ModernaTX, Inc.

Protocol mRNA-1010-P304

A Phase 3, Randomized, Observer-blind, Active-controlled, Case-driven Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Seasonal Influenza Vaccine Compared with a Licensed Inactivated Seasonal Influenza Vaccine in Adults ≥ 50 Years of Age

Statistical Analysis Plan

Version: 2.0

Date: 02JUN2025

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DOCUMENT HISTORY

Version	Date	Description of major updates
2.0	02JUN2025	1. Clarified that the hypothesis testing at the IA will be performed with the full 1-sided alpha of 2.5%, given the case accrual has exceeded the total target of CCI for the study (powered for the primary NI objective) per the ongoing case monitoring, in Sections 4.3 and 6.6, as well as in statistical analyses in Section 6.3.1.2. 2. Added a supportive analysis for the primary analysis using all RT-PCR confirmed protocol-defined ILI cases starting from vaccination to the end of the influenza season. 3. Added an age subgroup (≥ 65 to < 75 years old) in Table 3 of Section 6.1. 4. Added a summary of solicited AR eDiary compliance in Section 6.5.1. 5. Updated the threshold for summarizing common unsolicited AE PTs from 1% to 0.3% due to the large sample size in Section 6.5.2.2. 6. Updated the SMQ list in Appendix I. 7. updated description of two ICEs (prohibited medication use and non-study influenza vaccine use, Appendix J).
1.0	19FEB2025	Version 1.0 based on the study protocol amendment 1 dated 12FEB2025.

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LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BMI	Body Mass Index
CCISS	Case-control immunogenicity subset
CEAC	Cardiac Event Adjudication Committee
CDC	Centers For Disease Control and Prevention
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Concomitant Medication
CoP	Correlate of Protection
COPD	Chronic Obstructive Pulmonary Disease
CoR	Correlate of Risk
COVID-19	Coronavirus Disease 2019
CP	Conditional Power
DBL	Database Lock
DCO	Data Cut-off
DSMB	Data and Safety Monitoring Board
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eDiary	electronic Diary
EFS	Edmonton Frail Scale
EoS	End of Study
FAS	Full Analysis Set
GBS	Guillain-Barre Syndrome
GLSM	Geometric Least Square Mean
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio

GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
HCP	Healthcare Professional
HELLP	Hemolysis, Elevated Liver Enzymes, and Low Platelet Count
HR	Hazard Ratio
IA	Interim Analysis
IcEv	Intercurrent Event
ILI	Influenza-Like Illness
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
MN	Microneutralization
mRNA	Messenger Ribonucleic Acid
NH	Northern Hemisphere
NI	Noninferiority
NIM	Noninferiority Margin
NP	Nasopharyngeal
PP	Per-Protocol
PPIS	Per-Protocol Immunogenicity Subset
PPISMN	Per-Protocol Immunogenicity Subset for MN Assay
PT	Preferred Term
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
rVE	relative Vaccine Efficacy
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAS	Statistical Analysis System
SMQ	Standardized MedDRA Queries
SoA	Schedule of Activities
SOC	System Organ Class
SS	Sample Size
TIV	Trivalent Influenza Vaccine
ULOQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1. Introduction

This SAP, which describes the planned analyses for Study mRNA-1010-P304, is based on the most recent approved study protocol amendment 1, dated 12FEB2025, and the most recent approved eCRF, Version 177 dated 30Apr2025.

In addition to the information presented in the statistical analyses section of the protocol (Section 9.4), which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. This SAP also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

PPD Biostatistics and Programming team, the designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the efficacy, immunogenicity, and safety. SAS Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the planned IA and treatment unblinding for the study.

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

2. Study Objectives

2.1. Primary Objectives

The primary objective is to evaluate:

- The safety and reactogenicity of mRNA-1010
- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains

2.2. Secondary Objectives

The secondary objectives are to evaluate:

- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains

- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains
- The humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 2400 participants
- The HAI titers as a surrogate of risk and protection against RT-PCR-confirmed protocol-defined ILI (CoR and CoP) for mRNA-1010 and an active comparator

2.3. Exploratory Objectives (May be Performed)

The following exploratory objectives may be performed to evaluate:

- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed CDC-defined ILI caused by any influenza A or B strains
- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed WHO-defined ILI caused by any influenza A or B strains
- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) caused by any influenza A or B strains
- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed influenza infection regardless of whether clinical symptoms meet ILI case definitions
- The rVE of mRNA-1010 versus an active comparator against culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI caused by any influenza A or B strains
- The rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with similarity and/or antigenic match to the vaccine strains
- The humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains measured by MN assay in a subset of participants
- The characteristics of the cellular immune response of mRNA-1010 versus an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 200 participants

- The characteristics of the effect of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains by baseline frailty status in participants ≥ 65 years of age
- The rVE of mRNA-1010 versus an active comparator to prevent health outcomes associated with RT-PCR-confirmed protocol-defined ILI
- The effect of mRNA-1010 versus an active comparator on the frequency of reported symptoms of RT-PCR-confirmed protocol-defined ILI
- The further characteristics of the pre-existing immune responses as well as the immune responses to mRNA-1010 and an active comparator

3. Study Endpoints

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Solicited local and systemic ARs from Day 1 (Baseline) to Day 7 in a subset of approximately 6000 participants
- All unsolicited AEs from Day 1 to Day 28
- MAAEs from Day 1 (Baseline) to Month 6 (Day 181)
- AEs leading to discontinuation from Day 1 (Baseline) to Month 6 (Day 181)
- SAEs from Day 1 to Month 6 (Day 181)
- AESIs from Day 1 (Baseline) to Month 6 (Day 181)

3.1.2. Primary Efficacy Endpoint

- The first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains

The definition of RT-PCR-confirmed protocol-defined ILI is further defined in Section 6.3.1.1

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints

- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains
- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza A or B strains with the antigenic match to the vaccine strains
- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza A or B strains with the antigenic match to the vaccine strains

The definitions of the secondary efficacy endpoints are further provided in Section 6.3.2.

3.2.2. Secondary Immunogenicity Endpoints

- GMT on Day 29 as measured by HAI
- Proportion of participants reaching seroconversion on Day 29 as measured by HAI
- Frequency of participants with an HAI titer ≥ 1:40 on Day 29
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI

The definitions of GMT and GMFR are further provided in Section 6.4.2. The secondary immunogenicity endpoints above will be based on a subset of approximately 2400 participants and the details of the subset are provided in Section 5.4.

- The HAI titers on Day 29
- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains

3.3. Exploratory Endpoints (May be Performed)

3.3.1. Exploratory Efficacy Endpoints

- First episode of RT-PCR-confirmed CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza A or B strains

- First episode of RT-PCR-confirmed WHO-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains
- First episode of RT-PCR-confirmed ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains
- First episode of RT-PCR-confirmed influenza infection that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains regardless of whether clinical symptoms meet ILI case definitions
- First episode of culture-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains
- First episode of culture-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains
- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains with similarity and/or antigenic match to the vaccine strains
- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains with similarity and/or antigenic match to the vaccine strains
- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains in participants ≥ 65 years of age by baseline EFS status
- Frequencies of symptoms in cases of protocol-defined ILI with RT-PCR confirmation and regardless of RT-PCR confirmation

The definitions of RT-PCR-confirmed CDC-defined ILI, WHO-defined ILI, ILI as defined in mRNA-1010-P302, and culture-confirmed influenza infection are further provided in Section 6.3.3.

3.3.2. Exploratory Immunogenicity Endpoints

- GMT on Day 29 as measured by MN assay
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by MN assay

- T-cell response after mRNA-1010 or active comparator in a subset of 200 participants

3.3.3. Endpoints Described in Separate Analysis Plans

Analyses of the following endpoints will be presented in separate analysis plans:

- Secondary endpoint: CoR and CoP of influenza illness to be evaluated basing on HAI titers after study vaccination (i.e., Day 29 HAI titers) among participants with an episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains with and without similarity or antigenic match to the vaccine strains.
- The following exploratory endpoints in the cases of protocol-defined ILI with and without RT-PCR confirmation that begin at least 14 days after study vaccination through the end of the influenza season:
    - Pneumonia beginning within 30 days after respiratory symptom onset
    - New onset or exacerbation of cardiorespiratory disease (e.g., CHF, COPD, asthma) beginning within 30 days after respiratory symptom onset
    - Healthcare encounters (e.g., hospitalization, emergency room visit, outpatient visit) beginning within 30 days after respiratory symptom onset

4. Study Design

4.1. Overall Study Design

This is a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 versus an active comparator in adults ≥ 50 years of age. Approximately 56,000 participants are planned to be randomized in 2 seasons (NH 2024-2025 and NH 2025-2026), with approximately CCI of participants to be enrolled in the first season. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator (Table 1). Randomization will be stratified by age category (≥ 50 to < 65 years or ≥ 65 years) at Screening and influenza vaccine status in the previous influenza season (received or not received). Approximately 50% of enrolled participants will be ≥ 65 years of age at Screening, including approximately 10% who are ≥ 75 years of age at Screening. See protocol Section 4.1 for details.

The study duration (including screening) is expected to be approximately 6 to 8 months for each participant but could be longer if the influenza season is longer than expected. Participants will have up to 3 in-person visits (Screening, Day 1 [Baseline], and Day 29) and up to 4 telephone contacts (Day 8, Month 3 [Day 91], Month 6 [Day 181], and the End of the Influenza Season Visit). Additionally, in-person unscheduled visits will be arranged for participants who meet the criteria for protocol-defined respiratory illness.

Table 1: Treatment Groups and Dose Levels

Intervention Name	mRNA-1010	Active Comparator (Fluarix, Fluarix Tetra, Influsplit Tetra, Alpharix Tetra)
Unit Dose Strength	37.5 µg of mRNA	45 µg (TIV) or 60 µg (QIV) of protein
Dosage Volume	Single dose of 0.5 mL	Single dose of 0.5 mL
Route of Administration	IM	IM

Abbreviations: IM = intramuscular; mRNA=messenger ribonucleic acid; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.

4.2. Statistical Hypotheses

The primary efficacy objective of this study is to evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains. Cases will be counted starting 14 days after study vaccination. The testing sequences for the primary endpoint are displayed in

Figure 1.

The null hypothesis to be tested first is the rVE of mRNA-1010 versus an active comparator is inferior, CCI

CCI

The rVE is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs. active comparator). Equivalently, the null hypothesis to be tested can be formulated in terms of an HR: CCI

The study will be considered to meet the primary efficacy objective by demonstrating the NI of mRNA-1010 to an active comparator if the CCI at the IA or final analysis on the PP Set (see Section 5.3 and Section 6.6.1).

Once NI is demonstrated, rVE will be further evaluated using the same endpoint for superiority. The null hypothesis to be tested is:

CCI

Equivalently, the null hypothesis can be formulated as CCI

The superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be concluded if the CCI at the IA or final analysis on the PP Set. If superiority is demonstrated, the rVE will be further evaluated using the same endpoint for super-superiority. The null hypothesis to be tested is:

CCI

Equivalently, the null hypothesis can be formulated as CCI

Super-superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be concluded if the CCI

CCI [redacted] at the IA or final analysis on the PP Set.

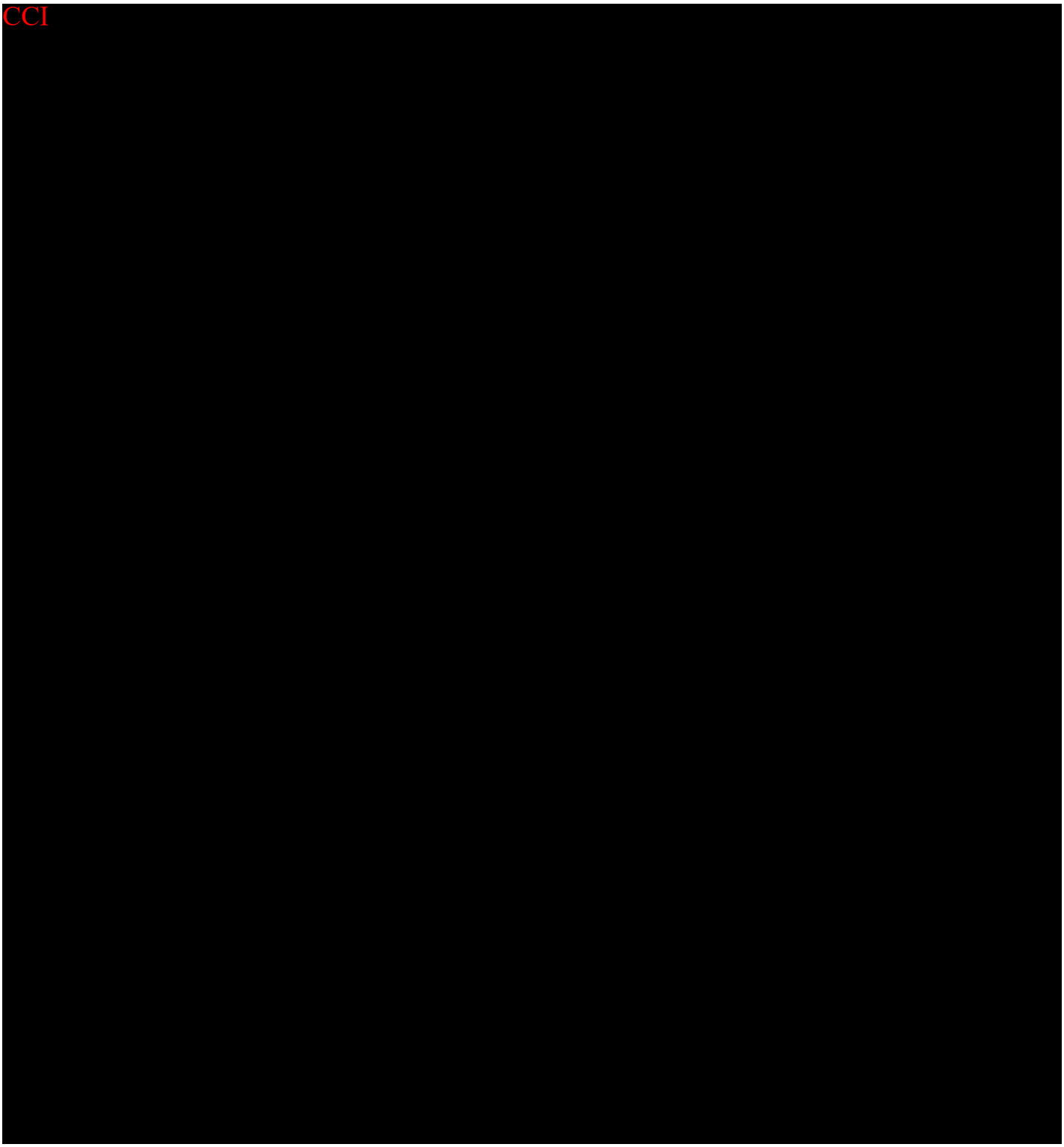
In summary, the type I error rate is controlled for the primary efficacy endpoint:

1) over the sequence of hypotheses: NI, superiority and super-superiority, using a hierarchical sequential procedure; and

2) over the two (potential) planned analyses: interim analysis (end of season 1), and final analysis (if season 2 is warranted), using CCI [redacted].

CCI [redacted]

Figure 1. CCI



4.3. Sample Size and Power

The sample size is driven by the total number of cases to demonstrate NI in terms of rVE (mRNA-1010 vs. active comparator) to prevent the first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination caused by any influenza A or B strains.

A total of CCI in the PP Set will provide at least CCI power to establish an NI claim with a selected CCI assuming a true rVE of 10% using a log-rank test statistic with an overall 1-sided Type I error rate of 2.5%. Approximately 56,000 participants are needed to accrue CCI.

The calculations were performed with the following additional assumptions:

CCI

CCI The actual nominal alpha will be adjusted based on the actual information fraction at the IA (see Section 6.6.1).

Once NI is demonstrated at either the IA or the final analysis, rVE will be further evaluated using the same endpoint for the superiority of mRNA-1010 versus an active comparator. After superiority is demonstrated, at the IA or final analysis, the rVE will be further evaluated using the same endpoint for the super-superiority of mRNA-1010 versus the active comparator with a super-superiority margin of CCI

Following the hierarchical testing procedure described in

Figure 1, the NI, superiority, and super-superiority hypotheses will be tested for the two secondary efficacy endpoints (see Section 4.2), as appropriate. CCI [redacted]

Due to the unusually high transmission activity for the 2024-2025 influenza season, the case accrual was faster than expected. Per the ongoing case monitoring during the season, the case accrual has exceeded the total target of CCI [redacted] for the study (powered for the primary NI objective). The full 1-sided alpha of 2.5% will be allocated to the end of season 1 analysis for NI, superiority and super-superiority hypothesis testing in sequential order.

The Sponsor will have the ultimate responsibility for the decision of further enrollment.

The sample size and power calculations are based on the log-rank test for a survival endpoint using EAST® software (version 6.5.2).

4.4. Randomization

Randomization will be performed using an IRT. Approximately 56,000 participants are planned to be randomized in 2 seasons, with approximately CCI [redacted] of participants to be enrolled in the first season. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator (see Table 1). Randomization will be stratified by age category (≥ 50 to < 65 years or ≥ 65 years) at Screening and influenza vaccine status in the previous influenza season (received or not received). Approximately 50% of enrolled participants will be ≥ 65 years of age at Screening, including approximately 10% who are ≥ 75 years of age at Screening.

4.5. Blinding and Unblinding

This is an observer-blinded study in which the investigator, blinded study personnel, participants, blinded site monitors, and blinded 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 listed in Section 6.4 of the protocol. An independent unblinded statistical and programming team will perform the pre-planned IA. Sponsor team members will be prespecified to be unblinded to the IA and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants.

The DSMB may review data, as appropriate, to safeguard the interests of participants and to help ensure the integrity of the study.

5. Analysis Sets

5.1. Randomization Set

All participants who are randomized, regardless of the participants' treatment status in the study. Participants will be analyzed according to the treatment group to which they are randomized.

5.2. Full Analysis Set (FAS)

All randomized participants who received any study vaccination. Participants will be analyzed according to the treatment group to which they are randomized.

5.3. Per-Protocol Set (PP Set)

All participants in the FAS, excluding those with important protocol deviations that could adversely impact efficacy (e.g., disease or therapeutic intervention that might cause a suboptimal response to study vaccination). The PP Set will be used as the primary analysis set for efficacy endpoints. The PPS will be decided blindly by the blinded study team before the database lock for the interim or final analysis. Participants will be analyzed according to the study vaccination group to which they are randomized.

5.4. Immunogenicity Subset

A prespecified subset of participants in the FAS and have Day 1 (Baseline) and Day 29 humoral immunogenicity samples. Participants will be analyzed according to the study vaccination group to which they are randomized.

Additional information on the sampling of the Immunogenicity Subset is defined in Section 6.4.1.

5.5. Per-Protocol Immunogenicity Subset (PPIS)

All participants in the Immunogenicity Subset who received the planned dose of study vaccination and had no important protocol deviations that impacted the immunogenicity assessment. Participants with RT-PCR-confirmed influenza infection between Day 1 (Baseline) and Day 29 will be removed from the PPIS. PPIS will be decided blindly by the blinded study team before the database lock for the interim or final analysis.

The PPIS will be used for all analyses of immunogenicity measured by HAI assay unless specified otherwise. Participants will be analyzed according to the study vaccination group to which they are randomized. The PPIS may also be used for the analysis of immunogenicity measured by MN assay.

For PP Set and PPIS, 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 2**).

Table 2: Major Dosing Errors

Randomized Vaccine	Actual Vaccine Received	Major Dosing Errors
mRNA-1010 37.5 ug	mRNA-1010 < 75% of planned volume or dose	Yes
	mRNA-1010 ≥ 75% to ≤ 125% of planned volume or dose	No
	mRNA-1010 > 125% of planned volume or dose	Yes
	Any active comparator > 0 volume or dose	Yes
Active comparator	Active comparator < 75% of planned volume or dose	Yes
	Active comparator ≥ 75% to ≤ 125% of planned volume or dose	No
	Active comparator > 125% of planned volume or dose	Yes
	Any mRNA-1010 > 0 volume or dose	Yes

5.6. Safety Set

All randomized participants who received any study vaccination. The Safety Set will be used for all analyses of safety except for solicited ARs. Participants will be analyzed according to the study vaccination they actually received.

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

- mRNA-1010 37.5 µg group: if the received dose of mRNA-1010 is > 0 µg or mL, and any active comparator (QIV or TIV) is 0 µg or mL
- Active comparator group: If the received dose of any active comparator (QIV or TIV) is > 0 µg or mL, and mRNA-1010 is 0 µg or mL

5.7. Solicited Safety Subset

All randomized participants who are in a subset of approximately 6000 participants assigned via IRT, received any study vaccination and contributed any solicited AR data in the Reactogenicity eDiary. The Solicited Safety Subset will be used for all analyses of solicited ARs. Participants will be analyzed according to the study vaccination they actually received.

For the Solicited Safety Subset, the dosing ranges to be used to determine the participant's actual treatment group follow the ranges listed under the Safety Set.

6. Statistical Analysis

6.1. General Considerations

SoA 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, median, min, and max. For the summary statistics of all numerical variables, unless otherwise specified, the display precision will follow programming standards (see Section 9.3).

Categorical variables will be summarized using counts and percentages. 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" may 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 the study vaccine injection unless otherwise specified.

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

Vaccination groups: the following vaccination groups will be used for summary purposes:

- mRNA-1010 37.5 µg
- Active comparator (combining QIV and TIV)

All analyses and data summaries/displays will be provided by the vaccination group using the 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 injection will be calculated as: date of assessment/event – date of injection +1.

Unscheduled visits: measurements from the unscheduled visit will be included in the 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 9.2.

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 the 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, and it includes 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 data cutoff date: this period starts from the day of vaccination and continues through the data cutoff date applied at planned interim analyses as specified in Section 6.6.1.
- Throughout the study: this period starts on Day 1 and continues through the earliest of the following: study completion, discontinuation from the study, Day 181 (for safety reporting), or death.

For the IA, the analysis will include all participants' efficacy, immunogenicity, and safety data collected up to a DCO Date. DCO determination will be based on the end of the first influenza season when approximately CCI of target cases are expected to have accrued in the PP Set. The definition of the end of the first influenza season is provided in Protocol Section 4.4.1.

Incomplete/Missing Data: the following imputation rules will be implemented:

- Imputation rules for missing or partial dates of prior/concomitant medications, non-study vaccinations and procedures are provided in Section 9.4.
- Imputation rules for missing or partial AE dates are provided in Section 9.5.
- For summarizations of GMTs, antibody titers reported as below LLOQ will be replaced by 0.5 x LLOQ. Values that are greater than ULOQ will be converted to the ULOQ.
- Other incomplete/missing data will not be imputed unless otherwise specified.

Subgroup: the following subgroup analyses may be implemented for efficacy, immunogenicity, or safety (Table 3). Subgroups may also be combined with other subgroups as appropriate.

Table 3: Definitions of Subgroups

Subgroup Variable [a]	**Categories**
Age group	≥ 50 to < 65 years old ≥ 65 to < 75 years old ≥ 65 years old ≥ 75 years old
Flu vaccine status in the previous influenza season [b]	Received Not received
Race	White Black or African American Asian American Indian, Alaska Native, Native Hawaiian or Other Pacific Islander Other (including Not Reported and Unknown)
Sex assigned at birth	Male Female
BMI	< 30 kg/m^2 ≥ 30 kg/m^2

Baseline Frailty Score (in Participants aged 65 and older) [b]	Fit (0-3) Vulnerable (4-5) Frail (6 or more)
Regions [b]	North America Europe Rest of the World
Active Comparator Type [b]	Countries using TIV Active Comparator (North America) Countries using QIV Active Comparator (Not North America)
High-risk status [c]	High-risk Non-high-risk

a. Subgroup derivations will be based on the information from eCRF.
b. The subgroup analysis will only be performed for the efficacy or immunogenicity endpoints.
c. The high-risk derivation is provided in Appendix J.

6.2. Background Characteristics

6.2.1. Participant Dispositions

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

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

The percentage of participants who screened failure 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 the screen failure participants with reasons for screen failure. Participants who were randomized and 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 the Randomization Set, Safety Set, PP Set, Immunogenicity Subset, and PPIS:

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

A participant disposition listing for the Randomization Set will be provided, including the date of the informed consent, date/time of study injection, date of end of the study, disposition status, and reason for early discontinuation if not completing the study.

The number and percentage of participants in the following categories (analysis sets defined in Section 5) will be summarized based on the Randomization Set, except for the calculation of Solicited Safety Subset, which the denominators of the percentages will be based on the participants in the Safety Set:

- Randomization Set
- FAS
- PP Set
- PPIS
- Safety Set
- Solicited Safety Subset

The number and percentage of participants in the following categories will be summarized based on the FAS:

- Immunogenicity Subset
- PPIS

A summary table will be generated for randomized participants by country and region for each vaccination group and overall. A separate summary table will include the number and percentage of randomized participants by stratification factors as randomized via IRT and actual stratification factors for each vaccination group and overall. Additionally, a comparison table between the IRT randomization stratum and the actual 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
- Weight (kg)
- Height (cm)

- 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 (≥ 50 to < 65 years old, ≥ 65 to <75 years old, ≥ 65 years old, or ≥ 75 years old)
- Sex assigned at birth (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not Reported)
- Previous Year's Flu Vaccine Status (Received/Not received)
- 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 the Solicited Safety Subset.

6.2.3. Medical History

Medical history data will be coded by SOC and PT using the MedDRA version 25.0.

The number and percentage of participants with any medical history will be summarized by SOC and PT for the 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.

6.2.4. Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and non-study vaccinations will be coded using the WHODD, version Mar 2022 or above. 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.

Categorizations of prior and concomitant medications are summarized in Section 9.4.

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:

- Any concomitant medications and non-study vaccinations up to 28 days post-injection.

- Non-study seasonal influenza vaccine, up to EoS 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 and up to EoS post-injection.

The number and percentages of participants with at least one concomitant medication will be summarized by PT and vaccination group. Prior, concomitant medications, and non-study vaccination will be presented in a listing.

6.2.5. Study Exposure

The number and percentage of participants who received vaccine injection on Day 1 visit, study duration ≥ 7 days after vaccine injection, study duration ≥ 28 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. Participants who had dosing errors will be presented in a separate listing.

6.2.6. Important Protocol Deviations

The study protocol deviations will be reviewed on a regular basis and categorized into “Important” and “Non-important”. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the key study data or that may significantly affect a participant’s rights, safety, or well-being. Important protocol deviations will be identified based on the protocol at the start of the study and during the conduct of the study and finalized before DBL by the study team. Important protocol deviation rules will be developed and finalized before DBL.

The number and percentage of the participants with any important protocol deviation in each category will be provided by treatment group and overall, based on the Randomization Set.

The important protocol deviations leading to exclusion from the PP Set and/or PPIS will be determined and documented by the study team prior to DBL and unblinding. Reasons for exclusion from PP Set and/or PPIS will be summarized by treatment group. Important protocol deviations will also be presented in a listing.

6.3. Efficacy Analysis

Efficacy analyses will be performed using the PP Set and FAS. Participants will be included in the vaccination group to which they are randomized. CCI [redacted]

Figure 1.

In general, unless otherwise specified, the results of the NI/superiority/super-superiority analysis will be presented in a table, the number and percentage of participants who had a specified RT-PCR-confirmed ILI case will be summarized by treatment group. The ILI symptoms associated with the first identified episode of the specified RT-PCR-confirmed ILI case will be summarized by treatment group. A listing of the symptoms associated with the first identified episode of the specified ILI case will be presented.

6.3.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains

6.3.1.1. Derivation Rules

The derivation rules to identify the first episode of RT-PCR-confirmed protocol-defined ILI are given below:

- The participant has a positive influenza RT-PCR result performed at the global central laboratory or a local certified laboratory **AND**
- The participant experienced CCI [redacted]

For a RT-PCR-confirmed protocol-defined ILI, the start date will be set as either the sample collection date of the positive RT-PCR result or the earliest qualified symptom onset date, whichever occurs earlier. The identified first episode of the RT-PCR-confirmed protocol-defined ILI will be defined as the first case, and the identified start date of the first case based on derivation will be defined as the date of the first case. Protocol-defined ILI symptoms that are associated with the first case will be determined based all ILI symptoms that onset within +/- 7 days of the sample collection date of the positive RT-PCR result that is used to define the first case.

6.3.1.2. Analysis Methods

Efficacy analyses will first be performed using the PP Set. The same analyses will be repeated using the FAS as defined in Section 6.3.1.2.1 if the number of events is different between the PP Set and FAS. Subjects will be included in the treatment group to which they were randomized. The testing sequences of the primary and secondary analyses are presented in Section 4.2.

To assess the efficacy endpoint for the primary objective, the number and percentage of participants that have a first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after the study vaccination, and participants that are censored will be summarized.

6.3.1.2.1. Primary Analysis for Noninferiority

The stratified Cox proportional hazards regression model will be used to estimate HR, which can be used to estimate rVE. The rVE is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs. active comparator) and will be estimated by 1-HR, multiplied by 100%:

$$rVE = 100 \times (1 - HR)\ \%$$

The rVE will be estimated, along with the 2-sided 95% CI for testing the null hypothesis:

CCI [redacted]

Based on the PP Set, the stratified Cox proportional hazard model with Efron's method of tie handling and treatment group as a fixed effect will be used to estimate HR (mRNA-1010 vs active comparator). The stratification factors at randomization: age category (≥ 50 to < 65 years or ≥ 65 years) and influenza vaccine status in the previous influenza season (received or not received), will be applied as the strata variables.

In the estimand of the primary endpoint, the strategies to address the intercurrent events are presented in Section 9.9.

Time to event and censoring rules are defined as follows:

- Participants with episode(s) of RT-PCR-confirmed protocol-defined ILI:
    - If the first episode starts at least14 days after the vaccination and up to the end of the influenza season:
        - Cases will be counted for the primary efficacy endpoint.

- The time to the first episode of RT-PCR-confirmed protocol-defined ILI, in days, will be calculated as the first case start date – date of study vaccination +1.

- If the first episode starts before 14 days after the vaccination (i.e., early RT-PCR-confirmed protocol-defined ILI):
  - Participants will be censored at the start date of the early RT-PCR-confirmed protocol-defined ILI.
  - The time to the censored date, in days, will be calculated as the censored date – date of study vaccination +1.

- Participants without any episodes of RT-PCR-confirmed protocol-defined ILI throughout the study:
  - Participants will be censored at the end of the influenza season, the data cutoff date, date of early discontinuation, date of completing of the study, or death unrelated to influenza, whichever is the earliest.
  - The time to the censored date, in days, will be calculated as the censored date – date of study vaccination +1.

The NI of mRNA-1010 to the active comparator will be demonstrated if the 1-sided *p-value* for rejecting CCI is less than the 1-sided 2.5% alpha level.

6.3.1.2.2. Analysis for Superiority

Once NI of mRNA-1010 versus an active comparator is demonstrated using the PP Set, the superiority of mRNA-1010 versus an active comparator will be evaluated using the same endpoint and method as described in Section 6.3.1.2.1 on the PP Set.

The superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be tested for the null hypothesis:

CCI

The superiority of mRNA-1010 to the active comparator will be demonstrated if the 1-sided *p-value* for rejecting CCI is less than the 1-sided alpha of 2.5%.

6.3.1.2.3. Analysis for Super-Superiority

Once superiority of mRNA-1010 versus an active comparator is demonstrated using the PP Set, the super-superiority of mRNA-1010 versus an active comparator will be evaluated using the same endpoint and method as described in Section 6.3.1.2.2 for superiority on the PP Set.

The super-superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be tested on the null hypothesis:

CCI [redacted]

The super-superiority of mRNA-1010 to the active comparator will be demonstrated if the 1-sided *p-value* for rejecting CCI [redacted] is less than the 1-sided alpha of 2.5%.

6.3.1.2.4. Supplementary Analysis

The supplementary analysis will be conducted on the FAS for the supplementary estimand defined in Table 13 in Section 9.9, to obtain the rVE estimate with 95% CI for the prevention of RT-PCR-confirmed protocol-defined ILI cases caused by any influenza A or B strains. The same estimation method will be used with the same rules for case derivations and censoring as the primary analysis applied.

6.3.1.2.5. Sensitivity Analysis

For the primary efficacy endpoint, a sensitivity analysis adjusting for the actual stratification factors will be performed using the PP Set. This sensitivity analysis is the same as the primary analysis except that it adjusts for the actual stratification factors.

Additional sensitivity analyses described below will be performed using a different analysis method:

- rVE will be estimated by 1minus the ratio of incidence rates multiplied by 100%:

$$\text{rVE} = 100 \times \left(1 - \frac{\text{Incidence rate in mRNA}-1010\text{ group}}{\text{Incidence rate in active comparator group}}\right) \%$$

The 95% CI of rVE will be computed using the exact method conditional upon the total number of cases adjusted by the total person-time. The same censoring rules as described for the primary efficacy analyses will be followed.

Cases of RT-PCR-confirmed protocol-defined ILI will be counted starting 14 days post-vaccination up to the end of the influenza season. For participants with a case, the person-time is calculated as: the time from randomization to the date of the first case. For participants without a case, the person-time is calculated as the time from randomization to the date of the end of the influenza season, the date of completing of the study, the date of the data cutoff, the date of early discontinuation, or the date of death unrelated to influenza, whichever is earliest. Then each participant's person-time is adjusted by 180 days to obtain person-season, i.e.

$$\text{person-season} = \text{person-time} / 180.$$

The total number of person-seasons for each vaccination group is the sum of the individual person-season in the vaccination group. The incidence rate per 1000 person-seasons for each vaccination group will be calculated as the number of participants with a case divided by the total person-season in each vaccination group multiplied by 1000.

Summaries of total person-season and incidence rate, 95% CI, and the adjusted 1-sided significance level based on the CCI for incidence rate will be provided by the vaccination group. The 95% CI and the adjusted 1-sided significance level of the incidence rate will be calculated using the exact method (Poisson regression) and adjusted by person-time.

- The Kaplan-Meier method will be used to estimate the cumulative incidence rates over time by vaccination group. The Kaplan-Meier curves will be plotted to show the estimated cumulative incidence rates over time by vaccination group. The same rules for counting RT-PCR-confirmed protocol-defined ILI cases and censoring rules as described for the primary analyses will be followed.

6.3.1.2.6. Supportive Analysis

The following supportive analyses may be performed using the same estimation methods as for the primary analysis in the PP set:

- To estimate the rVEs with 95% CIs for the prevention of RT-PCR-confirmed protocol-defined ILIs caused by different strains per the RT-PCR test:
    - RT-PCR confirmed protocol-defined ILIs caused by any influenza A strain per RT-PCR starting 14 days post-vaccination up to tthe end of the influenza season

        - RT-PCR confirmed protocol-defined ILIs caused by influenza strain A/H1N1 per RT-PCR starting 14 days post-vaccination up to the end of the influenza season
        - RT-PCR confirmed protocol-defined ILIs caused by influenza strain A/H3N2 per RT-PCR starting 14 days post-vaccination up to the end of the influenza season
        - RT-PCR confirmed protocol-defined ILIs caused by influenza A with an unknown strain per RT-PCR starting 14 days post-vaccination up to the end of the influenza season
    - RT-PCR confirmed protocol-defined ILIs caused by influenza B per RT-PCR starting 14 days post-vaccination up to the end of the influenza season

The time to the first episode will be calculated as: Start date of the first RT-PCR confirmed protocol-defined ILI with the specified RT-PCR influenza strain – Date of study vaccination +1.

Similar censoring rules as for the primary efficacy endpoint will be applied. Additionally, for an RT-PCR confirmed protocol-defined ILI case, if the influenza strain is different from the one being analyzed, the participant will be censored at the start date of the confirmed ILI case.

- To estimate the rVEs with 95% CIs for the prevention of RT-PCR confirmed protocol-defined ILIs caused by any influenza A or B strains starting 14 days post-vaccination up to the end of the influenza season, with the following co-infected cases excluded from the analysis:
    - co-infection of influenza with COVID-19 and/or respiratory syncytial virus (RSV) as confirmed by the RT-PCR respiratory test panel.
    - co-infection of influenza with any other respiratory virus as confirmed by the RT-PCR respiratory test panel.

Co-infections are identified from the same NP swab, or 2 NP swabs collected within +/- 3 days of the collection date of positive RT-PCR NP swab result used to identify the first case.

- To estimate the rVEs with 95% CIs for the prevention of RT-PCR confirmed protocol-defined ILIs caused by any influenza A or B strains starting post-vaccination up to the end of the influenza season:

Cases of RT-PCR-confirmed protocol-defined ILI will be counted starting from post-vaccination up to the end of the influenza season for the supportive analysis.

6.3.1.2.7. Subgroup Analysis

The effect of mRNA-1010 versus active comparator against RT-PCR confirmed protocol-defined ILI caused by any influenza A or B strains will be performed in subgroup analysis. The primary efficacy endpoint will be analyzed in selected subgroup (Table 3) based on the PP Set, using similar methods as described for the primary analysis (see Section 6.3.1.2.1 and Section 6.3.1.2.2). rVE analysis may not be performed within the subgroup if the combined number of cases from mRNA-1010 and the active comparator is less than 20. Subgroups may also be combined with other subgroups as appropriate. Forest plots will be provided for rVE and its 95% CI for the subgroup in which the rVE is performed based on the PP Set.

6.3.2. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains.
- First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza with antigenic match to the vaccine strains.
- First episode of RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza with antigenic match to the vaccine strains.

6.3.2.1. Derivation Rules

RT-PCR-confirmed modified CDC-defined ILI caused by any A/B strains:

The derivation rules to identify an RT-PCR-confirmed modified CDC-defined ILI are given below:

- The definition of RT-PCR-confirmed protocol-defined ILI is met (Section 6.3.1) **AND**
- The participant experienced CCI [redacted]

Once a case is identified after considering all RT-PCR-confirmed modified CDC-defined ILI derivation rules, the start date for the RT-PCR-confirmed modified CDC-defined ILI will be set as either the sample collection date of the positive RT-PCR result or the earliest qualified modified CDC-defined symptom onset date, whichever occurs earlier. The identified first episode of the RT-PCR-confirmed modified CDC-defined ILI will be defined as the first case, and the identified start date of the first case based on derivation will be defined as the date of the first case.

The time to the first episode of RT-PCR-confirmed modified CDC-defined ILI, in days, will be calculated as Date of first case – Date of study vaccination +1.

Cases will be counted for the secondary efficacy endpoint when the first episode of RT-PCR-confirmed modified CDC-defined ILI starts 14 days after the vaccination and up to the end of influenza season.

Fever, cough, and sore throat symptoms that are associated with the first episode of RT-PCR-confirmed modified CDC-defined ILI will be determined based on the following:

- Any fever, cough, and sore throat symptoms that onset within +/- 7 days of the sample collection date of the positive RT-PCR result that is used to define the first case.

RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains:

The derivation rule for RT-PCR-confirmed protocol-defined ILI is defined in Section 6.3.1.1. After the identification of the subtype information (A/H1, A/H3, A/Unknown, and B) for a positive RT-PCR test performed by the central laboratory, the viral culture test on the NP swab will be subsequently performed to match to the selected vaccine strain based on the identified subtype. If an unknown A subtype is obtained by the central laboratory RT-PCR test, the viral test will be performed to determine antigenic match to both vaccine selected A/H1N1 and A/H3N2 strains.

The derivation rules to identify RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains are given below:

- The definition of RT-PCR-confirmed protocol-defined ILI is met (Section 6.3.1), **AND**
- A matched culture test result to at least one of the selected vaccine strains exists within +/- 7 days of the positive RT-PCR collection date.

- If a local certified laboratory test is used for RT-PCR confirmation (without strain information), the culture test cannot be performed on the same NP swab sample. An NP swab sample may be collected and processed by the central laboratory. If another positive RT-PCR test from the central laboratory exists within 7 days of the positive RT-PCR collection date from the local certified laboratory, and the other positive RT-PCR test also has available subsequent culture test result, then the information from this test can be used to derive the antigenic match. If a positive RT-PCR test from the central laboratory does not exist to provide supplemental information within 7 days, then the antigenic match result will be considered missing.

The start date for the case will be set as either the sample collection date of the positive RT-PCR result or the earliest qualified symptom onset date, whichever occurs earlier. The time to the first RT-PCR-confirmed protocol-defined ILI caused by influenza with antigenic match, in days, will be calculated as: Date of the first case – Date of study vaccination +1.

Cases will be counted when the first RT-PCR-confirmed protocol-defined ILI caused by any strains with antigenic match starts 14 days after the vaccination and up to the end of the influenza season.

Protocol-defined ILI symptoms (as defined in Section 6.3.1.1) that are associated with the first case will be determined based on the following:

- Any ILI symptoms that onset within +/- 7 days of the sample collection date of the positive RT-PCR result that is used to define the first case.

RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains:

The derivation rules for RT-PCR-confirmed modified CDC-defined ILI, rules to identify influenza A or B strains with antigenic match to the vaccine strains, and derivation for start date/counting of cases/symptom associated with the first case follow the same derivation rules as described for RT-PCR-confirmed protocol-defined ILI caused by any A/B strains with antigenic match.

6.3.2.2. Analysis Methods

General considerations for efficacy analyses are described in Section 6.3.1.2. If super-superiority on the primary efficacy endpoint is demonstrated, the secondary efficacy endpoints will be

evaluated for NI, superiority, and super-superiority using the 1-sided significance level of 2.5% for NI, superiority, and super-superiority. The testing sequences for the selected secondary efficacy endpoints are displayed in

Figure 1.

The endpoint relating to RT-PCR-confirmed modified CDC-defined ILI caused by influenza with antigenic match to the vaccine strains is not part of the testing sequence as presented in

Figure 1 so there will be no NI or superiority hypotheses tested for this endpoint. For this endpoint, the same stratified Cox proportional hazards regression model method as described in Section 6.3.1.2.1 will be used to estimate HR based on the PP Set. Relative vaccine efficacy will be estimated with a two-sided 95% CI based on the PP Set.

6.3.2.2.1. Analysis for Noninferiority, Superiority, and Super-superiority

To assess the following secondary efficacy endpoints, the same stratified Cox proportional hazards regression model will be used to estimate HR based on the PP Set as described in Section 6.3.1.2.1 for testing the NI hypothesis. Once the NI of mRNA-1010 versus an active comparator is demonstrated, the same method will be used to evaluate the secondary efficacy endpoints for testing the superiority hypothesis.

The potential intercurrent events and intercurrent event handling approach for the occurrence of secondary efficacy endpoints are similar to the primary efficacy endpoint. (Section 9.9). For the intercurrent event of RT-PCR-confirmed protocol-defined ILI not meeting the definitions of the secondary endpoints, the hypothetical strategy is applied and the subject will be censored at the occurrence of the event.

The testing order of the NI hypothesis and superiority hypothesis of each of the secondary endpoints are presented below:

- **The first Secondary efficacy endpoint: RT-PCR-confirmed modified CDC-defined ILI caused by any A/B strains**:

The endpoint will be tested based on the following NI hypothesis:

CCI [redacted]

Once NI of mRNA-1010 versus an active comparator is demonstrated using the PP Set based on the first secondary endpoint, the superiority of mRNA-1010 versus an active comparator will be evaluated for testing the superiority hypothesis:

CCI [redacted]

Once superiority of mRNA-1010 versus an active comparator is demonstrated using the PP Set based on the first secondary endpoint, the super-superiority of mRNA-1010 versus an active comparator will be evaluated for testing the super-superiority hypothesis:

CCI [redacted]

- **The second secondary efficacy endpoint: RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains**

If NI, superiority, super-superiority of mRNA-1010 versus an active comparator are demonstrated based on the first secondary endpoint, the second secondary endpoint will be evaluated for NI.

CCI [redacted]

Once NI of mRNA-1010 versus an active comparator is demonstrated using the PP Set based on the second secondary endpoint, the superiority of mRNA-1010 versus an active comparator will be evaluated for testing the superiority hypothesis:

CCI [redacted]

Once superiority of mRNA-1010 versus an active comparator is demonstrated using the PP Set based on the second secondary endpoint, the super-superiority of mRNA-1010 versus an active comparator will be evaluated for testing the super-superiority hypothesis:

CCI [redacted]

6.3.2.2.2. Additional Analysis

The same estimation method will be used to obtain the rVE estimates with 95% CIs on the FAS, as supplementary analyses. Sensitivity and subgroup analyses may be performed using methods described for the primary efficacy endpoint, if the noninferiority analyses are performed for the two secondary efficacy endpoints following the pre-specified testing sequence (

Figure 1).

The following supportive analyses will be performed using the same estimation methods as for the corresponding supportive analyses for the primary efficacy endpoint:

- To estimate the rVE with 95% CIs for the prevention of RT-PCR-confirmed modified CDC-defined ILIs caused by different influenza strains per the RT-PCR test:
  - RT-PCR confirmed modified CDC-defined ILIs caused by any influenza A strain per RT-PCR starting 14 days post-vaccination up to the end of the influenza season.
    - RT-PCR confirmed modified CDC-defined ILIs caused by influenza strain A/H1N1 per RT-PCR starting 14 days post-vaccination up to the end of the influenza season.
    - RT-PCR confirmed modified CDC-defined ILIs caused by influenza strain A/H3N2 per RT-PCR starting 14 days post-vaccination up to the end of the influenza season.
    - RT-PCR confirmed modified CDC-defined ILIs caused by influenza A with an unknown strain per RT-PCR starting 14 days post-vaccination up to the end of the influenza season.
  - RT-PCR confirmed modified CDC-defined ILIs caused by influenza B per RT-PCR starting 14 days post-vaccination up to the end of the influenza season.
- To estimate the rVE with 95% CIs for the prevention of RT-PCR confirmed protocol-defined ILIs with the antigenic match to the specific influenza strains contained in the vaccine:
  - RT-PCR confirmed protocol-defined ILIs with the antigenic match to either the A/H1N1 influenza strain or the A/H3N2 influenza strain contained in the vaccine starting 14 days post-vaccination up to the end of the influenza season.
    - RT-PCR confirmed protocol-defined ILIs with the antigenic match to the influenza A /H1N1 strain contained in the vaccine starting 14 days post-vaccination up to the end of the influenza season.
    - RT-PCR confirmed protocol-defined ILIs with the antigenic match to the influenza A /H3N2 strain contained in the vaccine starting 14 days post-vaccination up to the end of the influenza season.

- RT-PCR confirmed protocol-defined ILIs with the antigenic match to the influenza B/Victoria strain contained in the vaccine starting 14 days post-vaccination up to the end of the influenza season.

6.3.3. Analysis of Exploratory Efficacy Endpoints

The exploratory efficacy objectives will be assessed based on the exploratory endpoints described in the following sections. Except the efficacy endpoints of protocol-defined ILI regardless of RT-PCR confirmation and RT-PCR-confirmed influenza infection regardless of whether clinical symptoms meet ILI case definitions, all the other exploratory efficacy endpoints will only be derived among the participants who have an event of the primary efficacy endpoint.

6.3.3.1. Derivation Rules for RT-PCR-Confirmed CDC-Defined ILI

The first episode of RT-PCR-confirmed CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains regardless of vaccine match will be analyzed.

The RT-PCR-confirmed CDC-defined ILI is defined as:

- The definition of RT-PCR-confirmed protocol-defined ILI is met (Section 6.3.1) **AND**
- The participant experienced CCI [redacted]

The derivation rules to identify the first episode of RT-PCR-confirmed CDC-defined ILI are similar to the deviation rules as described for the primary efficacy endpoint (Section 6.3.1.1) based on the specified CDC-defined ILI symptoms.

The derivation for case starts date, counting of cases, and symptom associated with the first RT-PCR-confirmed CDC-defined ILI defined as follows:

- The start date for the RT-PCR-confirmed CDC-defined ILI will be set as either the sample collection date of the positive RT-PCR result or the earliest qualified CDC-defined ILI symptom onset date, whichever occurs earlier.
- Cases that start 14 days after the vaccination and up to the end of the influenza season will be counted.

- The time to the first episode of first RT-PCR-confirmed CDC-defined ILI (days) = Date of first case – Date of study vaccination +1.
- CDC-defined ILI symptoms that are associated with the first case will be determined based on the ILI symptoms that onset within +/- 7 days of the sample collection date of the positive RT-PCR result that is used to define the first case.

6.3.3.2. Derivation Rules for RT-PCR-Confirmed WHO-Defined ILI

The first episode of RT-PCR-confirmed WHO-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains regardless of vaccine match will be analyzed.

The WHO-defined ILI is defined as:

- The participant experienced an acute respiratory infection with a measured fever of ≥ 38.0°C (≥ 100.4°F) and cough, with the onset date occurring within the last 10 days (-10 days) of the sample collection date of the positive RT-PCR result.

The derivation rules to identify the first episode of RT-PCR-confirmed WHO-defined ILI are similar to the deviation rules as described for the primary efficacy endpoint (Section 6.3.1.1) based on the specified WHO-defined ILI symptoms:

- The definition of RT-PCR-confirmed protocol-defined ILI is met (Section 6.3.1) **AND**
- The participant experienced an acute respiratory infection with a measured fever of ≥ 38.0°C (≥ 100.4°F) and cough that onset within +/- 7 days of the sample collection date of the positive RT-PCR result and within +/- 10 days from each other.

The derivation for case starts date, counting of cases, and symptom associated with the first RT-PCR-confirmed WHO-defined ILI is defined as follows:

- The start date for the RT-PCR-confirmed WHO-defined ILI will be set as the earliest qualified WHO-defined ILI symptom onset date.
- Cases that start 14 days after the vaccination and up to the end of the influenza season will be counted.
- The time to the first episode of first RT-PCR-confirmed WHO-defined ILI (days) = Date of first case – Date of study vaccination +1.

- WHO-defined ILI symptoms that are associated with the first case will be determined based on the ILI symptoms that onset within 10 days (+/- 10 days) of the sample collection of the positive RT-PCR result date that is used to define the first case.

6.3.3.3. Derivation Rules for RT-PCR-Confirmed ILI as Defined in mRNA-1010-P302

The first episode of RT-PCR-confirmed ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains regardless of vaccine match will be analyzed.

The RT-PCR-confirmed ILI as defined in mRNA-1010-P302 is defined as:

- The definition of RT-PCR-confirmed protocol-defined ILI is met (Section 6.3.1) **AND**
- The participant experienced CCI [redacted]

The derivation rules to identify the first episode of RT-PCR-confirmed ILI as defined in mRNA-1010-P302 are similar to the deviation rules as described for the primary efficacy endpoint (Section 6.3.1.1) based on the specified ILI symptoms as defined in mRNA-1010-P302.

The derivation for case start date, counting of cases, and symptom associated with the first RT-PCR-confirmed ILI as defined in mRNA-1010-P302 are defined as follows:

- The start date for the RT-PCR-confirmed ILI as defined in mRNA-1010-P302 will be set as either the sample collection date of the positive RT-PCR result or the earliest qualified mRNA-1010-P302-defined ILI symptom onset date, whichever occurs earlier.
- Cases that start 14 days after the vaccination and up to the end of the influenza season will be counted.
- The time to the first episode of first RT-PCR-confirmed ILI as defined in mRNA-1010-P302 (days) = Date of first case – Date of study vaccination +1.

ILI symptoms as defined in mRNA-1010-P302 that are associated with the first case will be determined based on the ILI symptoms that onset within +/- 7 days of the sample collection date of the positive RT-PCR result that is used to define the first case.

6.3.3.4. Derivation Rules for RT-PCR-Confirmed Influenza Infection

The first episode of RT-PCR-confirmed influenza infection that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains regardless of whether clinical symptoms meet ILI case definitions is defined as:

- The first positive RT-PCR result obtained at the global central Laboratory or a local certified laboratory.

The derivation for case starts date and counting of cases for the first RT-PCR-confirmed influenza infection are defined as follows:

- The start date for the first RT-PCR-confirmed influenza infection will be set as:
  - the start date of the RT-PCR confirmed protocol-defined ILI, if the positive RT-PCR test result also identifies a protocol-defined ILI (Section 6.3.1.1);
  - the sample collection date of the positive RT-PCR result, otherwise.
- Cases will be counted when the first episode of RT-PCR-confirmed influenza infection starts 14 days after the vaccination and up to end of influenza season.
- The time to the first RT-PCR-confirmed influenza infection (days) = Start date for the first positive RT-PCR influenza infection – Date of study vaccination +1.

6.3.3.5. Derivation Rules for Culture-Confirmed Protocol-Defined ILI and Culture-Confirmed Modified CDC-Defined ILI

The First episode of culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by any influenza A or B strains with and without antigenic match to the vaccine strains will be analyzed.

The RT-PCR-confirmed protocol-defined ILI is defined in Section 6.3.1.1, and the RT-PCR-confirmed modified CDC-defined ILI is defined in Section 6.3.2.1.

The culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI is defined as:

- Identification of an RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1) or modified CDC-defined ILI (Section 6.3.2.1) with a positive RT-PCR-confirmed test, **AND**
- The positive RT-PCR result is confirmed by a culture test i.e. with the culture test result being either matched or not matched to the vaccine strain using the same or different stored NP-swab sample within +/- 7 days of the positive RT-PCR result.
    - If a local certified laboratory test is used for RT-PCR confirmation (without strain information), the culture test cannot be performed on the same NP swab sample. A NP swab sample may be collected and processed by the central laboratory. If another positive RT-PCR test from central laboratory exists within +/- 7 days of the positive RT-PCR date from local certified laboratory, and the other positive RT-PCR test also has available culture test result, then the participant is considered to have met the criteria for culture-confirmed influenza illness.

Matched cases are obtained with a culture test result of matched (Section 6.3.2.1) and mismatched cases are similarly obtained with a culture test result of not matched. Otherwise, if no culture test within +/- 7 days of the positive RT-PCR date exists with a matched or not matched result, the RT-PCR confirmed protocol-defined ILI cases will be considered as not culture-confirmed cases.

The derivation for case start date and counting of cases for culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI are defined as follows:

- The start date will be set as the start date of the RT-PCR confirmed protocol-defined ILI or the culture-confirmed modified CDC-defined ILI.
- Cases will be counted when the first episode starts 14 days after the vaccination and up to end of influenza season.
- The time to the first case (days) = Start Date of the first case – Date of study vaccination +1.

6.3.3.6. Derivation Rules for RT-PCR-Confirmed Protocol-defined ILI and Modified CDC-Defined ILI Caused by Influenza A or B Strains with Similarity and/or antigenic match to the Vaccine Strains

The first episode of RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI that begins at least 14 days after study vaccination through the end of the influenza season caused by influenza A or B strains with similarity and/or antigenic match to the vaccine strain will be analyzed.

The RT-PCR-confirmed protocol-defined ILI is defined in Section 6.3.1.1, and the RT-PCR-confirmed modified CDC-defined ILI is defined in Section 6.3.2.1.

After the identification of the subtype information (A/H1, A/H3, A/Unknown and B) for a positive RT-PCR test performed by the central laboratory, as for the viral culture test, the genomic sequencing test on the NP swab will be subsequently performed to obtain if the influenza strain is similar to the selected vaccine strain based on the identified subtype. If an unknown A subtype is obtained by the central laboratory RT-PCR test, the genomic sequencing test will be performed to determine similarity to both vaccine selected A/H1N1 and A/H3N2 strains.

The similarity and/or antigenic match to the vaccine strains is defined in (Table 4):

Table 4: Rules to Derive Similarity and Antigenic Match Using Culture Antigenic and Genetic Sequencing Test Results

		Sequencing test result		
		Similar	**Not Similar**	**Unknown/Not Reportable**
Culture antigenic testing result	**Matched**	Matched and Similar [a]	Matched and Similar [a]	Matched and Similar [a]
	Not Matched	Not Matched; Not Similar	Not Matched; Not Similar	Not Matched; Not Similar
	Unknown/Not Reportable	Similar but Unknown Antigenically [a]	Not Similar and Unknown Antigenically	Unknown for Both

a. Will be considered as similarity and/or antigenic match to the vaccine strains. Culture antigenic results will override discrepancy with the sequences based on prediction due to recognized uncertainties in predicting antigenic distance using influenza gene segments.

A/B strains with similarity and/or antigenic match to the vaccine strains are defined as follow:

- Identification of an RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1) or modified CDC-defined ILI (Section 6.3.2.1) with a positive RT-PCR-confirmed test, **AND**
- A genomic sequencing and/or a culture test with the sequencing and culture test results being "Matched and Similar" or "Similar but Unknown Antigenically" (Table 3) using the same or different stored NP-swab sample exist within +/- 7 days of the positive RT-PCR result.
    - If a local certified laboratory test is used for RT-PCR confirmation (without strain information), the culture antigenic and genetic sequencing tests cannot be performed on the same NP swab sample. A NP swab sample may be collected and processed by the central laboratory. If another positive RT-PCR test from the central laboratory exists within +/- 7 days of the positive RT-PCR collection date from local certified laboratory with available culture antigenic and genetic sequencing test results, then the information from this test can be used to derive the similarity and/or antigenic match. If a positive RT-PCR test from the central laboratory does not exist to provide supplemental information within +/- 7 days, then the similarity and/or antigenic match results will be considered missing.

The derivation for case starts date, counting of cases, and symptom associated with the specified first RT-PCR-confirmed ILI caused by influenza A or B strains with similarity and/or antigenic match to the vaccine strains are defined as follows:

- The start date for the RT-PCR-confirmed ILI will be set as either the sample collection date of the positive RT-PCR result, or the earliest qualified symptom onset date, whichever occurs earlier.
- Cases that start 14 days after the vaccination and up to the end of the influenza season will be counted.
- The time to the first episode (days) = Date of first case – Date of study vaccination +1.

6.3.3.7. Derivation Rules for Protocol-Defined ILI Symptoms Regardless of RT-PCR Confirmation

Protocol-defined ILI symptoms regardless of RT-PCR confirmation is defined as:

- A systemic symptom with at least one respiratory symptom occurring at least 14 days after the vaccination that is within 14 days from the systemic symptom.
- A respiratory symptom with at least one systemic symptom occurring at least 14 days after the vaccination that is within 14 days from the respiratory symptom.

Symptoms will be counted from 14 days after the vaccination up to the end of influenza season.

6.3.3.8. Analysis Methods

For each of the exploratory efficacy endpoints discussed in Section 6.3.3.6 to Section 6.3.3.6, rVE will be estimated along with a two-sided 95% CI based on the PP Set and FAS set. The stratified Cox proportional hazards model will be used to estimate the HR, similar to the analyses performed for the secondary endpoints.

To characterize the effect of mRNA-1010 versus an active comparator against protocol-defined ILI caused by any influenza A or B strains by baseline frailty status, subgroup analysis will be performed by baseline frailty status (categorized as Fit: 0-3, Vulnerable: 4-5, Frail: 6 or more) for participants aged 65 years and older. The number of participants aged 65 years and older with any episode of RT-PCR-confirmed protocol-defined ILI by baseline frailty status will also be summarized.

To evaluate the effect of mRNA-1010 versus an active comparator on the frequency of reported symptoms of protocol-defined ILI regardless of RT-PCR confirmation, the number and percentages of participants experiencing specific ILI symptoms during the first episode of protocol-defined ILI regardless of RT-PCR confirmation will be summarized.

The potential intercurrent events and censoring rules for the occurrence of exploratory efficacy endpoints are similar to the primary efficacy endpoint. The same intercurrent event handling approach used for the primary efficacy endpoints will be used to address the intercurrent events for the analysis of exploratory efficacy endpoints (see Section 9.9).

6.3.4. CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4. Immunogenicity Analysis

The secondary immunogenicity endpoints will be analyzed using the PPIS (Section 5.5) and the Immunogenicity Subset (Section 5.4) by the vaccination group unless otherwise specified.

Immune responses, as measured by GMT and seroconversion rate in the mRNA-1010 group based on Day 29 HAI titers, will be compared to that in participants receiving the active comparator for all 3 strains (A/H1N1, A/H3N2, and B/Victoria).

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.

6.4.1. Sampling of Immunogenicity Subset

For the 2024 -2025 season, PPD independent unblinded biostatistician will select a stratified random sub-cohort of 3200 participants and provide the list of selected participants with only subject ID information. Should the study continue to a second season, a similar sampling may be selected, which will be pre-specified in a separate sampling plan before the final database lock.

After the last participant (except South Korea participants) in the first season completes the Day 29 visit, the random sub-cohort will be selected among participants in the FAS of the first season who have both Day 1 and Day 29 immunogenicity samples within each of the 8 strata and each of the

two treatment groups as shown in Table 5. The detailed steps of sampling and roles/responsibilities are provided in Immunogenicity Sampling Plan (Version 1.0, dated 10Mar2025).

- 2400 participants from North America

  The North America subset will be used to derive the Immunogenicity Subset and the PPIS.
- 800 participants from rest of the world.

Table 5: Number of Participants in the Stratified Random Sub-cohort

Actual Vaccine Received on Day 1	Stratified Random Sub-cohort [N=3200]								Total
	North America - Immunogenicity Subset [N =2400]				Rest of the World [N =800]				
	S1	S2	S3	S4	S5	S6	S6	S8	
mRNA-1010	300	300	300	300	100	100	100	100	1600
Active Comparator	300	300	300	300	100	100	100	100	1600
Total	600	600	600	600	200	200	200	200	3200

S1 to S8 are strata combination 1 to 8, basing on region, age, and flu vaccine status as following

	Region	Age in Years at Baseline [a]	Flu Vaccine in the Previous Flu Season [a]
S1	North America	>=50 to <65	Received
S2	North America	>=50 to <65	Not Received
S3	North America	>=65	Received
S4	North America	>=65	Not Received
S5	Rest of the World	>=50 to <65	Received
S6	Rest of the World	>=50 to <65	Not Received
S7	Rest of the World	>=65	Received
S8	Rest of the World	>=65	Not Received

a. based on the actual strata from the eCRF.

Immunogenicity Assessment

The following 3 strains will be measured by HAI:

- Influenza A/H1N1
- Influenza A/H3N2
- Influenza B/Victoria-lineage

6.4.2. Analysis of Secondary Immunogenicity Endpoints

- GMT on Day 29 as measured by HAI

The GMT 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*.

An ANCOVA model will be carried out. The model will include the log-transformed HAI titers on Day 29 as the dependent variable, treatment group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The 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.

The GMR for mRNA-1010 vs. active comparator, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference and calculated by back-transforming of the difference estimated from the ANCOVA model. The corresponding 2-sided 95% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 group compared to the active comparator group on Day 29.

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 in bar charts at each time point respectively.

- GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.

The GMFR will be calculated using the following formula:

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

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 same descriptive statistics and figures as GMT analysis will be provided for GMFR as measured by HAI with corresponding 95% CI on Day 29 over Day 1 (Baseline).

- Proportion of participants reaching seroconversion on Day 29 as measured by HAI.

The number and percentage of participants with seroconversion on Day 29 or HAI titer ≥ 1:40 on Day 29 will be provided with 2-sided 95% CI using the Clopper-Pearson method. To compare the seroconversion rates between the treatment groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in seroconversion rates on Day 29.

- Frequency of participants with an HAI titer ≥ 1:40 on Day 29.

The number and percentage of participants with HAI titer ≥ 1:40 on Day 29 will be provided with 2-sided 95% CI using the Clopper-Pearson method.

6.4.2.1. Subgroup Analysis

To assess the consistency of the immunogenicity response of mRNA-1010 across subgroups, subgroup analysis of the secondary immunogenicity endpoints may be conducted by subgroups defined by age group, previous year's flu vaccine status, race, sex, and BMI category (Table 3) based on PPIS. For each subgroup category, the immunogenicity endpoints will be analyzed using the same statistical methods as the analysis of secondary immunogenicity endpoints. Subgroup GMT, GMFR, GLSM, and seroconversion rates may be plotted as forest plots.

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

6.4.3. Analysis of Exploratory Immunogenicity Endpoints

- GMT on Day 29 as measured by MN assay.
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by MN assay.

The same ANCOVA model and descriptive statistics as methods used for the secondary analysis may be carried out for GMT on Day 29 as measured by MN assay (see Section 6.4.2). The GMT and GMFR with corresponding 95% CI will be plotted at each time point respectively.

- T-cell response after mRNA-1010 and active comparator in a subset of approximately 200 participants.

Descriptive statistics may be performed on cellular immunogenicity response.

6.5. Safety Analysis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Subset. All safety analyses will be provided by the vaccination group corresponding to the study vaccination that was actually received, unless otherwise specified.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs), unsolicited AEs (including any clinical safety laboratory abnormalities), treatment-related AEs, severe AEs, SAEs, MAAEs, AEs leading to discontinuation from study participation, AESIs, vital sign measurements, and physical examination findings.

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.

6.5.1. Solicited Adverse Reactions

Solicited local and systemic ARs will be collected only in a subset of approximately 6000 participants (defined as Reactogenicity Subset), which will be assigned via IRT.

Solicited ARs are predefined local and systemic events for assessment of reactogenicity. The term “reactogenicity” refers to the occurrence of transient adverse effects associated with study vaccination administration. The eDiary will solicit daily participant reporting of ARs using a structured checklist. Participants in the Reactogenicity Subset will record such occurrences in the eDiary on the day of study vaccination dosing and 6 subsequent days.

If a participant reports an event consistent with reactogenicity that starts after Day 7, it should not be recorded as reactogenicity in EDC, but as an AE. Causality for these events will be determined per assessment by the Investigator. However, any solicited AR that meets any of the following criteria must be entered into the participant’s source document and must also be recorded by the clinic staff in EDC, where reactogenicity is collected:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE)

- Solicited local or systemic AR leading to discontinuation
- Solicited local or systemic AR lasting beyond Day 7
- Solicited local or systemic AR that otherwise meets the definition of an SAE

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Section 9.6) will be used to categorize local and systemic solicited ARs.

The following local ARs will be solicited by the eDiary: injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.
The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over body), arthralgia (joint aches in several joints), nausea/vomiting, chills, and fever (oral).

Analyses of solicited ARs will be provided by the vaccination group based on the Solicited Safety Subset, unless otherwise specified. All solicited ARs (overall, local, and systemic) that started during the 7-day follow-up period after injection will be summarized. The number and percentage 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 that started in the 7-day follow-up period after the injection will be provided.

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 toxicity grade of Grade 1 or greater) that started during the 7-day follow-up period after injection will be provided by toxicity grade. If the grade was inaccurately entered in eDiary and the corrected assessment was entered in EDC, the assessment from EDC will be used for analysis.

The number and percentage of participants with the 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 solicited AR by vaccination 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.

The number and percentage of participants who completed the solicited AR eDiary on each day (from Day 1 to Day 7), as well as the number and percentage of participants who completed the eDiary for all 7 days will be presented by vaccination group.

The same analyses described above may be conducted for subgroups defined by age group, previous year's flu vaccine status, race, and sex (Table 3).

6.5.2. Unsolicited Adverse Events

The definitions of AEs, SAEs, AESIs, solicited ARs, and MAAEs are provided in protocol Section 8.3.1. Summary tables and listings for unsolicited AEs (including MAAEs, AESIs, SAEs, AEs leading to discontinuation, SMQ) will be based on unsolicited AEs occurred after exposure to study IP, unless otherwise specified.

Detection of all AEs will be through 28 days after study vaccination dosing (i.e., the day of study vaccination dosing and 27 subsequent days). Detecting MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Day 181 (Month 6)

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT or by PT only. Listings for unsolicited SAEs will be provided and unsolicited SAEs that occurred before the IP administration will be flagged.

Unsolicited AEs will be summarized up to 28 days after vaccine injection. MAAEs, AESIs, SAEs, and AEs leading to discontinuation from study participation will be summarized throughout the study (up to Day 181/EoS). Additional unsolicited AE summaries up to 7 days after vaccine injection may be performed.

In addition, number of participants with occurrences of selected unsolicited identified by a list of SMQs will be summarized. Participants reporting these select unsolicited AE events will be summarized by SMQ, sub-SMQ if applicable, and PT. Detailed description of the list of SMQs is presented in Section **Error! Reference source not found.**. Additional SMQs may be summarized, as necessary.

6.5.2.1. Summary of Unsolicited AEs

An overall summary of unsolicited AEs up to 28 days after vaccine injection including the number and percentage of participants who experienced the following will be presented:

- Any unsolicited AEs
- Any unsolicited treatment-related AEs
- Any SAEs
- Any treatment-related SAEs
- Any unsolicited severe AEs
- Any unsolicited treatment-related severe AEs
- Any unsolicited MAAEs
- Any unsolicited treatment-related MAAEs
- Any unsolicited AESI per investigator assessment
- Any unsolicited AEs leading to discontinuation from participation in the study

Listings containing individual participant's unsolicited AEs leading to discontinuation from the study, SAEs, AESI, MAAEs, and SMQ will be provided separately.

6.5.2.2. Unsolicited AEs by SOC and PT

The following summary tables of unsolicited AEs up to 28 days after vaccine 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 AEs
- Any unsolicited treatment-related AEs
- Any SAEs
- Any treatment-related SAEs
- Any unsolicited severe AEs
- Any unsolicited treatment-related severe AEs
- Any unsolicited MAAEs
- Any unsolicited treatment-related MAAEs
- Any unsolicited AESI per investigator assessment

- Any unsolicited AEs leading to discontinuation from participation in the study

Unsolicited AEs and unsolicited treatment-related AEs will be summarized by SOC and PT for AEs with occurrence in ≥ 0.3% of participants in any vaccination group based on PT, and also presented by SOC, PT, and severity using frequency counts and percentages.

Summary tables for all unsolicited SAEs, AESIs, MAAEs, AE leading to discontinuation from the study, and AE leading to death through Day 181/EoS will also be provided by SOC and PT as applicable.

6.5.2.3. Unsolicited AEs by PT

The summary tables of unsolicited AEs will be provided by PT sorting by frequency on the mRNA-1010 group

6.5.2.4. Unsolicited AEs by SOC, PT, and Severity

The following summary tables of unsolicited AEs in up to 28 days will be provided by severity using frequency counts and percentages:

- All unsolicited AEs
- All unsolicited treatment-related AEs

6.5.2.5. Independent Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in the protocol Section 10.1.6.2) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

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

6.5.2.6. Subgroup Analysis of Unsolicited AEs

Analysis of unsolicited AEs may be conducted for subgroups defined in Table 3. Overall summary of the unsolicited AEs up to 28 days may be provided for each subgroup. Summary tables for

unsolicited AE, treatment-related AEs, and SAEs by SOC and PT may also be provided for each subgroup up to 28 days after the vaccine injection.

6.5.2.7. Death

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

6.5.3. Pregnancy Test

A point-of-care urine pregnancy test will be performed at the Screening Visit and before study vaccination if Day 1 is not on the same day as the Screening Visit. Additional serum or urine pregnancy tests may be performed at any time during the pregnancy -reporting period (through Month 3 [Day 91]), as determined necessary by the Investigator or as required by local regulation, to establish the absence of pregnancy. Pregnancy test results will be listed by participant.

6.5.4. Vital Sign

Vital signs including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature (oral) will be measured on Day 1 as indicated in the SoA (Section 9.1). Vital signs may be collected at other clinic/in-person visits in conjunction with a symptom-directed physical examination.

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. Participants with any abnormal vital sign measurement where toxicity grade (Grade 3 or higher) will be listed separately.

6.6. Planned Analyses

6.6.1. Interim Analysis

Based on the initial study design, the interim analysis (IA) is planned at the end of the first influenza season when approximately CCI of target cases are expected to have accrued in the PP Set. This IA may occur before the end of the first influenza season, when at least CCI of target cases have been accrued. If an IA is conducted before the end of the first season, a supportive analysis will also be performed at the end of the first season.

CCI [redacted]

For the IA planned at the end of the first influenza season, the CCI [redacted] will be used to preserve the 1-sided 2.5% Type 1 error rate over the IA and the final analysis. The alpha level is CCI [redacted] 1-sided, at both the IA and the final analysis if the IA is performed with exactly CCI [redacted] of the total planned cases. The actual alpha will be adjusted based on the actual information fraction calculated as the actual number of cases accrued in the PP Set across both arms divided by the total number of planned cases (CCI [redacted] powered for the non-inferiority hypothesis. The planned information fraction, number of cases and operating characteristics for the NI hypothesis testing at the IA and the final analysis are summarized in Table 6.

Table 6: CCI [redacted]

CCI [redacted]

Per the ongoing case monitoring during the first season, the case accrual has exceeded the total target of CCI [redacted] planned for the study (powered for the primary NI objective). Therefore, the NI of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be evaluated at the 1-sided 2.5% alpha level.

Once NI is demonstrated at the IA, the superiority hypothesis CCI [redacted] will be tested in the PP Set using 1-sided 2.5% alpha level. If superiority is demonstrated at IA, the super-superiority hypothesis CCI [redacted] will be tested in the PP Set using the 1-sided 2.5% alpha level.

Similarly, the hypothesis tests planned for the 2 secondary endpoints will be conducted at IA, if NI, superiority and super-superiority for the primary endpoint have been achieved, according to the hierarchical testing order specified in

Figure 1.

There will be no plan for sample size re-assessment based on the IA results. The Sponsor will have the ultimate responsibility for the decision of further enrollment.

6.6.2. Final Analysis

If the Sponsor decides to continue to a Season 2, there will be no formal statistical hypothesis testing.

6.6.3. End-of-Study Analysis

An End-of-Study analysis may be performed when all study participants have completed the final visit on Day 181 (Month 6) or have withdrawn from the study. This analysis can occur after the first season if the study is completed after Season 1 or after the second season if the study continues to the second season. Of note, this analysis may be combined with the IA or the final analysis.

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: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007b [cited 2021 Aug 19]. Available from:

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World Health Organization (WHO). WHO surveillance case definitions for ILI and SARI [Internet]. 2014 Jan [cited 2024 Feb 23]. Available from:

https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari

9. Appendices

9.1. Appendix A. Scheduled of Events

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**EOS[c] M6[b] (Day 181)**	**EOS[c] End of the Influenza Season[d]**	**Up to the End of the Influenza Season[d]**
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
ICF, demographics, and vaccination and medical history[e]	X							
Inclusion/exclusion criteria	X	X						
Physical examination[f]	X	X						
Vital signs[g]	X	X						X
Pregnancy testing (for POCBP)[h]	X	X						
Record all prior/concomitant medications[i]	X	X	X	X				
Record all concomitant procedures/surgeries[i]	X	X	X	X	X	X	X	
Record MAAEs, AEs leading to discontinuation, SAEs, and AESIs, as well as relevant concomitant medications/procedures[j]	X[k]	X[k]	X	X	X	X	X[l]	
Randomization		X						
EFS[m]		X						
Blood collection for humoral immunogenicity		X[n]		X				
Blood collection for cellular immunogenicity[o]		X		X				
Study intervention (including 30-minute postinjection observation period)		X						

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**EOS[c]** **M6[b] (Day 181)**	**EOS[c]** **End of the Influenza Season[d]**	**Up to the End of the Influenza Season[d]**
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
Reactogenicity eDiary will be used to collect solicited ARs only in a subset of approximately 6000 participants								
Activation of Reactogenicity eDiary		X						
Solicited AR reporting in the Reactogenicity eDiary		D1 (Baseline) to D7						
Review Reactogenicity eDiary and contact participants[p]		D1 (Baseline) to D7	X					
Symptom eDiary will be used to screen for protocol-defined respiratory illness[q] in all participants								
Activation of Symptom eDiary		X						
Symptom reporting in Symptom eDiary[r]		Twice weekly from D1 (Baseline) to the end of the influenza season						
Review Symptom eDiary and contact participants[q,s]		D1 (Baseline) to the end of the influenza season						
Record unsolicited AEs			X[t]	X				
Follow ongoing AEs, SAEs, AESI, and MAAEs at least monthly[u]			D8 to EOS[c]					
Record all concomitant medications that may lead to the elimination of a participant from PP analyses and all nonstudy vaccinations[v]					X	X	X	X
Review symptom history (including dates of onset)								X
Record concomitant medications[w] and nonstudy HCP visits related to or for the treatment of protocol-defined respiratory illness[q]								X

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**EOS[c]** **M6[b] (Day 181)**	**EOS[c]** **End of the Influenza Season[d]**	**Up to the End of the Influenza Season[d]**
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
NP swab for virus detection[x]								X
Contact to follow-up on protocol-defined respiratory illness[q,y]		D1 (Baseline) to the end of the influenza season						
Study completion						X[c]		

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic/in-person visit; D = day; eDiary = electronic diary; EFS = Edmonton Frail Scale; EOS = end of study; FSH = follicle-stimulating hormone; HCP = healthcare professional; ICF = informed consent form; ILI = influenza-like illness; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; POCBP = person of childbearing potential; PP = Per-Protocol; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SC = safety contact; SoA = schedule of activities; T = telephone contact; USV = unscheduled visit.

a. The Screening and Day 1 (Baseline) activities may be performed on the same day or on different days. Additionally, Screening Visit activities may be performed over multiple visits if within the 28-day screening window.
b. One month is defined as 30 days.
c. Study completion (EOS) will occur at either the Month 6 (Day 181) Visit or at the End of the Influenza Season Visit, whichever is later. The Month 6 (Day 181) Visit and the End of the Influenza Season Visit may be combined if both visits are within the relevant window periods.
d. The end of the influenza season is defined in protocol Section 4.4.1.
e. Verbal medical history is acceptable. Any sign, symptom, or disease identified or starting before study intervention should be recorded as medical history. If the full date is unknown, all known date information should be collected.
f. A full physical examination, including height and weight, will be performed at Screening. On Day 1 (Baseline), physical examination will be limited to examination of the arm receiving the injection and the associated lymph node before study intervention; any abnormalities should be documented.
g. Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature (oral). On Day 1 (Baseline), vital signs will be collected before study intervention and again approximately 30 minutes after study intervention.
h. Point-of-care urine pregnancy test at the Screening Visit and before study intervention on Day 1 (Baseline) (if Day 1 [Baseline] is not on the same day as the Screening Visit). At the discretion of the Investigator, a pregnancy test can be performed at any time during the pregnancy-reporting period (through Month 3 [Day 91]). The participant's FSH level may be measured at the Screening Visit, as necessary and at the discretion of the Investigator, to confirm postmenopausal status.
i. Prior/concomitant medications and procedures should be recorded as described in protocol Section 6.9.
j. Concomitant medications/procedures relevant to or for the treatment of an MAAE, AE leading to discontinuation, SAE, or AESI will be recorded from Day 1 (Baseline) through Month 6 (Day 181).

k. SAEs will be collected from signing of the ICF through Month 6 (Day 181).
l. SAEs considered related to study intervention by the Investigator will be collected through the end of the study. No other AEs or SAEs should be collected after Month 6 (Day 181).
m. Only for participants ≥ 65 years of age.
n. Day 1 (Baseline) collection must be before study intervention.
o. Blood collection for cellular immunogenicity is only in a subset of approximately 200 participants. Day 1 (Baseline) collection must be before study intervention.
p. If a participant does not respond to the eDiary questions according to the SoA, study staff will follow-up with the participant. The site should also contact the participant under the following circumstances: a Grade 4 solicited AR is reported (contact participant as soon as possible), a Grade 3 solicited AR is reported on 2 consecutive days, and at the Investigator's discretion.
q. The definition of protocol-defined respiratory illness is new onset or worsening (>24 hours) of at least 1 of the following symptoms: sneezing, nasal congestion, rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing (refer to protocol Table 4).
r. Participants are encouraged to respond to the eDiary as soon as possible if they have any respiratory symptoms and, upon experiencing respiratory symptoms, contact study staff. For participants with protocol-defined respiratory illness, oral temperature measurements should be performed daily while symptoms are ongoing, preferably at approximately the same time each day. Any body temperature >37.2°C (>99.0°F) should be reported to study staff as a possible symptom of protocol-defined ILI.
s. If a participant does not respond to the eDiary questions according to the SoA, study staff will follow-up with the participant. If a participant reports experiencing respiratory symptoms, study staff should contact the participant as soon as possible (preferably within 24 hours) to confirm protocol-defined respiratory illness and to arrange an unscheduled visit to collect an NP swab sample for RT-PCR testing.
t. Signs and symptoms that are consistent with any of the solicited AR terms in protocol Table 6 that start on or before Day 7 should not be recorded as unsolicited AEs, unless the event meets seriousness criteria and the investigator considers it related to study intervention, in which case the event will be reported as an SAE.
u. All ongoing AEs/SAEs/AESIs/MAAEs will be followed at least monthly until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
v. Refer to protocol Section 6.9.3 for medications that may lead to the elimination of a participant from PP analyses.
w. Record any new concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) or altered doses/frequencies of existing concomitant medications resulting from protocol-defined respiratory illness.
x. An NP swab sample will be collected from any participant with protocol-defined respiratory illness, preferably within 72 hours after symptom onset. Samples collected within 5 days after symptom onset are acceptable.
y. For participants with protocol-defined respiratory illness, study staff will contact the participant twice weekly until resolution of symptoms (or until the end of the window period for the End of the Influenza Season Visit) to update and review symptoms and concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) related to the participant's respiratory illness. Study staff will also contact the participant upon resolution of symptoms or 30 days after the onset of symptoms (or at the end of the window period for the End of the Influenza Season Visit), whichever is earlier, to collect information about healthcare usage and concomitant medications related to the participant's respiratory illness.

9.2. Appendix B. 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, and 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.

Table 7: Analysis Visit Window

Visit	Target Study Day	Visit Window in Study Day for Immunogenicity Subset	Visit Window in Study Day for PPIS
Immunogenicity			
Day 1	1 (Date of Injection)	Pre-vaccination	Pre-vaccination
Day 29	29	≥ 2	[22, 43]

9.3. Appendix C. Standards for Variables Display in TLFs

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 standard deviation will be presented to two decimal places more than the original results; the min and max will be presented to the same precision as the original results. For model-based estimates or immunogenicity analyses, the results may be presented up to three 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.

9.4. Appendix D. Imputation Rules for Missing Dates of Prior/Concomitant Medication

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 the 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 the 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 the injection or is missing AND the start year of the medication coincides with the start year of the first injection. In this case, use the date of the injection.
- If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant, unless the stop date is not completely missing and indicates differently.

2) Missing or partial medication stop date:

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

Table 8: Categorization of Medication

	Medication End Date	
Medication Start Date	< Injection Date of IP	≥ Injection Date and ≤ Injection Day + 27 Days After Injection [a]
< Injection Date of IP [b]	P	P, C
> Injection Date and < 28 days after injection	-	C
Throughout the study [c]	-	C

C= Concomitant; P=Prior
a. Includes medications with completely missing end date.
b. Includes medications with completely missing start date.
c. For selected concomitant medications such as non-study influenza vaccine

9.5. Appendix E. Imputation Rules for Missing Dates of AEs

1) Missing or partial AE start date:
   - If only Day is missing, use the first day of the month, unless the AE end date is on/after the date of the 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 the 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 be imputed as the date of the injection and the AE will be considered as occurred after exposure to. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE.
2) Missing or partial AE end dates will not be imputed.

9.6. Appendix F. Solicited Adverse Reactions and Grades

Table 9: Adults and Adolescent Solicited Adverse Reactions and Grades

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

9.7. Appendix G. Toxicity Grades of Vital Sign Abnormalities

Table 10: Toxicity Grading of Vital Sign Abnormalities

Vital Signs [a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b] (°F)[b]	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[c]	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

[a] Participant should be at rest for all vital sign measurements.
[b] Oral temperature; no recent hot or cold beverages or smoking.
[c] When resting heart rate is between 60 – 100 beats per minute. Clinical judgement should be used when characterizing bradycardia among some healthy participant populations, for example, conditioned athlete.

9.8. Appendix H. Definitions of SMQs

Table 11: List of SMQs

#	SMQ/CMQ Name [a]	Type of MedDRA Query	SMQ Level [a]	SMQ Code [a]	Search Criteria
1	Anaphylactic Reaction	SMQ	1	20000021	Algorithm A or (B and C) or (D and (B or C))
2	Arthritis	SMQ	1	20000216	Narrow/Broad
3	Cardiac Arrhythmias	SMQ	1	20000049	Narrow/Broad
	Arrhythmia Related Investigations, Signs and Symptoms	SMQ	2	20000051	Narrow/Broad
	Cardiac Arrhythmia Terms (including bradyarrhythmias and tachyarrhythmias)	SMQ	2	20000050	Narrow/Broad
4	Convulsions	SMQ	1	20000079	Narrow/Broad
5	Demyelination	SMQ	1	20000154	Narrow/Broad
6	Guillain-Barre Syndrome	SMQ	1	20000131	Narrow/Broad
7	Haematopoietic Cytopenias	SMQ	1	20000027	Narrow/Broad
	Haematopoietic Cytopenias Affecting More Than One Type of Blood Cell	SMQ	2	20000028	Narrow/Broad
	Haematopoietic Erythropenia	SMQ	2	20000029	Narrow/Broad
	Haematopoietic Leukopenia	SMQ	2	20000030	Narrow/Broad
	Haematopoietic Thrombocytopenia	SMQ	2	20000031	Narrow/Broad
8	Hypersensitivity	SMQ	1	20000214	Narrow/Broad
9	Immune-mediated/Autoimmune Disorders	SMQ	1	20000236	Narrow/Broad
10	Noninfectious Myocarditis/Pericarditis	SMQ	1	20000239	Narrow/Broad
11	Peripheral Neuropathy	SMQ	1	20000034	Narrow/Broad

[a] Based on MedDRA 25.0

Table 12: Algorithm 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

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

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

9.9. Appendix I. Estimands and Intercurrent Events Handing Strategies

Label	Intercurrent Event Type [a]
IcEv1 (early discontinuation)	Early discontinuation or death unrelated to influenza
IcEv1.1 (early discontinuation by Day 29)	Early discontinuation or death unrelated to influenza before or by the immunogenicity sample collection for Day 29
IcEv2 (early RT-PCR-confirmed protocol-defined ILI)	RT-PCR-confirmed protocol-defined ILI starting <14 days after study vaccination
IcEv2.1 (early infection by Day 29)	RT-PCR-confirmed influenza infection before or by the immunogenicity sample collection for Day 29
IcEv2.2 (protocol-defined ILI but not modified-CDC-defined ILI)	First RT-PCR-confirmed protocol-defined ILI but not meeting RT-PCR-confirmed modified CDC-defined ILI
IcEv2.3 (ILI without antigenic match)	RT-PCR-confirmed protocol-defined ILI without antigenic match to the vaccine strains
IcEv3 (major violation of eligibility criteria)	Major violation of eligibility criteria of inclusion and/or exclusion
IcEv4 (alternative influenza vaccine)	Use of alternative non-study Influenza vaccine during the study, and starting before the efficacy endpoint if the participant had the endpoint
IcEv4.1 (alternative influenza vaccine by Day 29)	Use of alternative non-study Influenza vaccine before or by the immunogenicity sample collection for Day 29
IcEv5 (prohibited medications)	Use of prohibited medications deemed to impact immunogenicity/efficacy response, and starting before the efficacy endpoint if the participant had the endpoint
IcEv5.1 (prohibited medications by Day 29)	Use of prohibited medications before or by the immunogenicity sample collection for Day 29 and the medications are deemed to impact on immunogenicity/efficacy response on Day 29
IcEv6.1 (no vaccination)	Not received any study vaccine
IcEv6.2 (wrong vaccination)	Received a wrong vaccine, or a major wrong dose of the assigned vaccine
IcEv7 (sample collection out of the window)	Immunogenicity sample collection is out of the window

IcEv = intercurrent event.

a. Some intercurrent events are not mutually exclusive, for example, InEv5.1 is a subset of InEv5.

Table 13: Summary of Estimand for rVE Against RT-PCR-confirmed Protocol-defined ILI with Rationale for Strategies to Address Intercurrent Events

Objective: To evaluate the rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains.		
Estimand Label	**Primary Estimand 1a** (on the PP Set)	**Supplementary Estimand 1b** (on the FAS)
Estimand Description	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants **without major protocol deviations that could impact efficacy.** HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains beginning at least 14 days after the study vaccination	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants who received a non-zero dose of one study vaccine, **irrespective of any major protocol deviations that could impact efficacy**. HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains beginning at least 14 days after the study vaccination
Target Population	Adults aged at least 50 years who received the planned IP without any important protocol deviations that may impact the key or critical data.	Adults aged at least 50 years who received a non-zero dose of one study vaccine
Endpoint	First RT-PCR-confirmed protocol-defined ILI, caused by any influenza A or B strains, beginning at least 14 days after the study vaccination	As per Estimand 1a.
Treatment Conditions	mRNA-1010 vs. an active comparator	As per Estimand 1a.
Population-Level Summary	rVE defined as 1-HR (mRNA-1010 vs. an active comparator). HR is the hazard ratio of having an RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains starting at least 14 days after the vaccination, and the HR is estimated via the Cox proportional model with the vaccination group as the independent variable, adjusted for the stratification factors (age group and influenza vaccination status in the previous season) used for the randomization.	As per Estimand 1a.

Intercurrent Event Strategy		
Intercurrent Event [a]	**Primary Efficacy Estimand 1a** (on the PP Set)	**Supplementary Efficacy Estimand 1b** (on the FAS)
IcEv1 (early discontinuation)	Hypothetical: censored at the time of discontinuation or death	As per Estimand 1a.
IcEv2 (early RT-PCR-confirmed protocol-defined ILI)	Hypothetical: censored at the start date of the RT-PCR-confirmed protocol-defined ILI which starts < 14 days after study vaccination	As per Estimand 1a.
IcEv3 (major violation of eligibility criteria)	Principal stratum	Treatment policy
IcEv4 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv5 (prohibited medications)	Principal stratum	Treatment policy
IcEv6.1 (no vaccination)	Principal stratum	As per Estimand 1a.
IcEv6.2 (wrong vaccination)	Principal stratum	Treatment policy

Rationale for Strategies	This Estimand is to understand the efficacy response to RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains on adults aged at least 50 years who receive the IP administration and comply with key protocol criteria. A principal stratum strategy is used for any major violation of eligibility criteria or not receiving the assigned vaccination, as well as having received prohibited medications or any non-study influenza vaccine during the study, so the analysis is a sub-population composed of participants free from these intercurrent events. A hypothetical strategy is used for early discontinuation or unrelated death, or the early RT-PCR-confirmed protocol-defined ILI before Day 14, because the event status will be either unknown or the development of the event could be impacted by the intercurrent event. The hypothetical strategy is used for the early RT-PCR-confirmed protocol-defined ILI before Day 14 because only the event that occurred from Day 14 of the vaccination is the endpoint.	This Estimand is to understand the efficacy response to RT-PCR-confirmed protocol-defined ILI by the influenza vaccine on adults aged at least 50 years, regardless of whether complying with the key protocol criteria. A treatment policy strategy is used for any major violation of eligibility criteria, receiving a wrong vaccine, or having prohibited medications or any non-study influenza vaccine during the study. Participants with any of these intercurrent events are considered as not complying with the key protocol criteria, the intercurrent events will be ignored and the participants will be analyzed per the randomized study vaccine. The treatment policy strategy is used for these intercurrent events in 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 hypothetical or principal stratum strategy is employed for the other intercurrent events that match Estimand 1a.

a. Participants could have more than one intercurrent event and the strategy will be based on the strategy of the 1st occurred intercurrent event.

Table 14: Summary of Estimand for the rVE Against RT-PCR-confirmed Modified CDC-defined ILI with Rationale for Strategies to Address Intercurrent Events [a]

Objective: To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains.		
Estimand Label	**Primary Estimand 2a** (on the PP Set)	**Supplementary Estimand 2b** (on the FAS)
Estimand Description	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants without major protocol deviations that could impact efficacy. HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains beginning at least 14 days after the study vaccination	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants who received a non-zero dose of one study vaccine, irrespective of any major protocol deviations that could impact efficacy. HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains beginning at least 14 days after the study vaccination
Target Population	Adults aged at least 50 years who received the planned IP without any important protocol deviations that may impact the key or critical data.	Adults aged at least 50 years who received a non-zero dose of one study vaccine
Endpoint	First RT-PCR-confirmed modified CDC-defined ILI, caused by any influenza A or B strains, beginning at least 14 days after the study vaccination	As per Estimand 2a.
Treatment Conditions	mRNA-1010 vs. an active comparator	As per Estimand 2a.
Population-Level Summary	Relative efficacy response to seasonal influenza vaccine, defined as rVE, is measured by 1-HR (mRNA-1010 vs. an active comparator). HR is the hazard ratio of having an RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains starting at least 14 days after the vaccination, and the HR is estimated via the Cox proportional model with the vaccination group as the independent variable, adjusted for the stratification factors (age group and influenza vaccination status in the previous season) used for the randomization.	As per Estimand 2a.

Intercurrent Event Strategy		
Intercurrent Event [b]	**Primary Efficacy Estimand 2a** (on the PP Set)	**Supplementary Efficacy Estimand 2b** (on the FAS)
IcEv1 (early discontinuation)	Hypothetical: censored at the time of discontinuation or death	As per Estimand 2a.
IcEv2 (early RT-PCR-confirmed protocol-defined ILI)	Hypothetical: censored at the start date of the RT-PCR-confirmed protocol-defined ILI which starts < 14 days after study vaccination	As per Estimand 2a
IcEv2.2 (protocol-defined ILI but not modified-CDC-defined ILI)	Hypothetical: censored at the start date of the first RT-PCR-confirmed protocol-defined ILI	As per Estimand 2a
IcEv3 (major violation of eligibility criteria)	Principal stratum	Treatment policy
IcEv4 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv5 (prohibited medications)	Principal stratum	Treatment policy
IcEv6.1 (no vaccination)	Principal stratum	As per Estimand 2a.
IcEv6.2 (wrong vaccination)	Principal stratum	Treatment policy

Rationale for Strategies	This Estimand is to understand the efficacy response to RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains on adults aged at least 50 years who receive the IP administration and comply with key protocol criteria. A principal stratum strategy is used for any major violation of eligibility criteria or not receiving the assigned vaccination, as well as having received prohibited medications or any non-study influenza vaccine during the study, so the analysis is a sub-population composed of participants free from these intercurrent events. A hypothetical strategy is used for early discontinuation or unrelated death, or the early RT-PCR-confirmed protocol-defined ILI before Day 14 because the event status will be either unknown or the development of the event could be impacted by the intercurrent event. The hypothetical strategy is used for the early RT-PCR-confirmed protocol-defined ILI before Day 14 because only the event that occurred from Day 14 of the vaccination is the endpoint.	This Estimand is to understand the efficacy response to RT-PCR-confirmed modified CDC-defined ILI by the influenza vaccine on adults aged at least 50 years, regardless of whether complying with the key protocol criteria. A treatment policy strategy is used for any major violation of eligibility criteria, receiving a wrong vaccine, or having prohibited medications or any non-study influenza vaccine during the study. Participants with any of these intercurrent events are considered as not complying with the key protocol criteria, the intercurrent events will be ignored and the participants will be analyzed per the randomized study vaccine. The treatment policy strategy is used for these intercurrent events in 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 hypothetical or principal stratum strategy is employed for the other intercurrent events that match Estimand 2a.

a. Participants could have more than one intercurrent event and the strategy will be based on the strategy of the 1st occurred intercurrent event.

Table 15: Summary of Estimand of rVE Against RT-PCR-confirmed Protocol-defined ILI with Antigenic Match to the Vaccine Strains or RT-PCR-confirmed Modified CDC-defined ILI with Antigenic Match to the Vaccine Strain with Rationale for Strategies to Address Intercurrent Events [a]

Objective: To evaluate the rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed Protocol-defined ILI with Antigenic Match to the Vaccine Strains or RT-PCR-confirmed Modified CDC-defined ILI with Antigenic Match to the Vaccine Strains		
Estimand Label	**Primary Estimand 3a** (on the PP Set)	**Supplementary Estimand 3b** (on the FAS)
Estimand Description	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants **without major protocol deviations that could impact efficacy.** HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains, beginning at least 14 days after the study vaccination	This estimand is to evaluate rVE of mRNA-1010 vs. active comparator, as measured by 100 x (1-HR) among participants who received a non-zero dose of one study vaccine, **irrespective of any major protocol deviations that could impact efficacy**. HR = hazard ratio (mRNA-1010 vs. an active comparator) of RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains, beginning at least 14 days after the study vaccination
Target Population	Adults aged at least 50 years who received the planned IP without any important protocol deviations that may impact the key or critical data.	Adults aged at least 50 years who received a non-zero dose of one study vaccine
Endpoint	First RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or first RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains, beginning at least 14 days after the study vaccination	As per Estimand 3a.
Treatment Conditions	mRNA-1010 vs. an active comparator	As per Estimand 3a.

Population-Level Summary	rVE defined as 1-HR (mRNA-1010 vs. an active comparator). HR is the hazard ratio of having an RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or an RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains, starting at least 14 days after the vaccination, and the HR is estimated via the Cox proportional model with the vaccination group as the independent variable, adjusted for the stratification factors (age group and influenza vaccination status in the previous season) used for the randomization.	As per Estimand 3a.
Intercurrent Event Strategy		
Intercurrent Event [a]	**Primary Efficacy Estimand 3a** (on the PP Set)	**Supplementary Efficacy Estimand 3b** (on the FAS)
IcEv1 (early discontinuation)	Hypothetical: censored at the time of discontinuation or death	As per Estimand 3a.
IcEv2 (early RT-PCR-confirmed protocol-defined ILI)	Hypothetical: censored at the start date of the first RT-PCR-confirmed protocol-defined ILI which starts < 14 days after study vaccination	As per Estimand 3a.
IcEv2.2 (protocol-defined ILI but not modified-CDC-defined ILI)	Hypothetical: for the endpoint of RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains: censored at the start date of the first RT-PCR-confirmed protocol-defined ILI	As per Estimand 3a.
IcEv2.3 (ILI without antigenic match)	Hypothetical: censored at the start date of the first RT-PCR-confirmed protocol-defined ILI	As per Estimand 3a.
IcEv3 (major violation of eligibility criteria)	Principal stratum	Treatment policy
IcEv4 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv5 (prohibited medications)	Principal stratum	Treatment policy
IcEv6.1 (no vaccination)	Principal stratum	As per Estimand 3a.
IcEv6.2 (wrong vaccination)	Principal stratum	Treatment policy

Rationale for Strategies	This Estimand is to understand the efficacy response to RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains on adults aged at least 50 years who receive the IP administration and comply with key protocol criteria. A principal stratum strategy is used for any major violation of eligibility criteria or not receiving the assigned vaccination, as well as having received prohibited medications or any non-study influenza vaccine during the study, so the analysis is a sub-population composed of participants free from these intercurrent events. A hypothetical strategy is used for early discontinuation or unrelated death, or the early RT-PCR-confirmed protocol-defined ILI, because the event status will be either unknown or the development of the event could be impacted by the intercurrent event. The hypothetical strategy is used for the early RT-PCR-confirmed protocol-defined ILI before Day 14 because only the event that occurred from Day 14 of the vaccination and with antigenic match to the vaccine strains is the endpoint	This Estimand is to understand the efficacy response to RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains or RT-PCR-confirmed modified CDC-defined ILI with antigenic match to the vaccine strains on adults aged at least 50 years, regardless of whether complying with the key protocol criteria. A treatment policy strategy is used for any major violation of eligibility criteria, receiving a wrong vaccine, or having prohibited medications or any non-study influenza vaccine during the study. Participants with any of these intercurrent events are considered as not complying with the key protocol criteria, the intercurrent events will be ignored and the participants will be analyzed per the randomized study vaccine. The treatment policy strategy is used for these intercurrent events in 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 hypothetical or principal stratum strategy is employed for the other intercurrent events that match Estimand 3a.

a. Participants could have more than one intercurrent event and the strategy will be based on the strategy of the 1st occurred intercurrent event.

Table 16: Summary of Estimand for the Humoral Immune with Rationale for Strategies to Address Intercurrent Events

Objective: To evaluate the humoral immunogenicity of mRNA-1010 relative to an active comparator against vaccine-matched influenza A or B strains.		
Estimand Label	**Primary Estimand 4a** (on the PPIS)	**Supplementary Estimand 4b** (on the Immunogenicity Set)
Estimand Description	This estimand is to evaluate humoral immune response to vaccine-matched influenza A or B strains, measured as, on Day 29, GMT, Proportion of participants reaching seroconversion, frequency of participants with an HAI titer ≥1:40, and GMFR comparing to Day 1 among participants **without major protocol deviation affecting the immunogenicity outcomes**.	This estimand is to evaluate humoral immune response to vaccine-matched influenza A or B strains, measured as, on Day 29, GMT, Proportion of participants reaching seroconversion, frequency of participants with an HAI titer ≥ 1:40, and GMFR comparing to Day 1, **irrespectively of any major protocol deviations affecting the immunogenicity outcomes**.
Target Population	Adults aged at least 50 years in the Immunogenicity Subset who received the planned IP without any important protocol deviations that may impact immunogenicity response.	Adults aged at least 50 years in the Immunogenicity Subset who received a non-zero dose of one study vaccine, irrespective of any major protocol deviations that could impact immune response.
Endpoint	• GMT on Day 29 as measured by HAI. • Proportion of participants reaching seroconversion on Day 29 as measured by HAI. • Frequency of participants with an HAI titer ≥1:40 on Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI**.**	As per Estimand 4a.
Treatment Conditions	mRNA-1010 vs. an active comparator	As per Estimand 4a.
Population-Level Summary	Immune response to vaccine-matched influenza A and B strains, defined as, on Day 29, GMT, seroconversion rate, frequency of participants with an HAI titer ≥1:40, and GMFR comparing to Day 1 (Baseline) as measured by HAI	As per Estimand 4a.

Intercurrent Event Strategy		
Intercurrent Event [a]	**Primary Estimand 4a** (on the PPIS)	**Supplementary Estimand 4b** (on the Immunogenicity Set)
IcEv1.1 (early discontinuation by Day 29)	Principal stratum	As per Estimand 4a
IcEv2.2 (early infection by Day 29)	Principal stratum	Treatment policy
IcEv3 (major violation of eligibility criteria)	Principal stratum	Treatment policy
IcEv4.1 (alternative influenza vaccine by Day 29)	Principal stratum	Treatment policy
IcEv5.1 (prohibited medications by Day 29)	Principal stratum	Treatment policy
IcEv6.1 (no vaccination)	Principal stratum	As per Estimand 4a
IcEv6.2 (wrong vaccination)	Principal stratum	Treatment policy
IcEv7 (sample collection out of window)	Principal stratum	Treatment policy

Rationale for Strategies	This Estimand is to understand the immune response to vaccine-matched influenza A or B strains on adults aged at least 50 years who receive the planned IP and comply with key protocol criteria. A principal stratum is used to exclude participants with major deviations (such as the use of alternative vaccines and prohibited medications) so that analysis is a sub-population composed of participants free from such intercurrent events.	This Estimand is to understand the immune response to vaccine-matched influenza A or B strains on adults aged at least 50 years who receive the non-zero of study vaccine, regardless of whether complying with the key protocol criteria. A treatment policy strategy is used for following up on immune response including all participants in the subset who have a baseline and Day 29 antibody assessment by HAI assay, irrespective of early infection or whether they subsequently were found not to strictly meet the important protocol criteria (i.e., important protocol deviations affecting immune response, use of the alternative influenza 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.

a. Participants could have more than one intercurrent event and the strategy will be based on the strategy of the 1st occurred intercurrent event.

9.10. Appendix J. Derivation of High-risk

Participants will be in the high-risk group if their baseline BMI was ≥ 30 or having at least one high-risk factor below in the medical history:

High-risk factor	**SMQ or HLT**		
Autoimmune/immune-mediated disease	Immune-mediated/autoimmune disorders	SMQ	Narrow
Blood disorders	Coagulation disorders congenital	HLT	
	Haemoglobinopathies congenital	HLT	
Cardiac disorders	Cardiac conduction disorders	HLT	
	Supraventricular arrhythmias	HLT	
	Ventricular arrhythmias and cardiac arrest	HLT	
	Cardiomyopathy	SMQ	Narrow
	Ischemic heart disease	SMQ	Narrow
Nervous system disorders	Cerebrovascular embolism and thrombosis	HLT	
	Parkinson's disease and parkinsonism	HLT	
	Paralysis and paresis (excl cranial nerve)	HLT	
	Demyelination	SMQ	Narrow
Diabetes mellitus	Diabetes mellitus (incl subtypes)	HLT	
Renal disorders	Chronic kidney disease	SMQ	Narrow
Hepatic disorders	Hepatocellular damage and hepatitis NEC	HLT	
	Hepatic fibrosis and cirrhosis	HLT	
Mental impairment disorders	Intellectual disabilities	HLT	
	Dementia	SMQ	Narrow
Pulmonary disorders	Bronchospasm and obstruction	HLT	
	Interstitial lung disease	SMQ	Narrow
	Pulmonary hypertension	SMQ	Narrow

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