collection date + 7 days).

Step 2: Within this time window, determine the earliest eligible symptoms for protocol-defined ILI. Considering the symptoms listed in (Table 8) that onset within the positive RT-PCR collection date window from Step 1, eligible symptoms are defined as those that meet either of the criteria given below, based on their start and end dates:

- The occurrence of at least 1 respiratory illness symptom and at least 1 systemic symptom that overlap for at least 1 day or
- The occurrence of any 2 or more respiratory symptoms that overlap for at least 1 day.

Step 3: The start date for the RT-PCR confirmed protocol-defined ILI will be set as either the positive RT-PCR date or the earliest eligible symptom onset date, whichever occurs earlier.

The following summaries will be provided for influenza infection:

- The number and percentage of participants with an RT-PCR test results (Positive, Negative, Not Applicable, Missing) at Baseline will be summarized by vaccination group (as defined in Section 2.6.1).

- The number and percentage of participants with an RT-PCR test results (Positive, Positive and <=14 Days After Injection, Positive and > 14 Days After Injection, Negative, Not Applicable, Missing) excluding Baseline will be summarized by vaccination group (as defined in Section 2.6.1).
- The number and percentage of participants with RT-PCR confirmed protocol-defined ILI within the period starting from 14 days post-injection up through EoS will be summarized by strain of influenza virus, and by time period. A 2-sided 95% CI using the Clopper-Pearson method will be provided for the percentage of participants with the RT-PCR confirmed influenza infection.
- The number and percentage of participants with RT-PCR confirmed protocol-defined ILI within the period starting from 14 days post-injection up through EoS will be summarized by respiratory symptoms and systemic symptoms
- A listing presenting the RT-PCR test results for influenza will be provided.
- A listing presenting the symptom assessment for protocol-defined ILI will be provided.

2.6.5.3. SARS-CoV-2 Infection

Symptomatic COVID-19 is defined by the presence of one of the CDC-listed symptoms (CDC, 2020) and a positive RT-PCR test on a respiratory sample. SARS-CoV-2 should be suspected if the participant experiences any one of the symptoms listed below lasting at least 48 hours (except for fever and/or respiratory symptoms) (CDC, 2020) :

- Fever (temperature ≥38.0°C [100.4°F]) or chills (of any duration, including ≤48 hours)
- Cough (of any duration, including ≤48 hours)
- Shortness of breath and/or difficulty breathing (of any duration, including ≤48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste and/or smell
- Sore throat, congestion, or runny nose
- Nausea or vomiting

- Diarrhea

Symptomatic COVID-19 is defined by the presence of one of the CDC-listed symptoms (CDC, 2020) and a positive RT-PCR test on a respiratory sample.

If the participant had known exposure to COVID-19 (eg, exposure to someone with a confirmed case of COVID-19), it will be captured in the COVID-19 exposure form, and the participant will continue to follow all remaining study assessments as scheduled. Likewise, participants with a confirmed case of COVID-19 will continue to follow all remaining study assessments as scheduled.

The following summaries will be provided:

- The number and percentage of participants with an RT-PCR test results (Positive, Negative, Not Applicable, Missing) at Baseline will be summarized by vaccination group (as defined in Section 2.6.1).
- The number and percentage of participants with an RT-PCR test results (Positive, Positive and <=14 Days After Injection, Positive and > 14 Days After Injection, Negative, Not Applicable, Missing) excluding Baseline will be summarized by vaccination group (as defined in Section 2.6.1).
- The number and percentage of participants with, and the number of events of RT-PCR confirmed SARS-CoV-2 Infection, and RT-PCR Symptomatic SARS-CoV-2 Infection within the period starting from 14 days post-injection up through EoS will be summarized by time period.
- A listing presenting the RT-PCR test results for SARS-CoV-2 infection will be provided.
- A listing presenting the symptom assessment for SARS-CoV-2 infection will be provided.

2.6.6. Other Exploratory Endpoints

Transcriptomic and genomic samples will be part of the optional biomarker assessment. Exploratory assessments may include assessment of biomarkers for safety, reactogenicity, and inflammation. Serologic markers of disease severity, immune response to SARS-CoV-2 or influenza, RT-PCR of nasal swab samples, genetic sequences of SARS-CoV-2 or influenza

strains isolated from participants' samples, and genomic and transcriptomic samples may also be evaluated. Analyses and reporting of these endpoints will be covered in a separate analysis plan if applicable.

2.6.7. Planned Analyses

2.6.7.1. Interim Analysis

An interim analysis of safety, reactogenicity, and immunogenicity is planned after all the participants in Cohort A and B have completed the Day 29 visit. The interim analysis as of completion of Day 29 will be performed by the study statistician and programmers. The group-level unblinded summary data of the Day 29 interim analyses may be reviewed by the Sponsor project team for safety monitoring and/or clinical development planning purposes for the mRNA-1083 project. More details will be documented in the study Data Blinding Plan.

In addition, another interim analysis for reactogenicity data up to Day 8 only may be performed after all the participants in Cohort A and B have completed the Day 8 visit. The potential interim analysis as of completion of Day 8 may be performed by an independent team of unblinded statistician and programmers. More details will be documented in the study Data Blinding Plan.

2.6.7.2. Final Analysis

The final analysis will be performed after all the participants in both Cohort A and Cohort B have completed the Day 181/EoS visit.

3. Part 2

3.1. Study Objectives

3.1.1. Primary Objectives

The primary objectives are:

- To evaluate the safety and reactogenicity of study intervention administration across study treatment arms
- To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at Day 29

3.1.2. Secondary Objectives

The secondary objective is:

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

3.1.3. Exploratory Objectives

The following exploratory objectives may be assessed:

- To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms
- To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms
- To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Solicited local and systemic ARs through 7 days after injection

- Unsolicited AEs through 28 days after injection
- Unsolicited Severe AEs through 28 days after injection
- Unsolicited MAAEs from Day 1 to Day 181/EoS
- Unsolicited AESIs from Day 1 to Day 181/EoS
- SAEs from Day 1 to Day 181/EoS
- Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS
- GMT and GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay
- SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥4-fold if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline titer is <LLOQ in nAb titers measured by PsVNA

3.2.2. Secondary Endpoints

- GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, as defined in Section 3.2.1
- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.2.1

3.2.3. Exploratory Endpoints

- GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, as defined in Section 3.2.1
- SARS-CoV-2: Percentage of participants with seroresponse, as defined in Section 3.2.1

- GMT and GMFR at all evaluable time points compared to Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

3.3. Study Design

3.3.1. Overall Study Design

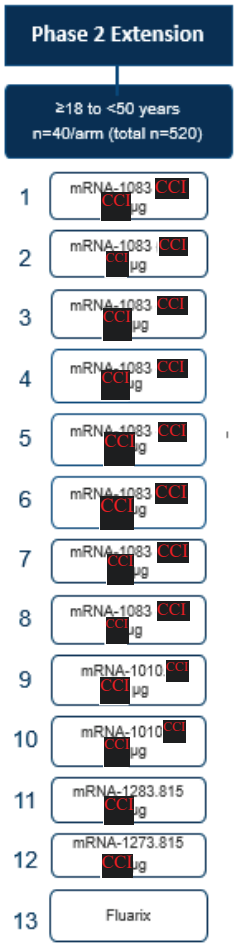
Part 2 of the study will be a Phase 2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.815, mRNA-1273.815, and licensed active-control vaccine, Fluarix in healthy adults ≥18 to <50 years of age. Approximately 520 participants ≥18 to <50 years of age will be enrolled. Participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since Sept 2023). Table 9 lists the details of study cohorts and dose levels for study vaccine administration. All participants will receive a single IM injection of study intervention administered in a deltoid muscle on Day 1.

Table 9 Study Arm(s) and Interventions (Part 2)

Part 2 Arm: (≥18 to <50 years), n=40/arm, 520 total	Intervention	Total mRNA Dose (µg)[a]	Intervention Type
1	mRNA-1083 CCI	CCI	IP
2	mRNA-1083		IP
3	mRNA-1083		IP
4	mRNA-1083		IP
5	mRNA-1083		IP
6	mRNA-1083		IP
7	mRNA-1083		IP
8	mRNA-1083		IP
9	mRNA-1010 CCI		Non-IP experimental comparator
10	mRNA-1010		Non-IP experimental comparator
11	mRNA-1283.815		Non-IP experimental comparator
12	mRNA-1273.815		Licensed vaccine comparator
13	Fluarix	-	Licensed vaccine comparator

All participants of the study will participate in a Screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and a follow-up period (up to 6 months after vaccination). The study schema is presented in Figure 2 Study Schema. Please refer to the Part 2 Schedule of Activities (SoA) available in Appendix A.

Figure 2 Study Schema (Part 2)



Abbreviation: mRNA = messenger ribonucleic acid

3.3.2. Statistical Hypotheses

See Section 2.3.2 for details.

3.3.3. Sample Size and Power

Approximately, 520 participants will be enrolled at an evenly allocated ratio across the 13 treatment arms for adults ≥18 to <50 years of age, with 40 participants planned for each arm. Approximately 40 participants in each group receiving an investigational injection have approximately 80.5% (or 87.1%) probability to observe at least 1 participant with an AE given the true underlying incidence rate of AE is 4% (or 5%) (Table 10).

Table 10 Sample Size Determination (Part 2)

Sample Size	True AE Rate	Probability of 0 AEs	Power to Detect at Least 1 AE
40	2.0%	44.6%	55.4%
40	3.0%	29.6%	70.4%
40	4.0%	19.5%	80.5%
40	5.0%	12.9%	87.1%

3.3.4. Randomization

Participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since Sept 2023).

3.4. Blinding and Unblinding

The planned analyses including a Day 29 interim analysis are described in Section 3.6.6 of this SAP. For further details on preidentified sponsor and CRO team members (identified by role), and the level of unblinding (treatment group level unblinding and/or subject level unblinding) at the IAs and the Final analysis, please refer to the study Data Blinding Plan.

3.5. Analysis Sets

3.5.1. Randomization Set

See Section 2.5.1 for details.

3.5.2. Full Analysis Set (FAS)

See Section 2.5.2 for details.

3.5.3. Per Protocol (PP) Set

The PP Set in Part 2 consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a Baseline and at least 1 post-injection assessment at Day 29 (-7 to +14 days), have no documented infection (confirmed by RT-PCR test) of either influenza or SARS-CoV-2 on Day 1, have no major dosing error, and have no major protocol deviations or conditions/medications that affect the immune

response. 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.

The major dosing error ranges, available in Table 11, will be used to determine participant exclusion from the PP analysis populations:

Table 11 Exclusion Condition for Dosing Errors (Part 2)

Randomized Group	Exclusion Conditions
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤CCI µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤CCI µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤[redacted] µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI ([redacted] µg)	Any of the following received: mRNA-1083 CCI ≤[redacted] µg OR mRNA-1083 CCI >[redacted] µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤CCI µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤CCI µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI (CCI µg)	Any of the following received: mRNA-1083 CCI ≤[redacted] µg OR mRNA-1083 CCI >CCI µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1083 CCI ([redacted] µg)	Any of the following received: mRNA-1083 CCI ≤[redacted] µg OR mRNA-1083 CCI >[redacted] µg OR mRNA-1083 [redacted] OR mRNA-1010[redacted] OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1010[redacted] (CCI µg)	Any of the following received: mRNA-1010[redacted] ≤CCI µg OR mRNA-1010[redacted] >CCI µg OR mRNA-1083 CCI OR mRNA-1083 CCI OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1010[redacted] ([redacted] µg)	Any of the following received: mRNA-1010[redacted] ≤[redacted] µg OR mRNA-1010[redacted] >CCI µg OR mRNA-1083 CCI OR mRNA-1083 CCI OR mRNA-1283.815 OR mRNA-1273.815 OR Fluarix
mRNA-1283.815 (CCI µg)	Any of the following received: mRNA-1283.815 ≤[redacted] µg OR mRNA-1283.815 >CCI µg OR

Randomized Group	Exclusion Conditions
	mRNA-1083 [redacted] OR mRNA-1083 [redacted] OR mRNA-1010 [redacted] OR mRNA-1273.815 OR Fluarix
mRNA-1273.815 ([redacted] µg)	Any of the following received: mRNA-1273.815 ≤ [redacted] µg OR mRNA-1273.815 > [redacted] µg OR mRNA-1083 [redacted] OR mRNA-1083 [redacted] OR mRNA-1010 [redacted] OR mRNA-1283.815 OR Fluarix
Fluarix	Any of the following received: Fluarix ≤ 30 µg OR mRNA-1083 [redacted] OR mRNA-1083 [redacted] OR mRNA-1010 [redacted] OR mRNA-1283.815 OR mRNA-1273.815

3.5.4. Safety Set

See Section 2.5.4 for details. Participants will be included in the vaccination group corresponding to what they actually received according to the as treated scheme given below in Table 12.

Table 12 As Treated Grouping Scheme (Part 2)

Group Name	Inclusion condition
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg and ≤ [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg and ≤ [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] ≤ [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg and ≤ [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] > [redacted] µg and ≤ [redacted] µg
mRNA-1083 [redacted] ([redacted] µg)	Any dose of mRNA-1083 [redacted] ≤ [redacted] µg
mRNA-1010 [redacted] ([redacted] µg)	Any dose of mRNA-1010 [redacted] > [redacted] µg
mRNA-1010 [redacted] ([redacted] µg)	Any dose of mRNA-1010 [redacted] ≤ [redacted] µg
mRNA-1283.815 ([redacted] µg)	Any dose of mRNA-1283.815
mRNA-1273.815 ([redacted] µg)	Any dose of mRNA-1273.815
Fluarix	Any dose of Fluarix

3.5.5. Solicited Safety Set

See Section 2.5.5 for details.

3.6. Statistical Analysis

The SoA is provided in the Appendix A.

3.6.1. General Considerations

See Section 2.6.1 for details.

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

Table layouts will be presented according to vaccination group. First for the overall participants, then by subgroups as given in Table 13.

For Part 2, the following vaccination groups will be used for summary purposes for tables and figures outputs:

- Fluarix
- mRNA-1010 [redacted] µg
- mRNA-1010 [redacted] µg
- mRNA-1273.815 [redacted] µg
- mRNA-1283.815 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- mRNA-1083 [redacted] µg
- All mRNA-1083 [redacted] (all mRNA-1083 [redacted] vaccination groups combined; applicable to safety and reactogenicity analyses only)
- All mRNA-1083 [redacted] (all mRNA-1083 [redacted] vaccination groups combined; applicable to safety and reactogenicity analyses only)
- Overall (All vaccination groups combined; details are available below)

The “Overall” combined group will be presented for baseline summaries such as participant disposition, demographic summaries, concordance of randomization stratum, etc. as well as

major protocol deviation, medical history, concomitant medication and study duration summaries.

Subgroups: For Part 2, the following subgroups will be used for summary purposes, where indicated in this SAP. Unless otherwise specified, all subgroups are based on eCRF.

Table 13 Definition for Subgroups (Part 2)

Subgroup Variable	Categories
Influenza Vaccine Status Since Sept 2023	Received Not Received
Covid Vaccine Status Since Sept 2023	Received Not Received
Baseline SARS-CoV-2 Status	Positive Negative

3.6.2. Background Characteristics

3.6.2.1. Participant Disposition

See Section 2.6.2.1 for details.

3.6.2.2. Demographics and Baseline Characteristics

Descriptive statistics for age, weight, height, and BMI are described in Section 2.6.2.2.

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

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Other, Not Reported, Unknown)
- 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) per eCRF
- Covid vaccine status (received or not received since Sept 2023) per eCRF
- Childbearing Potential for female participants (Yes/No) and reason if “No”
- Baseline SARS-CoV-2 RT-PCR Results (positive, negative, or missing)
- Baseline Elecsys Anti-SARS-CoV2 Results (positive, negative, or missing)

- Baseline SARS-CoV-2 Status (positive, negative, or missing)

The summaries will be provided separately for all analysis sets (except Randomization Set and Solicited Safety Set) defined in the Section 3.5. The number and percentage of participants randomized by country and site will be provided as well.

3.6.2.3. Medical History

See Section 2.6.2.3 for details.

3.6.2.4. Prior and Concomitant Medications

See Section 2.6.2.4 for details.

3.6.2.5. Study Exposure

See Section 2.6.2.5 for details.

3.6.2.6. Major Protocol Deviations

See Section 2.6.2.6 for details.

3.6.3. Safety Analysis

See Section 2.6.3 for details.

3.6.3.1. Solicited Adverse Reactions

See Section 2.6.3.1 for details.

3.6.3.1.1 Overview of Solicited ARs

See Section 2.6.3.1.1 for details.

3.6.3.1.2 Solicited ARs by Toxicity Grade

See Section 2.6.3.1.2 for details.

3.6.3.1.3 Solicited ARs by Onset Day

See Section 2.6.3.1.3 for details.

3.6.3.1.4 Characteristics of Solicited ARs

See Section 2.6.3.1.4 for details.

3.6.3.1.5 Other solicited ARs summaries

See Section 2.6.3.1.5 for details.

3.6.3.2. Unsolicited Treatment-Emergent Adverse Events

See Section 2.6.3.2 for details.

Unsolicited AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher and presented by MedDRA system organ class (SOC) and preferred term (PT).

SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of the combined mRNA-1083 ([CCI]).

3.6.3.2.1 Overview of Unsolicited TEAEs

See Section 2.6.3.2.1 for details.

3.6.3.2.2 TEAEs by System Organ Class and Preferred Term

See Section 2.6.3.2.2 for details.

3.6.3.2.3 TEAEs by Preferred Term

Tables of all unsolicited TEAEs will be provided by PT sorted in a descending order starting with the frequency of the combined mRNA-1083 ([CCI]).

3.6.3.2.4 TEAEs by Severity

See Section 2.6.3.2.4 for details.

3.6.3.3. Death

See Section 2.6.3.3 for details.

3.6.3.4. Vital Signs

See Section 2.6.3.5 for details.

3.6.3.5. Pregnancy Testing

See Section 2.6.3.6 for details.

3.6.3.6. Other Safety Data

3.6.3.6.1 Safety Telephone Calls

See Section 2.6.3.7.1 for details.

3.6.3.6.2 Assessment for Respiratory Viral Infection

For Part 2, all participants will provide nasal swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments.

3.6.3.6.3 Physical examination

See Section 2.6.3.7.3 for details.

3.6.3.6.4 Electrocardiograms

See Section 2.6.3.7.4 for details.

3.6.4. Immunogenicity Analysis

The primary analysis population for immunogenicity will be the PP Set. Planned timepoints for all immunogenicity assessments are provided in the SoA available in Appendix A.

For Part 2, the following analytes will be measured:

- Influenza: Serum antibody level as measured by HAI assay and potentially serum neutralizing antibody (nAb) level as measured by microneutralization assay.

- SARS-CoV-2: Serum nAb titers as measured by pseudovirus neutralization assay (PsVNA) assay and potentially serum binding antibody titers by enzyme-linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.

See section 2.6.4 for primary, secondary and exploratory endpoints calculation methods.

3.6.4.1. Primary Immunogenicity Endpoints

- GMT and GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer [redacted] if Baseline is [redacted] or a 4-fold or greater rise if Baseline is [redacted] in anti-HA antibodies measured by HAI assay
- SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥ 4-fold if Baseline is ≥ LLOQ or ≥ 4 × LLOQ if Baseline titer is < LLOQ in nAb titers measured by PsVNA

For the primary immunogenicity endpoints, descriptive summaries statistics, including median, Q1, Q3, minimum, and maximum will be provided at Day 29 for the antibody titer values by treatment arm (available in Section 3.6.1) for the influenza and SARS-CoV-2 endpoints:

- GMT with corresponding 2-sided 95% CI
- GMFR of specific antibody titers with the corresponding 2-sided 95% CI at Day 29 over pre-injection Baseline at Day 1,

In addition, the following analysis statistics will be provided by treatment arm at Day 29 for the influenza and SARS-CoV-2 endpoints:

- Within treatment group, model-based GMT with the corresponding 95% CI,
- Between treatment group, pair-wise geometric mean ratios (GMR) with the corresponding 95% CI

The model-based GMT will be estimated by the geometric least square mean (GLSM) from the ANCOVA model for each treatment group and corresponding 2-sided 95% CI will be provided. In the ANCOVA model, the log-transformed antibody titer at Day 29 is treated as a dependent variable, with the treatment group as an explanatory variable and covariates listed in Table 14 for different assays and subgroups.

Table 14 Covariates Included in Different ANCOVA Models (Part 2)

Assay	Subgroup	Covariate(s)
PsVNA	Overall	Log-transformed baseline antibody value, Influenza Vaccine Status Since Sept 2023 (IRT)
	Overall	Log-transformed baseline antibody value
	Covid Vaccine Status Since Sept 2023: Received	Log-transformed baseline antibody value
	Covid Vaccine Status Since Sept 2023: Not Received	Log-transformed baseline antibody value
	Baseline SARS-CoV2 Status: Positive	Log-transformed baseline antibody value
	Baseline SARS-CoV2 Status: Negative	Log-transformed baseline antibody value
HAI	Overall	Log-transformed baseline antibody value, Influenza Vaccine Status Since Sept 2023 (IRT)
	Overall	Log-transformed baseline antibody value, Influenza Vaccine Status Since Sept 2023 (EDC)
	Influenza Vaccine Status Since Sept 2023 (EDC): Received	Log-transformed baseline antibody value
	Influenza Vaccine Status Since Sept 2023 (EDC): Not Received	Log-transformed baseline antibody value

For each pair of between-group comparison specified in Table 15, the GMR between the two treatment groups in each pair will be estimated from the ANCOVA model, with its 2-sided 95% CI provided accordingly.

Seroconversion rate (SCR) for influenza from Baseline will be summarized at Day 29 with its 2-sided 95% CI using the Clopper-Pearson method for participants in the groups receiving mRNA-1083, mRNA-1010 or Fluarix.

- SCR at Day 29 is defined as the percentage of participants with a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay

Seroresponse rate (SRR) for SARS-CoV-2 from Baseline will be summarized at Day 29 with its 2-sided 95% CI using the Clopper-Pearson method for participants in the groups receiving mRNA-1083, mRNA-1283.815 or mRNA-1273.815.

- SRR at Day 29 is defined as the proportion of participants with a Day 29 titer ≥ 4-fold if Baseline is ≥ LLOQ or ≥ 4 × LLOQ if Baseline titer is < LLOQ in nAb titers measured by PsVNA.

Additional comparisons or analysis statistics will be provided by treatment arm at Day 29 for the influenza and SARS-CoV-2 endpoints. For each pair of between-group comparison specified in Table 15, the difference of seroresponse/seroconversion rate (SRR/SCR) between the two treatment groups in each pair will be provided, with its 2-sided 95% CI estimated using Miettinen-Nurminen method.

SCR, SRR, GM levels, GMFR and GMR will be plotted at Day 29: Reverse Cumulative Distribution Function for each specific strain of influenza and SARS-CoV-2 will be provided, as well as box plot and bar plot for GMT and GMFR, and bar plot for GMR, SCR and SRR.

Listing presenting the antibody level, for each specific strain of influenza and SARS-CoV-2 will be provided. The ratio of post-Baseline/Baseline, LLOQ and ULOQ will be presented as well.

Table 15 Between-group Immunogenicity comparisons (Part 2)

Influenza Comparisons											
		Treatment Arm									
		mRNA-1010 [redacted] µg	mRNA-1010 [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg
Control Group	Fluarix	X	X	X	X	X	X	X	X	X	X
	mRNA-1010 [redacted] µg	NA	X	X	X	X	X	X	X	X	X
	mRNA-1010 [redacted] µg	NA	NA	X	X	X	X	X	X	X	X

SARS-CoV-2 Comparisons											
		Treatment Arm									
		mRNA-1283.815 [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA -1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg	mRNA-1083 ([redacted]) [redacted] µg
Control Group	mRNA-1273.815 [redacted] µg	X	X	X	X	X	X	X	X	X	X
	mRNA-1283.815 [redacted] µg	NA	X	X	X	X	X	X	X	X	X

3.6.4.2. Secondary Immunogenicity Endpoints

- GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion
- SARS-CoV-2: Percentage of participants with seroresponse

For the secondary immunogenicity endpoints, descriptive summaries statistics, including median, Q1, Q3, minimum, and maximum will be provided for each timepoints for the antibody titer values by treatment arm (available in Section 3.6.1) for the influenza and SARS-CoV-2 endpoints:

- GMT with corresponding 2-sided 95% CI
- GMFR of specific antibody titers with the corresponding 2-sided 95% CI at each post-basline timepoint Day 29 over pre-injection Baseline at Day 1

Additional descriptions will be provided by treatment arm (available in Section 3.6.1) for the following influenza and SARS-CoV-2 endpoints:

- Percentages of participants with seroconversion (influenza) and seroresponse (SARS-CoV-2) with the corresponding 2-sided 95% CI at each post-Baseline time point,
- Percentages of participants with a GMFR results >=2, and >=4 with the corresponding 2-sided 95% CI at each post-Baseline time point.

Reverse Cumulative Distribution Function for each specific strain of influenza and SARS-CoV-2 will be provided, as well as box plot and bar plot for GMT and GMFR, and bar plot for GMR, SCR and SRR at all evaluable timepoints.

3.6.4.3. Exploratory Immunogenicity Endpoints

The below exploratory analyses of immunogenicity may be performed:

- GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2
- Influenza: Percentage of participants with seroconversion, as defined above
- SARS-CoV-2: Percentage of participants with seroresponse, as defined above

- GMT and GMFR at all evaluable time points compared to Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
- Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

3.6.5. Other Exploratory Endpoints

Transcriptomic and genomic samples will be part of the optional biomarker assessment. Exploratory assessments may include assessment of biomarkers for safety, reactogenicity, and inflammation. Serologic markers of disease severity, immune response to SARS-CoV-2 or influenza, reverse transcription polymerase chain reaction (RT-PCR) of nasal swab samples, genetic sequences of SARS-CoV-2 or influenza strains isolated from participants' samples, and genomic and transcriptomic samples may also be evaluated. Analyses and reporting of these endpoints will be covered in a separate analysis plan if applicable.

3.6.6. Planned Analyses

3.6.6.1. Interim Analysis

An interim analysis of safety, reactogenicity, and immunogenicity is planned after all participants have completed the Day 29 visit. The interim analysis as of completion of Day 29 will be performed by the study statistician and programmers. The group-level unblinded summary data of the interim analyses may be reviewed by the Sponsor project team for safety monitoring and/or clinical development planning purposes for the mRNA-1083 project. More details will be documented in the study Data Blinding Plan.

3.6.6.2. Final Analysis

The final analysis will be performed after all participants in Part 2 have completed the Day 181/EoS visit.

4. Changes from Planned Analysis in Protocol

There are no changes in planned analysis.

5. References

CDC, Centers for Disease Control and Prevention. 2020. Coronavirus Disease 2019 (COVID-19) 2020 Interim Case Definition, Approved August 5, 2020. [Online] August 2020. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2020-08-05/.

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.

Nauta, Jozef. 2011. *Statistics in Clinical Vaccine Trials.* s.l. : Springer, 2011.

6. Appendices

Appendix A Schedule of Activities (SoA)

I. Part 1

Visit Number	SCRN	1	2	3	4, 5, 6, 7	8	USV
Type of Visit	C	C	C	C	SC	C	C
Month Time Point	NA			M1	M2-M5	M6	Up to M6
Visit Day	SCRN[a]	D1 (Baseline)[a]	D8	D29	D57, D91, D121, D151	D181/ EoS	NA
Window Allowance (Days)	-28	NA	-1 to +3	-7 to +3	±5	±14	NA
Informed consent form, demographics, concomitant medications, medical history	X						
Inclusion/exclusion criteria	X	X					
Blood collection for safety laboratory samples[b]	X		X				
Full physical examination[c]	X						
Axillary lymph nodes assessment[d]		X					
Symptom-directed physical examination[e]		X	X	X		X	X
Vital sign measurements[f]	X	X					
Electrocardiogram[g]		X					
Pregnancy testing[h]	X	X					
Randomization		X					
Study intervention (including 60-minute, postdose observation period)		X					
Blood collection for humoral immunogenicity[i]		X		X		X	
Blood collection for cellular immunogenicity[i]		X		X			
Optional blood collection for genomics[j]		X					
Optional blood collection for transcriptomics[j]		X	X	X			
Blood sample for potential cardiac biomarker analysis k		X					
Nasal swab for virus detection[l]		X					X
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X					
eDiary activation for recording solicited local and systemic ARs (7 days)[m]		X					
Review of solicited AR eDiary			X				
Follow-up safety call[n]					X		

Visit Number	SCRN	1	2	3	4, 5, 6, 7	8	USV
Type of Visit	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Month Time Point	**NA**			**M1**	**M2-M5**	**M6**	**Up to M6**
Visit Day	**SCRN[a]**	**D1 (Baseline)[a]**	**D8**	**D29**	**D57, D91, D121, D151**	**D181/ EoS**	**NA**
Window Allowance (Days)	**-28**	**NA**	**-1 to +3**	**-7 to +3**	**±5**	**±14**	**NA**
Recording of unsolicited AEs through Day 29		X	X	X			
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications associated with these events		X	X	X	X	X	X
Recording of nonstudy vaccinations	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction;; C=clinic visit; COVID-19=coronavirus disease 2019; D=day; ECG=electrocardiogram; EoS=end of study; ILI=influenza-like illness; IM=intramuscular; M=month; MAAE=medically attended adverse event; NA=not applicable; -SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SC=safety (telephone) call; SCRN=Screening; USV=unscheduled visit;

a. Screening and Day 1 will NOT be performed on the same day. Additionally, the Screening Visit may be performed over multiple visits within the 28-day Screening window.
b. Safety laboratory tests will consist of total white blood cell count, hemoglobin, hematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, creatinine, alkaline phosphatase, and total bilirubin. Safety laboratory tests will be performed by the central laboratory.
c. A full physical examination, including height and weight for calculation of body mass index, will be performed at Screening. Additional physical examinations may be performed during the study at the discretion of the Investigator.
d. On the day of study intervention administration, prior to injection, axillary lymph nodes of the injection arm will be examined, and any abnormalities will be documented.
e. Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full physical examination will be performed. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during postinjection study visits should be reported as an AE.
f. Vital sign measurements: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs must be collected at Screening and on the day of injection (Day 1), once before and at least 60 minutes after injection. Vital signs may be collected at other clinic visits 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.
g. For participants ≥18 to <51years of age only: A 12-lead ECG will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to injection. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis and/or pericarditis occurs within the conduct of the clinical trial. The ECG output should be filed in the participant's binder. Central reading of the ECG will not be performed. Incidental significant abnormal ECG findings should contribute to the Investigator's assessment of eligibility, at their discretion, as per Exclusion Criterion.
h. For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections 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. For participants of nonchildbearing potential, the follicle-stimulating hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.

i. Baseline samples for humoral and cellular immunogenicity must be collected prior to receipt of injection on Day 1. Cellular immunogenicity will be sampled and assessed in a subset of participants.
j. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Blood draws on Day 1 must occur prior to participants being administered the study intervention.
k. For participants ≥18 to <51years of age only: Plasma and serum samples will be collected and banked for potential future cardiac biomarker assessment.
l. A nasal swab to test for the presence of viral respiratory pathogens will be collected prior to the study intervention administration on Day 1 to document any prevacination infection. A nasal swab should be collected through study completion for protocol-defined ILI or SARS-CoV-2 ≤7 days of symptom onset.
m. The eDiary activiation and entries will be recorded by the participant starting approximately 60 minutes after injection while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day 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. Solicited local and systemic ARs will be recorded separately for each injection site.
n. Trained study staff will call all participants to collect information related to any SAEs, MAAEs, AESIs, AEs leading to study discontinuation, information on concomitant medications associated with those events, and any nonstudy vaccinations.

II. Part 2

Visit Number	SCRN	1	2	3	4, 5	6	USV
Type of Visit	C	C	SC	C	SC	C	C
Month Timepoint	NA			M1	M3-M5	M6	Up to M6
Visit Day	SCRN[a]	D1 (Baseline)[a]	D8	D29	D91, D151	D181/ EoS	NA
Window Allowance (Days)	-28	NA	-1 to +3	-7 to +3	±5	±14	NA
Informed consent form, demographics, concomitant medications, medical history	X						
Inclusion/exclusion criteria	X	X					
Full physical examination [b]	X						
Axillary lymph nodes assessment [c]		X					
Symptom-directed physical examination [d]		X		X		X	X
Vital sign measurements [e]	X	X					
Electrocardiogram [f]		X					
Pregnancy testing [g]	X	X					
Randomization		X					
Study intervention (including 60-minute, postdose observation period)		X					
Blood collection for humoral immunogenicity [h]		X		X		X	
Optional blood collection for genomics [i]		X					
Optional blood collection for transcriptomics [i]		X		X			
Blood sample for potential cardiac biomarker analysis [j]		X					
Nasal swab for virus detection [k]		X					
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X					
eDiary activation for recording solicited ARs (7 days) [l]		X					
Review of solicited AR eDiary			X				
Follow-up safety call [m]			X		X		
Recording of unsolicited AEs through Day 29		X	X	X			
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications associated with these events		X	X	X	X	X	X

Visit Number	SCRN	1	2	3	4, 5	6	USV
Type of Visit	C	C	SC	C	SC	C	C
Month Timepoint	NA			M1	M3-M5	M6	Up to M6
Visit Day	SCRN[a]	D1 (Baseline)[a]	D8	D29	D91, D151	D181/ EoS	NA
Window Allowance (Days)	-28	NA	-1 to +3	-7 to +3	±5	±14	NA
Recording of nonstudy vaccinations	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; EoS = end of study; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SCRN = Screening; 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 within the 28-day Screening window.
b. A full physical examination, including height and weight for calculation of body mass index, will be performed at Screening. Additional physical examinations may be performed during the study at the discretion of the Investigator.
c. On the day of study intervention administration, prior to injection, axillary lymph nodes of the injection arm will be examined, and any abnormalities will be documented.
d. Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full physical examination will be performed. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during postinjection study visits should be reported as an AE.
e. Vital sign measurements: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs must be collected at Screening and on the day of injection (Day 1), once before and at least 60 minutes after injection. Vital signs may be collected at other clinic visits 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. A 12-lead ECG will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to injection. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis and/or pericarditis occurs within the conduct of the clinical trial. The ECG output should be filed in the participant's binder. Central reading of the ECG will not be performed. Incidental significant abnormal ECG findings should contribute to the Investigator's assessment of eligibility, at their discretion, as per Exclusion Criterion.
g. For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections 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. For participants of nonchildbearing potential, the follicle-stimulating hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.
h. Baseline samples for humoral immunogenicity must be collected prior to receipt of injection on Day 1.
i. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Blood draws on Day 1 must occur prior to participants being administered the study intervention.
j. Plasma and serum samples will be collected prior to the study intervention administration on Day 1 and banked for potential future cardiac biomarker assessment.
k. A nasal swab to test for the presence of viral respiratory pathogens will be collected prior to the study intervention administration on Day 1 to document any prevaccination infection.
l. The eDiary activation and entries will be recorded by the participant starting approximately 60 minutes after injection while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day 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. Solicited local and systemic ARs will be recorded separately for each injection site.

m. Trained study staff will call all participants to collect information related to any SAEs, MAAEs, AESIs, AEs leading to study discontinuation, information on concomitant medications associated with those events, and any nonstudy vaccinations.

Appendix B Analysis Visit Windows

The following applies to Part 1 and Part 2:

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

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

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 16 below.

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

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

Table 16 Analysis Visit Windows for Immunogenicity Assessments

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

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

The following applies to Part 1 and Part 2:

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

a) 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 IP injection.
     - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of the IP injection.
     - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the month or the date of the IP injection - 1.
     - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of the IP injection or is missing, then use the date of the IP injection.
   - 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 IP injection.
     - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of the IP injection.
     - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the year or the date of the IP injection -1.
     - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of the IP injection or is missing, then use the date of the IP injection.
   - 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 study administration?" = "No"), then the medication will be treated as having begun after IP injection.
     - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study 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 IP injection).

b) 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 17 below.

Table 17 Prior, Concomitant, and Post Categorization of a Medication

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

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

Appendix D Imputation Rules for Missing AE dates

The following applies to Part 1 and Part 2:

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

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

b) Missing or partial AE end dates will not be imputed.

Appendix E Severity Grading of Laboratory Abnormalities

The following applies to Part 1 only:

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. A low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

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

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

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

Appendix F Severity Grading of Vital Sign Abnormalities

The following applies to Part 1 and Part 2:

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.

Appendix G Solicited Adverse Reactions and Grades

The following applies to Part 1 and Part 2:

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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

Note: Events listed above but starting >7 days post study intervention administration will be recorded on the AE page of the electronic case report form (eCRF). Causality for each event will be determined per assessment by the Investigator.

Appendix H TEAE of Specifical Interest by SMQ

The following applies to Part 1 and Part 2:

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

* Based on MedDRA 26.1

Algorithmic Approach for Anaphylactic Reaction:

The following criteria will be used to determine anaphylactic reaction:

a) A term from Category A or
b) 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
c) 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

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
B	Broad	Cough
B	Broad	Cough variant asthma
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Enhanced respiratory disease
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

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
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