ModernaTX, Inc.

Protocol mRNA-1010-P301

A Phase 3, Randomized, Stratified, Observer-blind, Active-controlled Study to Evaluate the Immunogenicity and Safety of mRNA-1010 Seasonal Influenza Vaccine in Adults 18 Years and Older

Statistical Analysis Plan

SAP Version 2.0

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	13 October 2022	Original Version (Version 1.0)
2.0	17 November 2022	• In Section 1, updated the date of the most recent approved electronic case report form (eCRF). • In Section 6.6.2 and Appendix, replaced Immune-Mediated/Autoimmune Disorder search using customized medical query (CMQ) by standardized medical query (SMQ) in MedDRA. • In Section 4.2 and Section 6.5, add clarification on study success criteria.

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BMI	Body Mass Index
CDC	Centers For Disease Control and Prevention
CI	Confidence Interval
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
eDiary	electronic Diary
EFS	Edmonton Frail Scale
EoS	End of Study
EQ-5D-5L	EuroQol 5-Dimension 5-Levels
FAS	Full Analysis Set
GLSM	Geometric Least Square Mean
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HR	Hazard Ratio
ILI	Influenza-Like Illness
IM	Intramuscular
IP	Investigational Product
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event
max	maximum

MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mITT	Modified Intent-To-Treat
MN	Microneutralization
mRNA	messenger Ribonucleic Acid
nAbs	neutralizing Antibodies
NP	Nasopharyngeal
PP	Per-Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
RT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
rVE	relative Vaccine Efficacy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Seroconversion Rate
SD	Standard Deviation
SH	Southern Hemisphere
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	WHO Drug Dictionary
WPAI	Work Productivity and Activity Impairment Questionnaire

1 Introduction

This statistical analysis plan (SAP) is based on clinical study Protocol Amendment 2, dated 19-July-2022, and the most recent approved electronic case report form (eCRF) dated 22-August-2022 for study mRNA-1010-P301.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9), which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan which are not "principal" in nature and result from information that was not available at the time of protocol finalization. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

Study mRNA-1010-P301 is a phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 vaccine as compared with an active comparator that is a licensed quadrivalent seasonal influenza vaccine (Fluarix Tetra) in adults ≥ 18 years of age.

PPD Biostatistics and Programming team, the designee of Moderna Biostatistics and Programming department, will perform the statistical analysis; Statistical Analysis System (SAS) Version 9.4 or higher will be used.

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

2 Objectives

2.1 Primary Objectives

The primary objectives of the study are:

- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of the active comparator against vaccine-matched influenza A and B strains at Day 29
- To evaluate the safety and reactogenicity of mRNA-1010

2.2 Secondary Objectives

The secondary objectives of the study are:

- To further evaluate the immunological response of mRNA-1010 (for superiority) relative to an active comparator against vaccine-matched influenza A virus strains at Day 29
- To evaluate relative vaccine efficacy to prevent influenza caused by any strain of influenza virus
- To evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29

2.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the humoral immunogenicity of mRNA-1010 to that of the active comparator against vaccine-matched or vaccine-mismatched influenza A and B strains, including the use of alternative methods
- To further characterize the immune response to mRNA-1010 and active comparator
- To describe the occurrence of clinical influenza cases throughout the study period

Other Exploratory Objectives are as follows

- To explore the number and percentage of participants aged 65 years and older with first episode of protocol-defined influenza-like illness (ILI) by baseline frailty status
- To describe EuroQoL 5-Dimension 5-Levels (EQ-5D-5L) health questionnaire utility score at regular intervals as well as for participants with protocol-defined ILI
- To describe Work Productivity and Activity Impairment Questionnaire Influenza-like Illness (WPAI:ILI) v2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with protocol-defined ILI.

3 Study Endpoints

3.1 Primary Endpoints

The **co-primary immunogenicity endpoints** are:

- Geometric mean titer (GMT) of anti-hemagglutinin (HA) antibodies as measured by hemagglutination inhibition (HAI) against vaccine-matched influenza A and B strains at Day 29

- Proportion of participants reaching seroconversion at Day 29 against vaccine-matched influenza A and B strains as measured by HAI

The GMT as measured by an assay will be calculated using the following formula:

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

where, for n participants, t_i is the immunogenicity titer measurement for participant i.

Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer.

The **primary safety endpoints** are:

- Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period post-vaccination
- Frequency and severity of any unsolicited adverse events (AE) during the 28-day follow-up period post-vaccination
- Frequency of any serious adverse events (SAE), adverse events of special interests (AESI), and medically attended adverse events (MAAE) and AEs leading to discontinuation from Day 1 through Day 361 (Month 12)/ End of Study (EoS).

3.2 Secondary Endpoints

The **secondary immunogenicity endpoints** are:

- GMT of anti-HA antibodies as measured by HAI against vaccine-matched influenza A strains at Day 29 (testing for superiority and super-superiority of mRNA-1010 vs. active comparator)
- The proportion of participants reaching seroconversion at Day 29 as measured by HAI assay
- The proportion of participants with an HAI titer ⩾ 1:40 at Day 29
- Geometric mean fold rise (GMFR) of anti-HA antibodies as measured by HAI against vaccine-matched influenza A and B strains comparing Day 29 to Day 1 (baseline)

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

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

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

The **secondary endpoints with respect to efficacy** are:

- First episode of reverse transcription polymerase chain reaction (RT-PCR)-confirmed protocol-defined ILI that begins at least 14 days post-vaccination through Day 181(Month 6)/end of influenza season, whichever occurs later, caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine.

  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 1.

  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 1: Respiratory and Systemic Symptoms for Protocol-defined ILI

• 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 > 37.2°C [> 99°F] Chills Tiredness Headache Myalgia Nausea/vomiting Diarrhea

- First episode of RT-PCR-confirmed protocol-defined ILI cases that begin at least 14 days post-vaccination through Day 181/end of influenza season caused by any strain of influenza

virus regardless of antigenic match to the strains selected for the seasonal vaccine, in participants aged 50 years and older or 65 years and older.

- First episode of RT-PCR confirmed Centers For Disease Control and Prevention (CDC)-defined ILI that begins at least 14 days post-vaccination through Day 181/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine.

  A CDC-defined ILI is defined as body temperature ≥ 37.8°C (100°F) accompanied by cough and/or sore throat.

  An RT-PCR-confirmed CDC-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 CDC-defined ILI at any time during the study period.

<u>The exploratory endpoints are:</u>

- GMT and GMFR of neutralizing antibodies (nAbs) by assays such as microneutralization (MN) assays and/or HAI assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (baseline)
- GMT and GMFR of anti-HA antibodies by HAI against vaccine-matched or vaccine-mismatched strains on Day 181 and Day 361 (Month 12)
- The proportion of participants with seroconversion, and the proportion of participants with an HAI titer ≥ 1:40 at Day 181 and Day 361 (Month 12), as measured by HAI assay
- Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses
- Number of cases of RT-PCR-confirmed protocol-defined ILI cases that begin at least 14 days post-vaccination through Day 361 (Month 12)/EoS caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine
- Number and percentage of participants aged 65 years and older with first episode of RT-PCR confirmed protocol-defined ILI by baseline frailty status

- EQ-5D health questionnaire utility score at regular intervals as well as for participants with ILI
- WPAI: ILI v2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with ILI

4 Study Design

4.1 Overall Study Design

This is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 influenza vaccine in adults aged 18 years and older.

Approximately 6,000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 vaccination groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Tetra). Randomization will be stratified by age categories (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) and influenza vaccine status in the prior 12 months (received or did not receive) at the time of screening. At least 50% of enrollees will be ≥ 50 years old, including approximately 20% who will be ≥ 65 years old. The Sponsor anticipates approximately 300 participants will be ⩾ 75 years old.

Table 2 lists the details of vaccination groups and dose levels for study vaccine administration. The mRNA-1010 vaccine to be tested includes mRNAs encoding for the surface HAs of the influenza strains recommended by the World Health Organization (WHO) for 2022 Southern Hemisphere (SH) cell or recombinant-based vaccines:

- A/Wisconsin/588/2019 (A/H1N1) like virus;
- A/Darwin/6/2021 (A/H3N2) like virus;
- B/Michigan/01/2021 (B/Victoria lineage) like virus;
- B/Phuket/3073/2013 (B/Yamagata lineage) like virus

Table 2: Vaccination Groups and Dose Levels

Vaccination Group	Vaccination Received	mRNA/Antigen HA (each) (µg)	Total Dose (µg)	Number of Participants
1	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	3,000
2	Active Comparator (Fluarix Tetra)	15 (of protein)	60 (of protein)	3,000

The study duration will be approximately 13 months for each participant with 12 months follow-up after vaccine injection. Study Schedule of Events is enclosed in Section 9.1. The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study.

The study vaccination (mRNA-1010 or the active comparator) will be administered as a single intramuscular (IM) injection into the deltoid muscle on Day 1. Participants will be monitored for a minimum of 30 minutes after administration of the study injection.

All participants will provide blood samples at baseline and on Day 29 (28 days post-vaccination) for assessment of GMT, GMFR, and seroconversion, as measured by HAI. In addition, the first 1000 randomized participants will also provide blood samples at Day 181 and Day 361 (Month 12), a subset of which will be used for immunogenicity analysis. These participants will require a clinic visit on Day 181 and Day 361 (Month 12)/EoS. There will be an optional visit on Day 4 at which blood will be drawn for future biomarker assessment.

Participants who manifest protocol-defined ILI will be evaluated by RT-PCR testing of nasopharyngeal (NP) swab specimen(s) for influenza (and other respiratory pathogens).

Participants will be instructed to report via Symptom Reporting electronic diary (eDiary) or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms occur, participants will be directed to return to the clinical site immediately, but no later than 72 hours after the onset of symptoms, for medical evaluation and NP swab(s). Unscheduled clinic visits for potential ILI symptoms and viral respiratory panel testing will be conducted as needed. The investigator may ask a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at

these visits as necessary to ensure the safety and well-being of participants during the study. For each unscheduled visit, eCRFs should be completed.

A participant is considered to have completed the study if they complete the final visit on Day 361 (Month 12) as showed in the Schedule of Events (Table 6).

4.2 Statistical Hypotheses

There are five statistical hypotheses for the study that will be tested according to the procedures described below:

To begin, the null hypotheses, H^1_0 and H^2_0, will be tested simultaneously, as below:

> The null hypothesis H^1_0: immunogenicity response to mRNA-1010, as measured by GMT or by seroconversion rate (SCR) at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for each individual A strains (H1N1, H3N2). Four co-primary immunogenicity endpoints (two methods per strain) will be tested for non-inferiority of mRNA-1010 vs. active comparator for A strains at a two-sided 0.025 level.
>
> The null hypothesis H^2_0: immunogenicity response to mRNA-1010, as measured by GMT or SCR at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for each individual B strains (B/Victoria, B/Yamagata). Four co-primary immunogenicity endpoints (two methods per strain) will be tested for non-inferiority of mRNA-1010 vs. active comparator for B strains at a two-sided 0.025 level.

At Day 29, the following endpoint comparison methods will be performed for each individual influenza virus strain:

- The non-inferiority in GMT in participants who received mRNA-1010 compared to that of participants who received active comparator will be demonstrated by the lower bound of the 97.5% confidential interval (CI) of the GMT ratio (geometric mean ratio [GMR]) ruling out 0.667 (lower bound > 0.667) using a non-inferiority margin of 1.5. The GMR is the ratio of the GMT of HAI titer in those receiving mRNA-1010 compared with the GMT of those receiving the active comparator.

- The SCR difference is defined as the rate of seroconversion in those receiving mRNA-1010 minus the seroconversion rate in those receiving active comparator. The non-inferiority in seroconversion rate in the mRNA-1010 group compared to that of the active comparator group will be demonstrated by the lower bound of the 97.5% CI of the SCR difference ruling out -10% (lower bound > -10%) using a non-inferiority margin of 10%.

The success criteria of non-inferiority for A strains are met if H^1_0 is rejected at two-sided 0.025 level on all four co-primary endpoints. Similarly, the success criteria of non-inferiority for B strains are met if H^2_0 is rejected at two-sided 0.025 level on all four co-primary endpoints.

The study success can only be declared if the success criteria of the non-inferiority for both A strains and B strains are met.

Once the non-inferiority success criteria of the co-primary endpoints for A strains are met, hypothesis testing will continue (sequentially) based on α_1 as defined below to support secondary objectives, as follows.

Hypotheses in support of the secondary objectives will be tested at a two-sided α_1=5% level if non-inferiority is demonstrated for both A and B strains (both H^1_0 and H^2_0 are rejected), and at an α_1=2.5% level if non-inferiority is only demonstrated for A strains (only H^1_0 is rejected).

> The null hypothesis H^3_0: immunogenicity response to mRNA-1010 compared to that in participants who received the active comparator, as measured by GMR at Day 29 using HAI assay, is 1 for each individual A strain (H1N1 and H3N2). The superiority success criteria in immunogenicity response are met if H^3_0 is rejected at two-sided α_1 level. Based on GMT, superiority will be demonstrated by the lower bound of the (100% - α_1) CI of the GMR ruling out 1 (lower bound > 1) for both A strains.

Once the success criteria of hypothesis H^3_0 are met, the next null hypothesis to be tested is H^4_0.

> The null hypothesis, H^4_0: immunogenicity response to mRNA-1010 compared to that in participants who received the active comparator, as measured by GMR at Day 29 using HAI assay, is 1.5 for each individual A strain (H1N1 and H3N2). The super-superiority success criteria in immunogenicity response are met if H^4_0 is rejected at two-

sided α_1 level. Based on in GMT, super-superiority will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1.5 (lower bound > 1.5) for both A strains.

Once the success criteria of hypothesis H^4_0 are met, the last null hypothesis to be tested is H^5_0.

The null hypothesis, H^5_0: immunogenicity response to mRNA-1010 compared to that in participants who received the active comparator, as measured by SCR difference at Day 29 using HAI assay, is not super-superior for each individual A strain (H1N1 and H3N2). The super-superiority success criteria based on SCR are met if H^5_0 is rejected at two-sided α_1 level. Based on SCR, super-superiority will be demonstrated by the lower bound of the (100%- α_1) CI of the SCR difference ruling out 10% (lower bound > 10%) for both A strains.

4.3 Sample Size and Power

Approximately 6,000 participants will be randomly assigned to vaccine in this study in a 1:1 ratio to receive either mRNA-1010 or an active comparator. With approximately 3,000 participants exposed to mRNA-1010, the study has approximately 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate.

Assuming approximately 15% of randomized participants will be excluded from the PP Immunogenicity Set, with approximately 5100 participants in the PP Immunogenicity Set (1:1 ratio; approximately 2550 in each vaccine group), this will provide at least 95% power to demonstrate non-inferiority of the immune response in all 4 strains, as measured by the GMT in participants receiving mRNA-1010 compared with that in the active comparator group, at a 2-sided alpha of 0.025 level, assuming an underlying GMR of 0.9 in all 4 strains and a non-inferiority margin of 1.5. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

This sample size will also provide at least 95% power to demonstrate non-inferiority of the immune response in all 4 strains as measured by SCR in the mRNA-1010 group compared with that in the active comparator group, at a 2-sided alpha of 0.025 level, assuming a SCR of 70% in influenza A strains and 60% in influenza B strains, respectively, in the mRNA-1010 group (a

true rate difference is 0 compared to the active comparator group), and a non-inferiority margin of 10%.

4.4 Randomization

Randomization will be performed using a centralizing interactive response technology (IRT). and stratified by age categories (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) and influenza vaccine status in the prior 12 months (received or did not receive) at the time of screening. At least 50% of enrollees will be ≥ 50 years old, including approximately 20% who will be ≥ 65 years old. The Sponsor anticipates approximately 300 participants will be ⩾ 75 years old.

4.5 Blinding and Unblinding

This study is an observer-blind study. The investigator, clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded for the final analysis with certain exceptions, please refer to Section 6.2 of the protocol for details. More details of blinding and unblinding processes are specified in the study data blinding plan.

Planned analyses are described in Section 6.8 of this SAP and Section 9.6 in the Protocol Amendment 2. At the primary analysis and other pre-planned analyses, pre-identified Sponsor team members and selected contract research organization (CRO) team members as specified in the study data blinding plan will be unblinded to conduct the analyses. After unblinding, this team will not participate in the conduct or execution of the subsequent course of the study. Meanwhile, a separate blinded biostatistics and programming team will be in place until the database lock for the Final Analysis. Participants and investigators will remain blinded until the end of this study.

An external Data Safety Monitoring Board (DSMB) will conduct safety review of study data to safeguard the interests of clinical study participants and to enhance the integrity of the study. The DSMB will review safety data up to 7 days post-vaccination from the first 500 enrolled participants and safety data up to 28 days post-vaccination from all participants, provided by the

independent unblinded statistician who has no other responsibilities associated with study design or study conduct.

5 Analysis Sets

Analysis sets for statistical analyses are Randomization Set, Full Analysis Set (FAS), Modified Intent-to-Treat (mITT) Set, PP Set for Efficacy, Immunogenicity Set, PP Immunogenicity Set, Solicited Safety Set, and Safety Set.

Randomization Set

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

Full Analysis Set

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

Modified Intent-to-Treat Set

The mITT Set consists of all participants in the FAS who provide any follow-up for ILI beginning at least 14 days following administration of study intervention. Participants will be analyzed according to the group to which they are randomized to.

The mITT Set is the primary population for the analysis of efficacy data.

PP Set for Efficacy

The PP Set for Efficacy consists of all participants in the mITT Set who have no significant protocol deviations that impact key or critical efficacy data. Participants will be analyzed according to the group they are randomized to.

Immunogenicity Set

The Immunogenicity Set consists of all participants in the FAS who have baseline and Day 29 antibody assessment via HAI assay. Participants will be analyzed according to the group to which they were randomized.

PP Immunogenicity Set

The PP Immunogenicity Set includes all participants in the Immunogenicity Set who received planned dose of IP, complied with the immunogenicity testing schedule, and had no significant protocol deviations that impact key or critical data. Participants with RT-PCR-confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity Set.

The PP Immunogenicity Set is the primary population for the analysis of immunogenicity data in the study unless specified otherwise. Participants will be analyzed according to the group to which they are randomized to.

For PP Set for Efficacy and PP Immunogenicity Set, the following major dosing error ranges for planned mRNA-1010 and active comparator will be used to determine participant exclusion from the analysis populations:

Table 3 Exclusion Criteria for Dosing Errors

Actual Vaccine Received	Planned (mRNA-1010 50 µg)
mRNA-1010 ≤ 37.5 µg	Yes[1]
mRNA-1010 >37.5 µg – 62.5 µg	No
mRNA-1010 > 62.5 µg	Yes
Active Comparator[2]	Yes

1. Yes means major dosing error
2. Active comparator is Fluarix Tetra (pre-filled syringe)

Table 4 Major Dosing Errors for Active Comparator

Actual Vaccine Received	Planned (Active Comparator[2])
Fluarix Tetra ≤ 45 µg	Yes[1]
Fluarix Tetra > 45 µg – 60 µg	No
Any mRNA-1010	Yes

1. Yes means major dosing error
2. Active comparator is Fluarix Tetra (pre-filled syringe)

Solicited Safety Set

The Solicited Safety Set consists of all randomized participants who received any study vaccination and contributed any solicited AR data, i.e., had at least one post-baseline solicited safety assessment.

The Solicited Safety Set will be used for the analyses of solicited ARs, and participants will be included in the vaccination group corresponding to the actual vaccine that they received.

Safety Set

The Safety Set includes all participants who were randomized and received any study vaccination.

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 the actual vaccine that they received.

For Solicited Safety Set and Safety Set, the following dosing ranges will be used to determine participant's actual vaccination group:

- mRNA-1010 50 µg group: If the received dose of mRNA-1010 is > 0 µg
- Fluarix Quadrivalent 60 µg group: If the received dose of active comparator (Fluarix Tetra) is > 0 µg and mRNA-1010 is 0 µg

6 Statistical Analysis

6.1 General Considerations

Study Schedule of Events is presented in Section 9.1.

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

Categorical variables will be summarized using counts and percentages.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Variable display standards are presented in Section 9.2.

When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that vaccination group within the analysis set of interest, unless otherwise specified.

Baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before vaccine injection, unless otherwise specified. For immunogenicity tests and NP swab tests, the baseline is defined as the most recent non-missing result/measurement (scheduled or unscheduled) collected before or on the date (and time, if applicable) of injection (Day 1).

Age: unless otherwise specified, age is calculated as the age at screening. In the analyses for subgroups defined by age, age at screening will be used for derivation of age groups.

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1010 50 ug
- Fluarix Quadrivalent 60 ug

All analyses and data summaries/displays will be provided by vaccination group using appropriate analysis population, unless otherwise specified. Summaries may also contain a display for all vaccination groups pooled together (i.e., overall group).

Study day relative to injection will be calculated as below:

- Study day prior to injection will be calculated as: date of assessment/event – date of injection.
- Study day on or after the date of injection will be calculated as: date of assessment/event – date of injection + 1.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline/last on-treatment values
- In the derivation of max/min on-treatment values and max/min change from baseline values for safety analyses
- In individual participant data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Section 9.3.

Analysis Periods:

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

- 7 days post-vaccination: this period includes the day of vaccination and 6 subsequent days. This analysis period will be used for solicited local/systemic ARs and SAEs that occur during this time.
- Up to 28 days post-vaccination: this period starts from the day of vaccination and spans 28 days to include the day of vaccination and 27 subsequent days. This analysis period will be used for unsolicited AE, except for solicited AR, unless specified otherwise.
- Up to 180 days post-vaccination: this period starts from the day of vaccination and spans to 180 days to include the day of vaccination and 179 subsequent days. This analysis period will be used for MAAEs, SAEs, and AESIs
- Up to data cutoff date: this period starts from day of vaccination and continues through the data cut-off date applied at planned analyses as specified in Section 6.8.
- Overall study period: this period starts on Day 1 and continues through the earliest of the following: study completion, discontinuation from the study, or death.

For the Day 29 primary analysis, the analysis will include all participants' immunogenicity data and safety data collected up to Day 29 post-vaccination. For the 6-months analysis, the analysis may include a subset of participants' immunogenicity data (the first 1000 randomized participants per study design) collected up to Day 181, vaccine efficacy data on Day 181/end of influenza season, and safety data up to 180 days post-vaccination. Additional details are presented in Section 6.8.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Section 9.4.
- Imputation rules for missing AE dates are provided in Section 9.4.
- For summarizations of GMTs, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.
- Other incomplete/missing data will not be imputed, unless otherwise specified.

Subgroups:

Table 5: Definition for Subgroups

Subgroup Variable	Categories
Age Group 1	≥ 18 to < 50 years old ≥ 50 to < 65 years old ≥ 65 years old
Age Group 2	≥ 18 to < 50 years old ≥ 50 to < 65 years old ≥ 65 to <75 years old ≥ 75 years old
Influenza vaccine status in the prior 12 months	Received previous season flu vaccine Did not received previous season flu vaccine
Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
Sex	Male Female
BMI (only for immunogenicity analyses)	BMI < 30 kg/m^2 BMI ≥ 30 kg/m^2

6.2 Background Characteristics

6.2.1 Participant Disposition

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 percentage of participants reporting each reason for screen failure will be based on the number of participants who screen failed. A separate listing will be provided for screen failure participants with reasons for screen failure. Participants with any inclusion and exclusion criteria violation will also be provided in a listing.

The number and percentage of participants in each of the following disposition categories will be summarized by vaccination group based on Randomization Set, Safety Set, Immunogenicity Set, and mITT Set.

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

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

The number and percentage of participants in the following categories (analysis sets defined in Section 5) will be summarized as defined in Section 6.1 (for general consideration) based on the Randomized set:

- Randomization Set
- Full Analysis Set
- mITT Set
- PP Set for Efficacy
- Immunogenicity Set
- PP Immunogenicity Set
- Safety Set
- Solicited Safety Set

The denominators of the percentages will be based on participants in the Randomization Set, unless otherwise specified.

A separate summary table will include the number and percentage of randomized participants by stratification factors as randomized via IRT and actual stratification factors derived from eCRF for each vaccination group and overall. Additionally, a comparison table between IRT randomization stratum and eCRF derived stratum will be provided.

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)
- EFS total score (for participants aged 65 years and older)

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

- Age group 1 (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) per eCRF
- Age group 2 (18 to < 50 years old, ≥ 50 to < 65 years old, ≥ 65 to < 75 years old, or ≥75 years old) per eCRF
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Country
- Influenza vaccine status in the prior 12 months at the time of screening (received previous season influenza vaccine or not received previous season influenza vaccine) per eCRF
- EFS total score category (Fit: 0-3, Vulnerable: 4-5, Frail: 6 or more)

The summaries will be provided separately for all analysis sets (except Solicited Safety Set) defined in the Section 5.

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) version 25.0 or higher.

The number and percentage of participants with any medical history will be summarized by SOC and PT for Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1010 vaccination group and then alphabetically within each SOC. All the medical history data will be presented in a listing.

6.2.4 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and non-study vaccinations will be coded using the WHO drug dictionary (WHODD) version Mar 2022. Imputation rules for missing dates of medications and non-study vaccinations are detailed in Section 9.4. The summary of concomitant medications will be based on the Safety Set.

Categorization of prior and concomitant medications are summarized in Table 8 in Section 9.5. An overall summary of medications and non-study vaccinations including the number and percentage of participants who take the following will be presented by vaccination group:

- Prophylactic antipyretics or analgesics medication up to 28 days post-injection
- Any concomitant medications and non-study vaccinations up to 28 days post-injection
- Non-study seasonal influenza vaccine up to 28 days post-injection
- Systemic steroids (≥ 10 mg/day prednisone or equivalent), immunosuppressants, immune-modifying drugs, immunoglobulins, and/or blood products administered at any time up to 28 days post-injection

The number and percentages of participants with at least one concomitant medication will be summarized by preferred terms and vaccination group. Prior, concomitant medications and non-study vaccination will be presented in a listing. Medications taken to prevent or treat pain or fever will also be presented in a listing. Concomitant procedures will be presented in a listing.

6.2.5 Protocol Deviations

The study protocol deviations will be reviewed on a regular basis and categorized in "Significant" and "Non-significant" based on the impacts on study results. Significant protocol deviations are a subset of protocol deviations that 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. Significant protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each significant protocol deviation type will be summarized by vaccination group and total based on the Randomization Set.

Significant protocol deviations that impact critical or key study data will be determined and documented by Sponsor prior to database lock and unblinding. Participants with such significant protocol deviations will be excluded from the PP analyses. Reasons of exclusion from PP analyses will be summarized.

Significant protocol deviations will be summarized in a table and presented in a listing.

6.2.6 Study Exposures

The number and percentage of participants received vaccine injection at Day 1 visit, study duration ≥ 7 days after vaccine injection, study duration ≥ 28 days after vaccine injection and study duration ≥ 180 days after vaccine injection as well as the study duration from vaccine injection to the EoS will be summarized by vaccination group and overall for Safety Set. Study vaccine administration data will be presented in a listing. Participants who had dosing errors will be presented in a separate listing.

6.3 Immunogenicity Analysis

For immunogenicity analysis, antibody titers reported as below the LLOQ will be replaced by 0.5 x LLOQ. Values that are greater than the ULOQ will be converted to the ULOQ.

The primary analysis population for immunogenicity will be the PP Immunogenicity Set, unless specified otherwise. In addition, the first 1000 randomized participants will also provide blood samples at Day 181 and Day 361 (Month 12), a subset of which will be used for immunogenicity analysis.

6.3.1 Analysis of Co-primary Immunogenicity Endpoints

There are four co-primary endpoints based on GMR and SCR differences for the two vaccine-matched A strains, and four co-primary endpoints based on GMR and SCR differences for the two vaccine-matched B strains. The primary objective of this study is to use the immunogenicity

response to infer efficacy in participants receiving mRNA-1010. The primary immunogenicity estimands are presented in detail in Table 12. The Day 29 primary analysis of immunogenicity will be performed after all participants have completed the Day 29 visit.

6.3.1.1 Primary Analysis

- Analysis of GMTs of anti-HA antibodies as measured by HAI against vaccine-matched influenza A and B strains at Day 29

An analysis of covariance model (ANCOVA) will be performed using the log-transformed HAI titers against a specific vaccine-matched strain at Day 29 as the dependent variable, vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The geometric least square mean (GLSM), and its corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale, as an estimate of the GMT for each vaccination group.

The GMR for mRNA-1010 vs. active comparator, estimated by the ratio of GLSM and the corresponding 2-sided 97.5% CI will be provided to assess the vaccine difference and calculated by back-transforming of the difference estimated from the ANCOVA model. The corresponding 2-sided 97.5% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 compared to the active comparator group at Day 29. For each strain, the non-inferiority of GMT will be considered demonstrated if the lower bound of the 97.5% CI of the GMR is > 0.667 based on a non-inferiority margin of 1.5. Refer to Immune Estimand 1a in Table 12.

Descriptive statistics (n, median, min, max) will also be provided for the GMT of HAI titers with corresponding 95% CI at each timepoint. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMT with corresponding 95% CI will be plotted at each time point respectively.

- Analysis of SCR against vaccine-matched influenza A and B strains as measured by HAI at Day 29

The number and percentage of participants with seroconversion due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method at Day 29. To compare the

seroconversion rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 97.5% CI for the difference in SCR. Refer to Immune Estimand 2a in Table 12. For each strain, the non-inferiority of SCR will be considered demonstrated if the lower bound of the 97.5% CI of the SCR difference is > -10% based on a non-inferiority margin of 10%.

6.3.1.2 Sensitivity Analysis

The primary analyses will be repeated using the Immunogenicity Set as a sensitivity analysis. Refer to Immune Estimand 1b and 2b in Table 12.

6.3.1.3 Subgroup Analysis

To assess the consistency of immunogenicity response of mRNA-1010 across subgroups, subgroup analysis of the co-primary endpoints will be conducted by subgroups defined by age group 1, age group 2, prior influenza vaccine status, race, sex, and BMI category (see Table 5), based on PP Immunogenicity Set. For each subgroup category, the co-primary immunogenicity endpoints will be analyzed using the same statistical methods as for primary analysis. Additional details are documented in Section 4.2.

If the number of participants in a subgroup is less than 10% of sample size in the analysis set, it may be combined with other subgroups for the subgroup analyses.

6.3.2 Analyses of Secondary Immunogenicity Endpoints

- Analysis of GMTs of anti-HA antibodies as measured by HAI against vaccine-matched influenza A strains on Day 29 (superiority and super-superiority testing)

If the non-inferiority is demonstrated for A strains only, superiority of mRNA-1010 relative to the active comparator against vaccine-matched influenza A strains at Day 29 will be tested at a two-sided α_1=2.5% level. If the non-inferiority is demonstrated for both A and B strains, superiority of mRNA-1010 relative to the active comparator against vaccine-matched influenza A strains at Day 29 will be tested at a two-sided α_1=5% level.

The same ANCOVA model for primary analysis will be applied. The superiority of GMT in participants who received mRNA-1010 compared to GMT in participants who received active

comparator will be demonstrated by the lower bound of the (100%- α_1) CI % of the GMR ruling out 1 (lower bound > 1).

If superiority is demonstrated based on lower bound of (100%- α_1) CI % of GMR > 1, the super-superiority of GMT in participants who received mRNA-1010 compared to participants who received active comparator will then be evaluated based on a lower bound of (100%- α_1) CI % of the GMR > 1.5.

- Analysis of SCRs of anti-HA antibodies as measured by HAI against vaccine-matched influenza A strains on Day 29 (super-superiority testing)

Rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer ⩾ 1:40 or a pre-vaccination HAI titer ⩾ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer. If super-superiority has been demonstrated based on GMT, the SCR of the vaccine-matched influenza A strains at Day 29 between the vaccination groups will be compared. The Miettinen-Nurminen's method will be used to calculate the (100%- α_1) CI for the difference in SCRs. For the A strains, the super-superiority of SCR will be considered demonstrated if the lower bound of the (100%- α_1) CI % of SCR difference is > 10%.

In addition, the number and percentage of participants that reached seroconversion at each time point will be provided with 2-sided 95% CI using the Clopper-Pearson method.

- Analysis of frequency of participants with an HAI titer ⩾ 1:40 on Day 29

The number and percentage of participants with an HAI titer ≥ 1:40 post-injection due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method.

- Analysis of GMT of vaccine-matched strain-specific anti-HA antibodies on Day 29 as measured by HAI

Descriptive statistics (n, median, min, max) will be provided as described in the immunogenicity primary analysis (Section 6.3.1.1).

- Analysis of GMFR of vaccine-matched strain-specific anti-HA antibodies comparing Day 29 to Day 1 (baseline) as measured by HAI

Descriptive statistics (n, median, min, max) will be provided for the GMFR of HAI titers with corresponding 95% CI at Day 29 over baseline. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMFR with corresponding 95% CI will be plotted at Day 29.

6.3.3 Analysis of Exploratory Immunogenicity Endpoints

- Analyses of GMT and GMFR of nAbs by MN assays against vaccine-matched or vaccine-mismatched strains on Day 29, compared with Day 1 (baseline)
- Analyses of GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29
- Analyses of GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-matched or vaccine-mismatched strains, on Day 181 and Day 361/EoS compared with Day 1 (baseline)

Descriptive statistics (n, median, min, max) will be provided for the following endpoints with corresponding 95% CI at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMT and GMFR with corresponding 95% CI will be plotted at each time point respectively.

The number and percentage of participants with an HAI titer ≥ 1:40 post-injection due to vaccination at Day 181 and Day 361 will be provided with 2-sided 95% CI using the Clopper-Pearson method.

To further characterize the immune response to mRNA-1010 and active comparator, frequency, specificities, or other endpoints may be determined for further characterization of immune responses. A reverse cumulative distribution function plot of anti-HA antibody levels for HAI assay by visit will be provided.

6.4 Efficacy Analysis

The primary analysis population for efficacy is the mITT Set, unless otherwise specified. Participants will be included in the vaccination group to which they are randomized. The complete efficacy analysis will be performed once all participants complete the Day 181 visit or at the end of influenza season, whichever occurs later.

The evaluation of vaccine efficacy is a secondary objective in the study. The efficacy endpoint, RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed CDC-defined ILI, are defined in Section 3.2.

6.4.1 Analysis of Secondary Efficacy Endpoints

The vaccine efficacy of preventing the first episode of RT-PCR-confirmed protocol-defined ILI case and RT-PCR confirmed CDC-ILI case that begins at least 14 days post-vaccination through Day 181 or end of influenza season, whichever occurs later, caused by any strain of influenza virus will be evaluated.

6.4.1.1 Endpoint Definition/Derivation

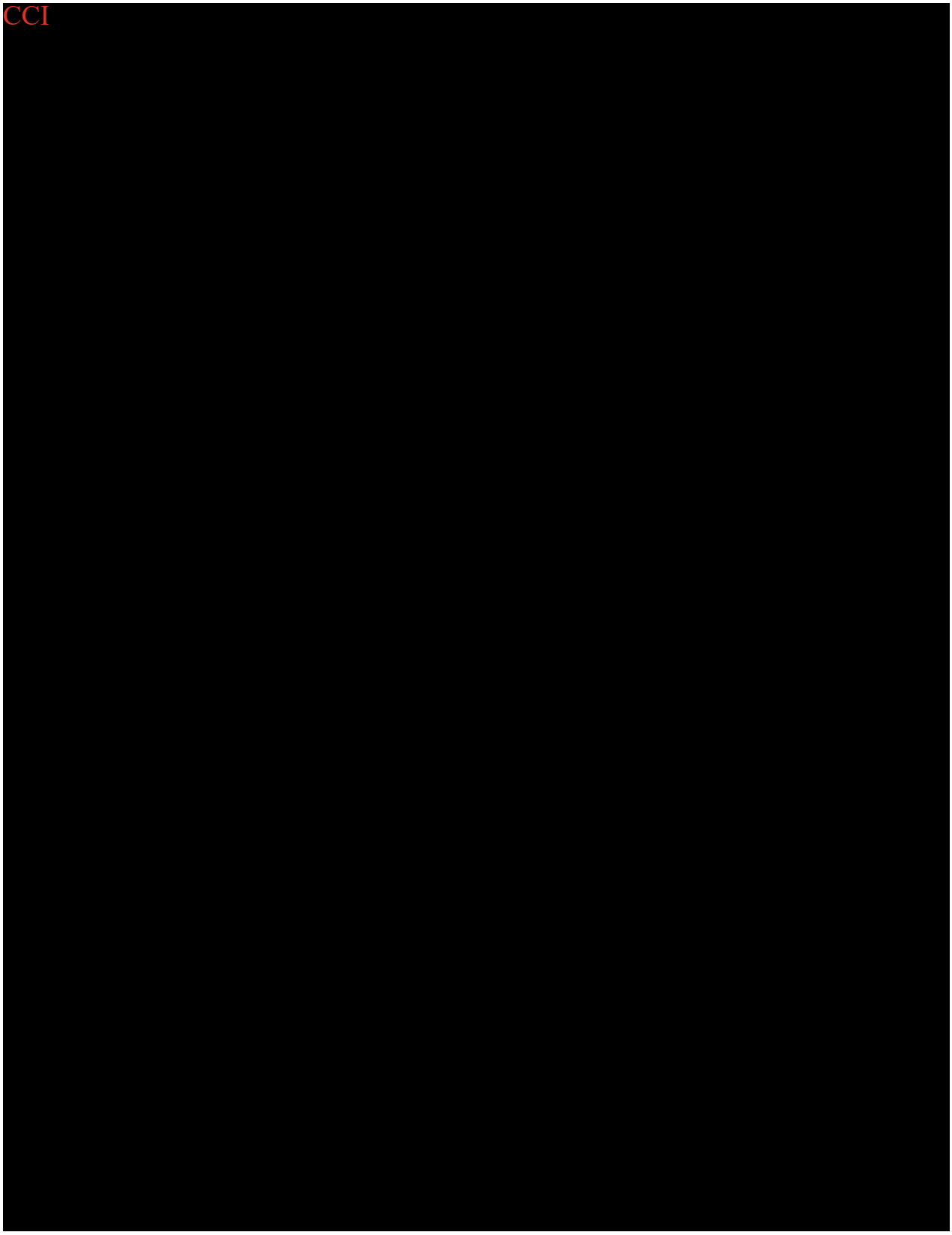
If ILI symptoms have been reported from Day 1 to Day 361 (Month 12)/EoS, the investigator must contact the participant to assess symptoms using the ILI eCRF and ensure an NP swab is collected if the participant's symptoms meet the criteria for protocol-defined ILI or CDC-defined ILI. Detailed description of protocol-defined ILI and CDC-defined ILI are presented in Section 3.2.

Both central laboratory RT-PCR results and local certified RT-PCR results will be used for case confirmation. More specifically, the following rules apply:

1. If at least one RT-PCR positive result is reported by either the central laboratory or a local certified laboratory, the RT-PCR result is considered as positive
2. The test collection date/time of positive result will be used in the analysis

CCI

CCI



Analysis of vaccine efficacy of RT-PCR-confirmed protocol-defined ILI are as follows:

The number and percentage of participants with RT-PCR-confirmed protocol-defined ILI will be summarized by vaccination group.

The incidence rate will be provided by vaccination group, calculated as the number of participants with a case (ie, first occurrence of ILI at least 14 days after the study injection through Day 181/end of influenza season) divided by the total person-time (years). The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

The relative vaccine efficacy (rVE) will be estimated by 1- the ratio of incidence rates (mRNA-1010 vs. active comparator) adjusting for person-time, multiplied by 100:

$$\text{rVE} = 100 \times \left(1 - \frac{\text{Incidence rate in mRNA}-101 \text{ group}}{\text{Incidence rate in active comparator group}}\right) \%$$

The estimated rVE of mRNA-1010 vs. active comparator will be provided with its 95% CI computed using the exact method conditional upon the total number of cases adjusted by the total person-time.

The person-time is calculated as the time from randomization to the date of the first episode for participants with a case, or the time from randomization to the date of discontinuation or death or Day 181/end of influenza season (whichever occurs later), whichever occurs first, for participants without a case.

The other secondary efficacy endpoints will be analyzed using similar methods:

- RT-PCR-confirmed CDC-defined ILI
- RT-PCR-confirmed protocol-defined ILI in participants aged 50 years and older
- RT-PCR-confirmed protocol-defined ILI in participants aged 65 years and older

Sensitivity analysis of these efficacy endpoints will be performed with the same methods described above based on the PP Set for Efficacy.

6.4.2 Analysis of Exploratory Efficacy Endpoints

As an exploratory analysis, the following endpoints will be summarized:

- The number of participants aged 65 years and older with any episode of RT-PCR-confirmed protocol-defined ILI by baseline frailty status (categorized as Fit: 0-3, Vulnerable: 4-5, Frail: 6 or more)

- The number of participants with cases of RT-PCR-confirmed protocol-defined ILI cases that begin at least 14 days post-vaccination through Day 361 (Month 12)/EoS caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine

6.5 Multiplicity Control

To control the overall type I error at 0.05 level for the study, a hierarchical testing strategy will be applied to test the four null hypotheses defined in Section 4.2 in the following order.

Step 1: Test null hypotheses H_0^1 and H_0^2 at 2-sided 0.025 level respectively.
If both null hypotheses H_0^1 and H_0^2 in Step 1 are rejected, the following steps will be performed at a two-sided α_1=5% level. If only null hypotheses H_0^1 is rejected, the following steps will be performed at a two-sided α_1=2.5% level.
Step 2: Test null hypotheses H_0^3 at α_1 level, if at least null hypothesis H_0^1 in Step 1 is rejected.
Step 3: Test null hypotheses H_0^4 at α_1 level, if the null hypotheses in Step 1 and Step 2 are all rejected.
Step 4: Test null hypotheses H_0^5 at α_1 level, if the null hypotheses in Step 1, Step 2, and Step 3 are all rejected.

The testing sequence can only continue to the next step if all prior steps achieve statistical significance at the specified α_1 level (per Step 1). If a step fails to demonstrate statistical significance at the specified α_1 level (per Step 1), then the testing sequence will stop, and all steps thereafter will not be conducted. Detailed descriptions are presented in Section 9.2 and Section 9.6.2 in Protocol Amendment 2.

All other endpoints are not controlled for multiplicity and the analyses are descriptive in nature.

The study success can only be declared if non-inferiority of mRNA-1010 vs. active comparator is demonstrated for both A strains and B strains on GMT ratio and SCR.

6.6 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, fatal events, AESIs, MAAEs, AEs leading to withdrawal from study participation. Solicited ARs and unsolicited AEs will be

coded by SOC and PT according to the MedDRA version 25.0 or higher. All safety endpoints will be summarized by vaccination group corresponding to actual IP they received for the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set.

When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE/AR or a continuing AE/AR will be counted once. Participants will be presented according to the highest severity/toxicity in the summaries by severity/toxicity, if participants reported multiple events under the same SOC and/or PT. SOC will be displayed in an internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1010 vaccination group within each SOC.

6.6.1 Analysis of Solicited Adverse Reactions

An AR is defined as any AE for which there is a reasonable possibility that the IP may have caused the AE. The term “Solicited Adverse Reaction” refers to selected signs and symptoms occurring after IP injection during a specified post-injection follow-up period (day of injection and 6 subsequent days).

The solicited ARs are recorded by the participant in the eDiary. The eDiary will solicit daily participant reporting of occurrence and intensity of ARs using a structured checklist from Day 1 through 7 days after the IP injection (i.e., the day of injection and 6 subsequent days). Any solicited ARs started during the 7-day follow-up period post-injection, if not reported in the eDiary, should be entered on the Reactogenicity eCRF and will be included in the evaluation of solicited ARs in addition to the eDiary.

If a solicited local or systemic AR starts on or after Day 8, it should be captured on the AE eCRF page until no longer reported.

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

- Solicited local or systemic AR that results in a visit to a healthcare practitioner
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR continuing beyond 7 days post-injection
- Solicited local or systemic AR that otherwise meets the definition of an SAE

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

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever (oral).

The solicited ARs will be graded based on the grading scales presented in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007b) in Section 9.6. Grading of Grade 4 events will be determined per investigator and assessment is recorded on the reactogenicity event page in the eCRF .

Analyses of solicited ARs will be provided by vaccination group based on the Solicited Safety Set, unless otherwise specified. All solicited ARs (overall, local, and systemic) reported during the 7-day follow-up period after injection will be summarized. The number and percentage along with its 2-sided 95% exact CI (using the Clopper-Pearson method) of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7-day follow-up period after the injection will be provided. The same analysis will be conducted for subgroups defined by age group1, age group 2, race, and sex (see Table 5).

The number and percentage of participants who reported each individual solicited local AR (has a toxicity grade of Grade 1 or greater) and solicited systemic AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after injection will be provided by toxicity grade. The same analysis will be conducted for subgroups defined by age group1, age group 2, race, and sex (see Table 5).

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

Descriptive statistics will be provided for the duration of solicited ARs (overall, local, and systemic) and each individual SAR by vaccine group. The duration of local or systemic solicited ARs, along with the specific individual solicited ARs, will be calculated as: reaction end date –

reaction start date +1, no matter it is intermittent or continued or if the solicited AR continues beyond 7 days.

All solicited ARs that continue beyond 7 days post-injection will be summarized. All delayed ARs with onset day after 7 days post-injection will also be summarized.

Solicited local and systemic ARs will be provided in a listing. All solicited ARs that continue beyond 7 days post-injection will be listed as well.

6.6.2 Unsolicited Treatment-Emergent AEs

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. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

AEs will also be evaluated by the investigator for the coexistence of MAAE and/or AESI. An MAAE is an AE that leads to an unscheduled or scheduled visit to a healthcare practitioner. AESIs for this study are pre-defined in the protocol appendix 3 including thrombocytopenia, neurologic diseases, anaphylaxis, and myocarditis/pericarditis.

Unsolicited AEs will be collected from Day 1 through 28 days after the IP injection on the AE page and reactogenicity page of the eCRF. SAEs, MAAEs, AESIs and AEs leading to withdrawal will be collected from Day 1 until the end of participation in the study. Analyses of unsolicited AE will be provided for up to 28 days after vaccination unless otherwise specified.

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT or by PT only for TEAEs with counts of participants included. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1010 group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

Unsolicited TEAEs will be summarized up to 28 days after vaccine injection. Treatment emergent SAEs, MAAEs, AESIs and AEs leading to withdrawal will be summarized for up to 180 days after vaccine injection and throughout the study (up to Day 361 (Month 12)/EoS).

In addition, number of participants with occurrences of selected TEAEs of clinical interests identified by SMQ will be summarized. SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in Table 13 and Table 14

6.6.2.1 Overview of Unsolicited TEAEs

An overall summary of unsolicited TEAEs up to 28 days after IP injection (or other time frames, as applicable) including the number and percentage of participants who experienced the following will be presented:

- Any unsolicited TEAEs
- Any unsolicited treatment-related TEAEs
- Any serious TEAEs
- Any treatment-related serious TEAEs
- Any unsolicited severe TEAEs
- Any unsolicited treatment-related severe TEAEs
- Any unsolicited medically attended TEAEs
- Any unsolicited treatment-related medically attended TEAEs
- Any unsolicited treatment emergent AESI
- Any unsolicited TEAEs leading to discontinuation from participation in the study.

Listings containing individual participant AE data for unsolicited AEs, unsolicited AEs leading to discontinuation from participation in the study, SAEs, AESI, MAAEs will be provided separately.

6.6.2.2 TEAEs by System Organ Class and Preferred Term

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

- Any unsolicited TEAEs

- Any unsolicited treatment-related TEAEs
- Any serious TEAEs
- Any treatment-related serious TEAEs
- Any unsolicited severe TEAEs
- Any unsolicited treatment-related severe TEAEs
- Any unsolicited medically attended TEAEs
- Any unsolicited treatment-related medically attended TEAEs
- Any unsolicited treatment emergent AESI
- Any unsolicited TEAEs leading to discontinuation from participation in the study.

Unsolicited TEAEs and unsolicited treatment related TEAEs will be summarized by SOC and PT for TEAEs with occurrence in ≥1% of participants in any vaccination group based on PT and also presented by SOC and PT and severity using frequency counts and percentages.

Summary tables for all unsolicited SAEs, AESIs, MAAEs, AE leading to discontinuation from the study, and TEAE leading to death up to 180 days after vaccine, and through Day 361 (Month 12)/EoS will be provided also be provided by SOC and PT as applicable.

6.6.2.3 TEAEs by Preferred Term

The following summary tables of TEAEs will be provided by PT sorting by frequency on the mRNA-1010 group:

- All unsolicited TEAEs
- SMQ

6.6.2.4 TEAEs by Severity

The following summary tables of TEAEs will be provided by the severity using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited treatment-related TEAEs

6.6.3 Subgroup Analysis of TEAEs

Analysis of unsolicited TEAEs will be conducted for subgroups defined in Table 5. Subgroup analysis for TEAE may be performed for the specified TEAE category based on Section 6.6.2.1.

Overall summary of the unsolicited TEAEs up to 28 days will be provided for each subgroup. Summary tables for TEAE, treatment related TEAEs, and SAEs by SOC and PT will also be provided for each subgroup up to 28 days after the vaccine.

6.6.4 Death

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

6.6.5 Other Safety Data

6.6.5.1 Pregnancy

A pregnancy test via blood or point-of-care urine test will be performed for all female participants of childbearing potential at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. Additional pregnancy testing during the study may also be performed at the discretion of the investigator. Pregnancy test results will be listed by participant.

6.6.5.2 Vital Signs

On the day of vaccination, vital signs measurements including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature will be collected once before vaccination and once 30 minutes after vaccination.

Observed value and change from pre-injection (baseline) to post- injection in vital signs will be summarized by vaccination group. Abnormal vital sign measurements will be graded per toxicity grading criteria provided in Section 9.7. A toxicity grade shift table of the vital signs from pre-injection to post-injection will be provided. Additionally, the values that are outside the reference ranges will be flagged in a data listing. Participant with any abnormal vital sign measurement where toxicity grade (Grade 3 or higher) will be listed separately.

6.7 Other Exploratory Analysis

6.7.1 Biomarker Analysis

Biomarker assessments will be evaluated as part of the study, which may include genomic and transcriptomic studies. Optional blood collections for DNA and mRNA sequencing will be performed and may be used for potential biomarker research. The biomarker analyses will not be covered in the plan and will be developed in a separate plan as needed.

6.7.2 COVID-19 Impact

A listing will be provided for the impact of COVID-19 on the execution of the study.

6.7.3 EQ-5D-5L and WPAI:ILI

Patient-reported outcomes associated with symptoms of ILI will be assessed at the specified time points. All participants will receive eDiary prompts to complete the EQ-5D-5L questionnaire on Day 1, Day 91, Day 181, Day 271, and Day 361 (Month 12)/EoS, and participants who report symptoms of ILI will receive eDiary prompts to complete EQ-5D-5L and WPAI: ILI questionnaires.

A separate analysis plan will be developed for analyzing these two endpoints (EQ-5D-5L and WPAI:ILI) of patient-reported outcomes.

6.8 Planned Analysis

The primary analysis of safety and immunogenicity will be performed after all participants have completed the Day 29 visit. All data relevant to the primary study analysis through the Day 29 Visit for immunogenicity and safety assessment will be cleaned and locked. visit .

A 6-month analysis may be performed once all participants complete the Day 181 Visit or the influenza season ends, whichever occurs later. All of safety, immunogenicity, and efficacy data will be cleaned and locked for the 6-month analysis.

Additional safety or efficacy analyses at other time points may be performed.

The above analyses will be performed by a separate team of unblinded programmers and statisticians. More details can be found in the study data blinding plan.

Final analysis of all safety, immunogenicity, and efficacy data will be performed once all participants complete the Day 361 (Month 12)/EoS Visit in descriptive nature.

Ongoing unblinded safety reviews by a DSMB will be conduct during the study on a periodic basis, as defined in a DSMB charter or as needed if potential safety concerns are identified.

7 Changes in the Planned Analysis

Not applicable.

8 References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Clinical data needed to support the licensure of pandemic influenza vaccines. May 2007a [cited 2021 Aug 19]. Available from: https://www.fda.gov/media/73691/download

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007b [cited 2021 Aug 19]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

9 Appendices

9.1 Schedule of Study Procedures

Table 6: Schedule of Events

Visit Number		1	2	3	4	5	6	7	8	9	USV
Type of Visit/Contact	C	C	C	SC	SC	C	SC	SC/C	SC	SC/C	C
Month Timepoint						M1	M3	M6	M9	M12	Up to M12
Study Visit	Screening[1]	D1 (Baseline)	D4	D8	D15	D29	D91	D181	D271	D361/EoS	USV
Window Allowance (Days)	-28	N/A	-2	±3	±3	-7 to +3	±5	±14	±14	±14	N/A
Informed consent form, demographics, concomitant medications, medical history[2]	X										
Inclusion/exclusion criteria	X	X									
Physical examination[3]	X										
Vital signs[4]	X	X									
Pregnancy testing[5]	X	X									
Randomization		X									
Study vaccination (including 30-minute post-dosing observation period)[6]		X									
Collection of Edmonton Frail Scale[7]		X									
Blood collection for humoral immunogenicity		X[8]				X		X[9]		X[9]	
Genomic sample (optional)		X[8]									
Transcriptomic sample (optional)		X[8]				X					

Visit Number		1	2	3	4	5	6	7	8	9	USV
Type of Visit/Contact	C	C	C	SC	SC	C	SC	SC/C	SC	SC/C	C
Month Timepoint						M1	M3	M6	M9	M12	Up to M12
Study Visit	Screening[1]	D1 (Baseline)	D4	D8	D15	D29	D91	D181	D271	D361/EoS	USV
Window Allowance (Days)	-28	N/A	-2	±3	±3	-7 to +3	±5	±14	±14	±14	N/A
Optional blood sample for potential biomarker analysis[10]			X								
NP swab for virus detection[11]											X
eDiary activation for recording solicited ARs (7 days)[12]		X									
Review of eDiary for solicited ARs				X							
Symptom Reporting eDiary activation [13]		X									
Symptom Reporting eDiary for collection of symptoms of ILI[14]		Once weekly									
Review of Symptom Reporting eDiary[15]		Review participant recorded ILI starting on Day 1 through Day 361 (Month 12)/EoS									
Follow-up safety call				X	X		X	X[16]	X	X[16]	
eDiary collection of EQ-5D-5L[17]		X	eDiary prompts[18]								
eDiary collection of WPAI:ILI[19]			eDiary prompts[20]								
Recording of unsolicited AEs		X		X	X	X					
Recording of SAEs, AESIs, and MAAEs, as well as AEs that led to discontinuation and relevant concomitant medications/procedures[21]		X		X	X	X	X	X	X	X	X

Visit Number		1	2	3	4	5	6	7	8	9	USV
Type of Visit/Contact	C	C	C	SC	SC	C	SC	SC/C	SC	SC/C	C
Month Timepoint						M1	M3	M6	M9	M12	Up to M12
Study Visit	Screening[1]	D1 (Baseline)	D4	D8	D15	D29	D91	D181	D271	D361/EoS	USV
Window Allowance (Days)	-28	N/A	-2	±3	±3	-7 to +3	±5	±14	±14	±14	N/A
Recording of concomitant medications and non-study vaccinations[22]		X		X	X	X					
Recording of hospitalizations and outpatient treatment-related to or for the treatment of the MAAE or SAE[23]		X		X	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; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; EFS = Edmonton Frail Scale; EoS = end of study; EQ-5D-5L = EuroQoL 5-dimension 5-levels; FDA = Food and Drug Administration; HRQoL = health-related quality of life; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (or contact by electronic means); USV = unscheduled visit; WPAI:ILI = Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness.
Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (FDA 2020), investigators may convert clinic visits to telemedicine visits with the approval of the Sponsor.

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.
3. Physical examination: A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as an MAAE.
4. Vital signs measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
5. A pregnancy test either via blood or point-of-care urine test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating- hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.
6. See Table 2 for dose levels and vaccination groups. All participants will be randomized to receive a single IM injection.

7. Assessment of EFS will only be performed for participants aged 65 years and older. EFS is a brief, valid and reliable tool for the assessment of frailty across 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.
8. Samples for humoral immunogenicity and transcriptomics must be collected prior to receipt of vaccination on Day 1.
9. Samples for humoral immunogenicity on Day 181 and Day 361 (Month 12)/EoS will be collected for the first 1000 participants and analyzed in a subset. These participants will require a clinic visit on Day 181 and Day 361 (Month 12)/EoS, .
10. Biomarker plasma and biomarker serum samples will be stored for potential future biomarker assessment
11. The NP swab specimen(s) for pathogens, including influenza virus and other respiratory pathogens (e.g., SARS-CoV-2) will be collected any time from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined- ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection as defined in the ILI Case Definitions in Section 3.2. If participants experience these signs or symptoms, they will be instructed to contact the clinic to have an NP swab collected for testing. Nasopharyngeal (NP) swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza and/or SARS CoV-2 testing results performed outside of the study should be captured in the eCRF.
12. The eDiary entries will be recorded at approximately 30 minutes after injection while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and the subsequent 6 days following injection. 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 and close out the event on the Reactogenicity page of the eCRF. If the participant reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF. All solicited ARs (local and systemic) will be considered causally related to dosing.
13. The Symptom Reporting eDiary will be activated for collection of ILI symptoms starting at Day 1 and lasting until Day 361 (Month 12)/EoS.
14. Symptom Reporting eDiary: Participants will be instructed to report via Symptom Reporting eDiary or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms occur, the investigator must contact the participant to assess symptoms and ensure an NP swab is collected within 72 hours of symptom onset. If possible, NP swabs should be collected prior to initiation of antiviral therapy. If there is no response to an eDiary prompt for 2 consecutive entries, the clinic staff will attempt to contact the study participant by telephone.
15. Review of eDiary for recording of symptoms of ILI.
16. Participants in the subset require a clinic visit on Day 181 and Day 361 (Month 12)/EoS for sample collection.
17. EQ-5D-5L is a well-validated, reliable, standardized instrument for measuring non-disease-specific HRQoL. EQ-5D-5L consists of a short descriptive system questionnaire and a visual analogue scale (EQ-VAS). The short descriptive questions are designed to assess 5 dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the health status on a scale between 0 and 100, with 0 indicating the worst imaginable health and 100 indicating the best imaginable health.
18. All participants will receive eDiary prompts to complete the EQ-5D-5L at Day 1 (baseline), Day 91, Day 181, Day 271, and Day 361 (Month 12)/EoS. For participants reporting symptoms of ILI, the EQ-5D-5L responses will be collected using the eDiary on the day of the symptoms reporting (+1 day) and 5 days (+1 day) later.
19. WPAI consists of 6 questions, which can quantitatively assess the amount of absenteeism, presenteeism, overall work impairment, and activity impairment attributable to a patient's health issues based on a 1-week recall period. The WPAI is available in different versions, such as WPAI: Specific Health Problem (WPAI:SHP), which can be adapted to a specific disease.
20. For participants reporting symptoms of ILI, the WPAI over the previous 7 days will be collected using the eDiary 5 days (+1 day) following the start of ILI symptoms reporting.
21. Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations. All concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 361 (Month 12)/EoS.
22. All concomitant medications and non-study vaccinations will be recorded through 28 days after IP injection (including receipt of any authorized or investigational COVID-19 vaccine).
23. All hospitalizations, outpatient/physician visits, emergency room/urgent care visits, and telemedicine visits associated with MAAEs or SAEs will be recorded from Day 1 through Day 361 (Month 12)/EoS.

9.2 Standards for Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimals place more than the original results; the min and max will be presented to the same precision as the original results. For model-based estimates, the results may be presented up to 3 decimal points, unless otherwise specified.

Categorical Variables: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

9.3 Analysis Visit Windows for Immunogenicity Analysis

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

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

Step 2: If the immunogenicity assessments are not collected at the scheduled visits, assessments collected at an unscheduled visit will be used using the analysis visit windows described in Table 7 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 7: Analysis Visit Windowing

Visit	Target Study Day	Visit Window in Study Day
Immunogenicity		
Day 1	1 (Date of Injection)	1, Pre-vaccination
Day 29	29	[2, 105]
Day 181	181	[106, 271]
Day 361	361	≥ 272

9.4 Imputation Rules for Missing Dates

Imputation rules for missing or partial start/stop dates of medication and non-study vaccinations are defined below:

1. Missing or partial medication start date:

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

The medication end date is on/after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection.

If Day and Month are both missing, use the first day of the year, unless:

The medication end date is on/after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection.

If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.

2. Missing or partial medication stop date:

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

    b. If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).

    c. If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

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

Missing or partial start date:

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

- The AE end date is on/after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if AE time was collected.

If Day and Month are both missing, use the first day of the year, unless:

- The AE end date is on/after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date and time of first injection, when time is available.

If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment emergent.

Missing or partial end dates will not be imputed.

9.5 Prior and concomitant categorization of a medication

Table 8: Categorization of Medication

	Medication End Date	
Medication Start Date	**< Injection Date of IP**	**≥ Injection Date and ≤ Injection Day + 27 Days After Injection [1]**
< Injection date of IP [2]	P	P, C
≥ Injection date and ≤ 28 days after injection	-	C
> 28 days after injection	-	-

C = Concomitant; P = Prior

[1] includes medications with completely missing end date

[2] includes medications with completely missing start date

9.6 Solicited Adverse Reactions and Grades

Table 9: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[1] (Life-threatening)
Local					
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24	Significant; any use of prescription pain	Requires emergency room

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[1] (Life-threatening)
			hours or some interference with activity	reliever or prevents daily activity	visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

1. Grading of Grade 4 events will be determined per investigator and assessment is recorded on the reactogenicity event page in the electronic case report form.

Note: Events listed above but starting > 7 days post-study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator. Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

9.7 Severity Grading of Vital Sign Abnormalities

Table 10: Severity Grading of Vital Sign Abnormalities

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

* Participant should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athlete

9.8 Estimands and Estimand Specifications

Table 11: Intercurrent Events

Label	Intercurrent Event Type
IcEv1 (early discontinuation or unrelated death)	Early discontinuation from study or unrelated death prior to Day 29, the first post-treatment immunogenicity result available.
IcEv2 (alternative influenza vaccine)	Use of alternative Influenza vaccine prior to Day 29.
IcEv3 (COVID-19 vaccine)	Use of COVID-19 vaccine prior to Day 29.
IcEv4 (prohibited medications)	Use of prohibited medications deemed to impact on immunogenicity prior to Day 29.
IcEv5 (early infection)	Infection starting up to 29 days after IP injection.
IcEv6 (wrong vaccination)	Receiving wrong vaccination.

Abbreviation: IcEv: intercurrent event.

Table 12: Summary of Primary Immunogenicity Estimands with Rationale for Strategies to Address Intercurrent Events

Objective: To evaluate the humoral immunogenicity of mRNA-1010 relative to that of the active comparator against vaccine-matched influenza A and B strains at Day 29 based on HAI assays		
Estimand Label	**Primary Immune Estimand 1a** (on the PP Immunogenicity Set)	**Supportive Immune Estimand 1b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as GMT ratio of anti-HA level as measured by HAI assay on Day 29 in adults aged 18 years or older who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment without significant protocol deviations impacting immune response and RT-PCR-confirmed influenza between Days 1 to 29.	Immune response to seasonal influenza measured as GMT ratio of anti-HA level as measured by HAI assay on Day 29 in adults aged 18 years or older who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment as measured by HAI assay.
Target Population	Adults aged 18 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection serum antibody assessment as measured by HAI assay after the IP administration, and have no significant protocol deviations impacting the immune response and RT-PCR-confirmed influenza between Days 1 to 29.	Adults aged 18 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment as measured by HAI assay.
Endpoint	GMT ratio of anti-HA levels on Day 29	As per Estimand 1a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Tetra)	As per Estimand 1a.

Population-Level Summary	Immune response to seasonal influenza defined as GMT ratio of anti-HA level as measured by HAI assay using an ANCOVA model on the log-transformed tiers on Day 29, with the vaccination group as the fixed variable, adjusted for stratified age group used for randomization and log-transformed baseline tiers.	As per Estimand 1a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination)	Principal stratum	Treatment policy

Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged 18 years or older who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events. A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of whether they are administered wrong vaccination. The analysis of immune response is based on the randomized vaccine group.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the key major protocol criteria (i.e. significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 1a.
Objective: to evaluate the humoral immunogenicity of mRNA-1010 relative to that of the active comparator against vaccine-matched influenza A and B strains at Day 29 based on HAI assays based on seroconversion rate		
Estimand Label	**Primary Immune Estimand 2a** (on the PP Immunogenicity Set)	**Supportive Immune Estimand 2b** (on the Immunogenicity Set)

Estimand Description	Immune response to influenza measured as seroconversion rate difference of antibody using HAI assay on Day 29 in adults aged 18 years or older who receive IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment without significant protocol deviations impacting immune response and RT-PCR-confirmed influenza between Days 1 to 29.	Immune response to influenza measured as seroconversion rate difference of antibody using HAI assay on Day 29 in adults aged 18 years or older who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment.
Target Population	Adults aged 18 years or older who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment after the IP administration, and have no significant protocol deviations impacting the immune response.	Adults aged 18 years or older who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and at least 1 post-injection antibody assessment.
Endpoint	Seroconversion rate difference of antibody measured by HAI assay on Day 29.	As per Estimand 2a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Tetra)	As per Estimand 2a.
Population-Level Summary	Immune response to influenza defined as seroconversion rate difference of antibody using Miettinen-Nurminen's method.	As per Estimand 2a.
Intercurrent Event Strategy		

IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged 18 years or older who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, wrong vaccination, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the key major protocol criteria (i.e. significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 2a.

9.9 Definition of TEAE of Special Interest by SMQ

Table 13: TEAE of Special Interest by SMQ

TEAE of Special Interest	Type of MedDRA Query	Broad or Narrow Search	SMQ Search Criteria
Hypersensitivity	SMQ	Broad/Narrow	Specified PT terms
Angioedema	SMQ	Broad/Narrow	Specified PT terms
Anaphylactic Reaction	SMQ	Broad/Narrow	Specified PT terms and algorithmic approach specified in Table 14
Immune-mediated/Autoimmune Disorder	SMQ	Broad/Narrow	Specified PT terms

Table 14: Algorithmic Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

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

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
A	Narrow	Anaphylactic reaction
A	Narrow	Anaphylactic shock
A	Narrow	Anaphylactic transfusion reaction
A	Narrow	Anaphylactoid reaction
A	Narrow	Anaphylactoid shock
A	Narrow	Circulatory collapse
A	Narrow	Dialysis membrane reaction
A	Narrow	Kounis syndrome
A	Narrow	Procedural shock
A	Narrow	Shock
A	Narrow	Shock symptom
A	Narrow	Type I hypersensitivity
B	Broad	Asthma
B	Broad	Bronchial oedema
B	Broad	Bronchospasm
B	Broad	Cardio-respiratory distress
B	Broad	Chest discomfort
B	Broad	Choking
B	Broad	Choking sensation
B	Broad	Circumoral oedema
B	Broad	Cough
B	Broad	Cough variant asthma
B	Broad	Cyanosis

B	Broad	Dyspnoea
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema
B	Broad	Laryngospasm
B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
B	Broad	Nasal obstruction
B	Broad	Oedema mouth
B	Broad	Oropharyngeal oedema
B	Broad	Oropharyngeal spasm
B	Broad	Oropharyngeal swelling
B	Broad	Pharyngeal oedema
B	Broad	Pharyngeal swelling
B	Broad	Respiratory arrest
B	Broad	Respiratory distress
B	Broad	Respiratory failure
B	Broad	Reversible airways obstruction
B	Broad	Sensation of foreign body
B	Broad	Sneezing
B	Broad	Stridor
B	Broad	Swollen tongue
B	Broad	Tachypnoea
B	Broad	Throat tightness
B	Broad	Tongue oedema
B	Broad	Tracheal obstruction
B	Broad	Tracheal oedema
B	Broad	Upper airway obstruction
B	Broad	Vaccine associated enhanced respiratory disease
B	Broad	Wheezing
C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling

C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria
C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest
D	Broad	Cardiovascular insufficiency
D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension

PPD	PPD Biostatistics and Programming
	Statistical Analysis Plan (SAP) Client Approval Form

Client:	**ModernaTX, Inc.**
Protocol Number:	**mRNA-1010-P301**

Document Description:	Statistical Analysis Plan
SAP Title:	A Phase 3, Randomized, Stratified, Observer-blind, Active-controlled Study to Evaluate the Immunogenicity and Safety of mRNA-1010 Seasonal Influenza Vaccine in Adults 18 Years and Older
SAP Version Number:	2.0
Effective Date:	17-November-2022

Author(s):

For PPD: PPD

Approved by:

PPD

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

PPD

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

PPD

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

PPD

Date *(DD-MMM-YYYY)*

ModernaTX, Inc.

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 17 November 2022 | 17:35 Viewed: 18 November 2022 | 12:50 Signed: 18 November 2022 | 12:51
Electronic Record and Signature Disclosure: Accepted: 18 November 2022 | 12:50 ID: 82eb1298-b005-4c9d-a55a-4645547d919b		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17 November 2022 | 17:35 Viewed: 17 November 2022 | 20:17 Signed: 17 November 2022 | 20:17
Electronic Record and Signature Disclosure: Accepted: 17 November 2022 | 20:17 ID: 2dcb627e-233b-4b98-a475-92205e62d4d5		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17 November 2022 | 17:35
Certified Delivered	Security Checked	17 November 2022 | 20:17
Signing Complete	Security Checked	17 November 2022 | 20:17
Completed	Security Checked	18 November 2022 | 12:51

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures