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ModernaTX, Inc.

mRNA-1010-P302

A Phase 3, Randomized, Observer-blind, Active-controlled Study to Evaluate the Safety and Efficacy of mRNA-1010 Candidate Seasonal Influenza Vaccine in Adults 50 Years and Older

Statistical Analysis Plan

Version 2.0

23FEB2023

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	02Dec2022	First version
2.0	03Feb2023	Per Protocol Amendment 1: 1. Added immunogenicity analyses. 2. Revised the mITT Set definition. 3. Removed the first interim analysis (IA) from the planned analyses and revised the planned IA timing. 4. Revised the statistical considerations for the IA and final analysis, including the alpha spending function , which was updated to the Lan-DeMets Pocock spending function to control for the overall Type 1 error rate. 5. Added sensitivity analyses in Sections 6.3.1.2.1 and 6.3.1.2.2 and supportive analyses in Section 6.3.1.2.3 for the primary efficacy endpoint. 6. For the supportive analysis of rVE for the primary efficacy endpoint using incidence rate (Section 6.3.1.2.3), the incidence rate is calculated based on person-season, instead of person-year.

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSP	clinical study protocol
DBP	data blinding plan
DSMB	data safety monitoring board
eCRF	electronic case report form
eDiary	electronic diary
EFS	Edmonton Frailty Scale
EoS	End of Study
FAS	full analysis set
GLSM	geometric least square means
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition
HR	hazard ratio
IA	interim analysis
IcEv	intercurrent event
ILI	influenza-like illness
IM	intramuscular
IP	investigational product
IRT	Interactive Response Technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MTP	multiple testing procedure
NH	Northern Hemisphere
NI	Noninferiority
NP	nasopharyngeal
PP	per-protocol

PRO	Patient-Reported Outcome
PT	preferred term
QoL	quality of life
RT-PCR	reverse transcription polymerase chain reaction
rVE	relative vaccine efficacy
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SMQ	standardized MedDRA query
SOC	system organ class
SoE	Schedules of Events
TEAE	treatment-emergent adverse event
TLFs	Tables, Listings and Figures
ULOQ	upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for the mRNA-1010-P302 study, is based on the clinical study protocol (CSP) Amendment 1, dated 02-February-2023 and the final electronic case report form (eCRF), dated 01-December-2022.

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

Study mRNA-1010-P302 is a Phase 3, randomized, observer-blind, active-controlled study to evaluate the safety and efficacy of mRNA-1010 candidate seasonal influenza vaccine as compared with an active comparator in adults ≥ 50 years of age.

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

In this document, injection of investigational product (IP), injection, vaccination, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objectives

2.1.1. Primary Safety Objective

The primary safety objective is to evaluate the safety and reactogenicity of mRNA-1010 during the treatment period and follow-up period.

2.1.2. Primary Efficacy Objective

The primary efficacy objective is to evaluate relative vaccine efficacy (rVE) of mRNA-1010 as compared to an active comparator against influenza caused by any influenza A or B virus strains using protocol-defined influenza-like illness (ILI) definition.

2.2. Secondary Objectives

The secondary efficacy objectives are:

- To evaluate rVE of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains with similarity to the vaccine strains using protocol-defined ILI definition.
- To evaluate rVE of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains antigenically matched to the vaccine strains using protocol-defined ILI definition.
- To evaluate rVE of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains (any strains or similar strains or antigenically matched strains) using CDC-defined ILI definition.
- To evaluate rVE of mRNA-1010 vaccine as compared to an active comparator against the first episode of culture-confirmed influenza caused by influenza A or B strains (any strains).
- To evaluate rVE of mRNA-1010 as compared to an active comparator to prevent hospitalizations associated with influenza illness.
- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains at Day 29.

2.3. Exploratory Objectives (may be performed)

The exploratory objectives are as follows:

- To evaluate immune response biomarkers after dosing with study intervention (in a subset of participants).

- To evaluate rVE of mRNA-1010 as compared to an active comparator to prevent the following events that begin at least 14 days post vaccination through Day 361 (Month 12)/end of study (EoS):
  - All-cause pneumonia,
  - Pneumonia-related hospitalization,
  - All-cause hospitalization,
  - Influenza-related mortality,
  - All-cause mortality.
- To evaluate rVE of mRNA-1010 as compared to an active comparator to prevent the following events that begin at least 14 days post vaccination through Day 361 (Month 12)/EoS:
  - Exacerbation of cardiorespiratory diseases (e.g., congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), asthma, and other chronic cardiorespiratory diseases),
  - Cardiorespiratory hospitalizations and death.
- To characterize the effect of mRNA-1010 as compared to an active comparator on other health outcomes including:
  - Number and frequency of participants aged 65 years and older with protocol-defined ILI definition by baseline frailty status.
  - EuroQoL 5 Dimension 5-Level (EQ-5D-5L) health questionnaire utility score at regular intervals as well as for participants with ILI.
  - Work Productivity and Activity impairment Questionnaire: Influenza-like Illness (WPAI: ILI) impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with ILI.
- To characterize the effect of mRNA-1010 as compared to an active comparator on prevention or mitigation of the following that are associated with reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed ILI or all-cause pneumonia:

  - Healthcare encounters (i.e., outpatient visits, emergency department visits, and hospitalizations).
  - Duration of hospital encounters including intensive care unit hospitalization, and endotracheal intubation/mechanical ventilation.
  - Prescriptions for medications (antibiotics, antivirals, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs).
- Economic Analysis: A separate economic analysis is planned to estimate the impact of vaccination with mRNA-1010 on quality of life (QoL)-adjusted survival and on healthcare costs in real-world practice in one or more geographic regions. If performed, this analysis would use information on clinical, QoL, and resource use outcomes collected within the study to estimate QoL and costs to a healthcare payer comparing a strategy of vaccination with mRNA-1010 vs. an active comparator. This analysis would be conducted under a separate analysis plan and is intended for submission to health technology assessment and payer audiences to support use of mRNA-1010 following launch.

The analyses for the exploratory objectives listed in this section will not be included in this SAP. Separate analysis plans will be developed for these analyses.

3. Study Endpoints

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days (i.e., the day of injection and 6 subsequent days) after study injection.
- Unsolicited adverse events (AEs) through 28 days (i.e., the day of injection and 27 subsequent days) after study injection.
- Medically-attended AEs (MAAEs) from Day 1 to Day 361 (Month 12)/ EoS.
- AEs of Special Interest (AESIs) from Day 1 to Day 361 (Month 12)/EoS.

- Serious AEs (SAEs) from Day 1 to Day 361 (Month 12)/EoS.
- AEs leading to discontinuation from study participation from Day 1 to Day 361 (Month 12)/EoS.

3.1.2. Primary Efficacy Endpoint

The primary efficacy objective will be evaluated by the primary efficacy endpoint, the rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6) or the end of influenza season, whichever occurs later, caused by any seasonal influenza A or B virus strains regardless of antigenic match to vaccine strains selected for the seasonal vaccine.

The rVE is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs. active comparator), i.e. 1 – hazard ratio (HR) between mRNA-1010 vs. active comparator, multiplied by 100%:

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

where the HR will be estimated using a stratified Cox proportional hazard model.

The RT-PCR confirmed protocol-defined ILI is defined based on the following criteria:

1. The participant must have experienced the following symptoms: Body temperature ≥ 37.5°C [≥ 99.5°F] **accompanied by** at least **ONE** of respiratory illness symptom: sore throat, cough, sputum production, wheezing, or difficulty breathing,

   AND
2. The participant must have a nasopharyngeal (NP) swab sample which tests positive for influenza infection by RT-PCR within 7 days of onset of protocol-defined ILI performed at any setting during the study period.

3.2. Secondary Endpoints

3.2.1. Key Secondary Efficacy Endpoints

The key secondary efficacy objectives will be evaluated by the following endpoints:

- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A or B strains with similarity to those selected for the seasonal vaccine.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A or B strains antigenically matched to the vaccine strains selected for the seasonal vaccine.

For the definitions of rVE and RT-PCR confirmed protocol-defined ILI, refer to primary endpoint analysis in Section 3.1.2.

Following a positive influenza result by a RT-PCR test on a NP swab, the antigenicity test on cultured laboratory isolates and sequencing of HA region will be performed to determine antigenic match and similarity to strains selected for the seasonal vaccine (see definitions in Section 4.1). Similarity and antigenic match to the selected strains are defined as follows:

Similarity to strains selected for the seasonal vaccine

A laboratory-confirmed isolate is deemed similar to one of the vaccine components if determined by antigenic testing of the cultured virus using specific antisera and/or by genetic sequencing of the HA segments showing identity of key antigenic residues with vaccine strain-like strains. Additional details for assigning similarity from the cultured virus antigenic test result and/or the genetic sequencing test result are provided in Table 3 in Section 6.3.2.1.

Antigenic match to strains selected for the seasonal vaccine

Culture-confirmed viruses are deemed to be antigenically matched to vaccine components by antigenic typing, using cultured viral isolate and vaccine-specific antisera. Additional details for assigning antigenic match are provided in Table 3 in Section 6.3.2.1.

3.2.2. Other Secondary Efficacy Endpoints

The other secondary efficacy objectives will be evaluated by the following endpoints:

RT-PCR confirmed US CDC-defined ILIs

- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by any influenza A or B strains regardless of antigenic match.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A or B strains with similarity to vaccine strains.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A or B strains that are antigenically matched to vaccine strains.

For the definition of rVE, refer to the primary endpoint analysis in Section 3.1.2.

US CDC-defined ILI criteria are defined as follows:

1. The participant must have experienced the following symptoms: Body temperature ≥ 37.8°C [≥ 100°F] **accompanied by** cough and/or sore throat,

   AND

2. The participant must have a NP swab sample which tests positive for influenza infection by RT-PCR within 7 days of onset of US CDC-defined ILI performed at any setting during the study period.

Culture-confirmed protocol-defined and US CDC-defined ILIs

- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of culture-confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by any influenza A or B virus strains.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of culture-confirmed US CDC-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by any influenza A or B virus strains.

For the definition of rVE, refer to the primary endpoint analysis in Section 3.1.2.

Culture-confirmed protocol-defined ILI is defined based on the following criteria:

1. The participant must have experienced the following symptoms: Body temperature ≥ 37.5°C [≥ 99.5°F] **accompanied by** at least **ONE** of respiratory illness symptom: sore throat, cough, sputum production, wheezing, or difficulty breathing.

   AND

2. The participant must have a positive result for influenza infection by viral culture following a positive result for influenza infection by RT-PCR performed within 7 days after protocol-defined ILI symptom onset. Viral cultures will only be done on samples with a positive result for influenza infection by RT-PCR.

Culture-confirmed US CDC-defined ILI is defined based on the following criteria:

1. The participant must have experienced the following symptoms: Body temperature ≥ 37.8°C [≥ 100°F] **accompanied by** at least **ONE** respiratory illness symptom: cough, and/or sore throat.

AND

2. The participant must have a positive result for influenza infection by viral culture following a positive result for influenza infection by RT-PCR performed within 7 days after US CDC-defined ILI symptom onset. Viral cultures will only be done on samples with a positive result for influenza infection by RT-PCR.

RT-PCR confirmed ILI caused by specific influenza A strain

- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A strain that is antigenically matched to the vaccine strain H1N1.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A strain that is antigenically matched to the vaccine strain H3N2.
- rVE of mRNA-1010 vaccine vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or end of influenza season, whichever occurs later, caused by influenza A strain that is antigenically matched to the vaccine strain H1N1 and/or H3N2.

For the definition of rVE and RT-PCR confirmed protocol-defined ILI definition, refer to the primary endpoint analysis in Section 3.1.2. Furthermore, antigenic match to the selected vaccine A/H1N1 and/or A/H3N2 strains needs to be confirmed by antigenic testing using cultured viral isolate from the NP swab.

Hospitalizations associated with RT-PCR confirmed protocol-defined ILI

- rVE of mRNA-1010 vaccine vs. the active comparator to prevent hospitalizations associated with RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6) or end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine.

The rVE is defined as the percent reduction in the risk of hospitalization associated with a RT-PCR confirmed protocol-defined ILI by the mRNA-1010 group, compared to active comparator group, i.e.

$$\text{rVE} = 100 \times (1 - \text{RR})\ \%,$$

where RR is the relative risk between mRNA-1010 vs. active comparator. The RR will be estimated by ratio of the observed incidence rates in the two vaccine groups (mRNA-1010 vs. active comparator).

3.2.3. Secondary Immunogenicity Endpoints

The secondary immunogenicity objective will be evaluated by the following endpoints:

Humoral Immunogenicity

- Geometric mean titer (GMT) at Day 29 as measured by hemagglutination inhibition (HAI) assay
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay
- The proportion of participants with a titer ≥ 1:40 at Day 29 as measured by HAI assay
- Geometric mean fold rise (GMFR) comparing Day 29 to Day 1 (Baseline) as measured by HAI assay

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

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

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

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

The GMFR measures the changes in immunogenicity titers within participants and 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, t_{ij} and t_{ik} are the observed immunogenicity titers for participant i at time point j (Day 29) and k is Day 1 (Baseline).

4. Study Design

4.1. Overall Study Design

This is a Phase 3, randomized, observer-blind, active-controlled study to evaluate the safety and efficacy in preventing seasonal influenza of mRNA-1010 vaccine in adults ≥ 50 years of age.

The vaccine to be tested includes mRNAs encoding for the surface glycoproteins of the strains recommended by the WHO for 2022-2023 Northern Hemisphere (NH) cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019 (H1N1) pdm09-like virus;
- A/Darwin/6/2021 (H3N2)-like virus;
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Immunizations are planned during the typical 2022/2023 NH vaccination campaign period.

Approximately 23,000 participants will be randomized in a 1:1 ratio to receive a single dose of mRNA-1010 at [CCI] µg total mRNA or a single dose of the active comparator.

Table 1: Vaccination Groups and Dose Levels

Vaccination Group	Vaccination Received	mRNA/Antigen HA (each) (µg)	Total Dose (µg)	Number of Participants (Approximately)
1	mRNA-1010	CCI (of mRNA)	CCI (of mRNA)	11,500
2	Active Comparator (Fluarix® Quadrivalent CCI µg)	CCI (of protein)	CCI (of protein)	11,500

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid.

Clinic visits for all participants will be comprised of a Screening visit and a Vaccination Visit (Day 1). The Screening visit will occur up to 28 days before the Day 1 visit or potentially on the same day as the Vaccination Visit on Day 1.

Approximately 1000 participants will be asked to provide blood samples at baseline and on Day 29 (28 days post vaccination) for assessment of immune responses to the study intervention (immune response biomarker subset). A clinic visit on Day 29 will be required for these participants.

All participants will be asked to complete an electronic diary (eDiary) for solicited ARs from Day 1 to Day 7. There will be 6 safety telephone call visits at Days 8, 29 (except for those participants who are in the immune response biomarker subset which requires a clinic visit on Day 29), 91, 181, 271, and 361 (Month 12)/EoS as specified in the Schedule of Events (SoE) in Appendix A. The study duration (including screening) is up to 13 months for each participant

Participants will be instructed to report whether ILI symptoms have been experienced, via a Symptom Reporting eDiary, twice weekly from Day 1 to Day 181 and once weekly from Day 182 to Day 361 (Month 12)/EoS. If participants experience ILI symptoms, they will be instructed to contact the clinic and have an NP swab collected for testing within 72 hours. NP swab should be collected prior to any antiviral therapy if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during

ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the eCRF.

Unscheduled clinic visits for ILI symptoms assessment and NP swab collection may be conducted. Participants who manifest protocol-defined ILI will be evaluated by real-time RT-PCR testing of NP swab specimen(s) for influenza and other respiratory pathogens.

4.2. Statistical Hypotheses

The primary efficacy objective of this study is to evaluate rVE of mRNA-1010 as compared to an active comparator, to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.

4.2.1. Noninferiority Test

For the primary efficacy objective, the null hypothesis to be tested first is that the rVE of mRNA-1010 as compared to an active comparator is inferior, using a pre-specified 10% noninferiority margin (NIM). The noninferiority (NI) hypotheses are as follows:

Null hypothesis: H_0^1: rVE $\leq -10\%$ (inferior) vs.

Alternative hypothesis: H_a^1: rVE $> -10\%$ (non-inferior).

The rVE is defined as the percent reduction in the hazards of the primary endpoint (mRNA-1010 vs. active comparator). Equivalently, the NI hypotheses are:

H_0^1: HR ≥ 1.1 (inferior) vs.

H_a^1: HR < 1.1 (non-inferior),

where HR is the hazard ratio between mRNA-1010 vs. active comparator.

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1010 and the active comparator, using the Per-Protocol (PP) Set.

This is a group sequential design trial. The trial will be considered to meet the primary efficacy objective by demonstrating NI of mRNA-1010 to the active comparator if the one-sided p-value for rejecting HR ≥ 1.1 is less than the nominal alpha based on the Lan-DeMets

Pocock approximation spending function (see Section 6.4) at the interim analysis (IA), or at the final analysis, based on the PP Set. Cases will be counted starting 14 days after the vaccination and up to Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

4.2.2. Superiority Test

Once NI is demonstrated, the rVE will be further evaluated using the same endpoint for superiority. The superiority hypotheses are as follows:

Null hypothesis: H_0^2: rVE $\leq$ 0% (not superior)

Alternative hypothesis: H_a^2: rVE > 0% (superior)

Equivalently, the superiority hypotheses are:

H_0^2: HR $\geq$ 1 (not superior)

H_a^2: HR < 1 (superior)

Superiority of mRNA-1010 vs. the active comparator on the primary efficacy endpoint will be concluded if the one-sided p-value for rejecting HR $\geq$ 1 is less than the nominal alpha based on the Lan-DeMets Pocock approximation spending function (see Section 6.4) at IA, on the Modified Intent-to-Treat (mITT) Set.

4.3. Sample Size and Power

This Phase 3 study will plan to randomize approximately 23,000 participants in a 1:1 ratio to the mRNA-1010 or the active comparator groups. Therefore, approximately 11,500 participants will be randomized to each group.

The sample size is driven by the total number of cases to demonstrate rVE (mRNA-1010 vs. active comparator) to prevent the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1010 and active comparator, a total of 365 cases in the PP Set will provide at least 93% power to establish a NI claim with a NIM = 10%, i.e., rejecting the null hypothesis H_0^1: rVE $\leq$ -10%,

with one IA using the Lan-DeMets Pocock boundary for efficacy and a log-rank test statistic with an overall one-sided Type I error rate of 2.5%.

The number of cases will be continuously monitored using external epidemiologic data (e.g., CDC.gov). It is projected that by middle of February 2023, approximately 274 cases (75% of the targeted cases) will be observed in the PP Set. In the scenario that fewer cases are observed by middle of February, the IA will still be conducted around this timeframe because of the seasonality of influenza in the Northern Hemisphere, and the nominal alpha to be spent at the IA and final analysis will be adjusted accordingly.

The total number of cases pertains to the PP Set accruing at least 14 days after study intervention. Approximately 23,000 participants will be randomized with the following assumptions:

- The target rVE of mRNA-1010 to the active comparator is 25% to prevent the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.
- An attack rate of 2% in the active comparator for the primary endpoint.
- One IA in the middle of February 2023 with approximately 75% of total target cases expected across 2 study intervention groups in the PP Set.
- A dropout rate ~ 10% (not evaluable for the PP Set).
- Type I error rate will be adjusted using the Lan-DeMets Pocock boundary.

If the IA is conducted exactly at 75% of total target cases, the nominal one-sided Type I error rate will be 2.07% at IA, and 1.2% at the final analysis for NI testing, respectively.

Once NI is demonstrated, the rVE will be further evaluated for superiority of mRNA-1010 over the active comparator. The planned sample size (23,000 participants) is expected to generate approximately 386 cases in the mITT Set and to provide approximately 76% power to support the superiority claim with the following assumptions:

- The target rVE of mRNA-1010 to the active comparator is 25% to prevent the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.
- An attack rate of 2% in the active comparator for the primary endpoint.
- An IA in the middle of February 2023 with approximately 290 cases (75% of total target cases) expected across 2 study intervention groups in the mITT Set.
- A dropout rate ~ 4% (not evaluable for the mITT Set).
- Type I error rate will be adjusted using the Lan-DeMets Pocock boundary.

The total number of cases pertains to the mITT Set accruing at least 14 days after the study intervention. If the interim superiority analysis is conducted exactly at 75% of total target cases, the nominal one-sided Type I error rate will be 2.07% at IA, and 1.2% at the final analysis for superiority, respectively.

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

4.4. Randomization

Approximately 23,000 participants will be randomized in a 1:1 ratio to receive a single dose of mRNA 1010 at [redacted] µg total mRNA or a single dose of the active comparator (Table 1). Randomization will be stratified by age categories (≥ 50 to < 65 years or ≥ 65 years) and influenza vaccine status in the previous influenza season (received or not received) at the time of screening. At least 50% of enrollees will be ≥ 65 years old, including at least 10% who will be ≥ 75 years old.

The randomization will be performed using an Interactive Response Technology (IRT) system at the Day 1 visit, in accordance with pre-generated randomization schedules. As the appearance of the study interventions differ, enrollment will be observer blinded to the treatment assignment.

4.5. Blinding and Unblinding

This is an observer-blind study. The Investigator, clinic staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until the study database is locked and unblinded, with the following exceptions:

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than the study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded clinic personnel will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.
- An independent unblinded CRO statistical and programming team will perform the preplanned interim analyses and final analysis. The unblinded CRO statistical team will not be involved in either study design or the regular study conduct.
- Should the planned IA or the final analysis result in the Sponsor's decision to file regulatory submissions, a designated Sponsor team may be unblinded to prepare regulatory submissions. Once unblinded, the unblinded sponsor team will not be involved in the regular study conduct or communicate the unblinded results to the blinded Sponsor personnel, Investigators, clinic staff, clinical monitors or study participants. A separate blinded Sponsor team will carry out the study conduct

through the end of study when all participants have completed the month-12 follow-up or have withdrawn from the study.

Except for the appropriately delegated unblinded pharmacists, vaccine administrators, clinical trial managers, and monitors, and selected Sponsor and CRO personnel to be unblinded per the study Data Blinding Plan (DBP), all other personnel involved in the conduct of the study will remain blinded until the study is completed at the end of the study, and after the database is cleaned and locked.

In addition to the routine study monitoring outlined in the protocol, an independent data and safety monitoring board (DSMB) will review the unblinded safety and efficacy data at IA, and the final analysis to safeguard the interests of clinical study participants and to enhance the integrity of the study. The DSMB will make recommendations to the Sponsor in terms of study results reporting and unblinding based on the efficacy success criteria as described in Section 6.4 of this SAP.

More details of blinding and unblinding processes are specified in the study DBP.

5. Analysis Populations

Analysis populations for statistical analyses include the Randomization Set, Full Analysis Set (FAS), mITT Set, PP Set, Solicited Safety Set, and Safety Set.

5.1. Randomization Set

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

5.2. Full Analysis Set

The FAS consists of all randomized participants who received any study intervention. Participants will be analyzed according to the vaccination group to which they were randomized.

5.3. Modified Intent-to-Treat Set

The mITT Set consists of all participants in the FAS except those who discontinued from the study prior to 14 days following administration of study intervention.

The mITT Set will be used as the primary analysis set for efficacy endpoints evaluating superiority. Participants will be analyzed according to the group to which they were randomized.

5.4. Per-Protocol Set

The PP Set consists of all participants in the mITT Set who did not have major protocol deviations that could adversely impact efficacy, e.g., disease or therapeutic intervention that might cause suboptimal response to the study intervention.

The PP Set will be used as the primary analysis set for efficacy endpoints evaluating NI. Participants will be analyzed according to the group to which they were randomized.

5.5. Solicited Safety Set

The Solicited Safety Set consists of all randomized participants who received any study intervention and contributed to any solicited AR data.

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

5.6. Safety Set

The Safety Set consists of all randomized participants who received any study intervention. The Safety Set will be used for all analyses of safety except for the solicited ARs, and participants will be included in the vaccination group corresponding to the study intervention that they actually received.

5.7. Immunogenicity Subset

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

5.8. Per-Protocol Immunogenicity Subset

The PP Immunogenicity Subset consists of all participants in the Immunogenicity Subset who received planned dose of IP, complied with the immunogenicity testing schedule, and had no major protocol deviations that impact the immunogenicity assessment. Participants with RT PCR confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity Subset.

The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise. Participants will be analyzed according to the group to which they were randomized.

6. Statistical Analysis

6.1. General Considerations

The SoE is provided in Appendix A.

6.1.1. Statistics for Continuous and Categorical Variables

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

Categorical variables will be summarized using counts (n) and percentages (%).

6.1.2. Baseline

The baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to study vaccine administration.

For weight and height, measurements collected on Day 1 post vaccination can be used in deriving the baseline.

6.1.3. Data Precision

For the summary statistics of numeric variables, unless otherwise specified, the display precision will follow the programming standards presented in Appendix B.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. If the count equals the denominator, the percentage will be displayed as 100.

A row denoted "Missing" will be included in count tabulations where specified on the mock shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in the vaccination group within the analysis set of interest, unless otherwise specified.

6.1.4. Reference Start Date and Study Day

The reference start date is used as the time point from which the study day is calculated. Study days prior to the reference start date will be negative, while study days after the reference start date are positive.
The reference start date is the date of study vaccine administration.

Study day will be calculated as below:

a) study day prior to the vaccination will be calculated as follows:
   date of assessment/event – the reference start date.
b) study day on or after the date of the vaccination will be calculated as follows:
   date of assessment/event – the reference start date + 1.

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

- In scheduled visit windows for immunogenicity analysis per specified visit windowing rules
- Included in the derivation of baseline measurements.
- Included in the derivation of maximum/minimum values after vaccination and maximum/minimum change from baseline values for safety analyses.
- Presented in individual participant data listings as appropriate.

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

6.1.5. Handling Missing and Incomplete Data

- Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations, and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- If the laboratory results are reported as below the lower limit of quantification (LLOQ) (e.g. < 0.1), the numeric values will be replaced by 0.5 × LLOQ in the summary when treating the results as continuous variables. If the laboratory results are reported as greater than the upper limit of quantification (ULOQ) (e.g. > 3000), the numeric values will be replaced by the ULOQ when computing summary statistics for continuous variables.
- Other incomplete/missing data will not be imputed, unless specified otherwise.

6.1.6. Vaccination group

The following vaccination groups will be used for summary purposes:

- mRNA-1010
- Fluarix Quadrivalent CCI µg

If a participant received any dose of mRNA-1010, regardless of the treatment group the participant is randomized to, the participant will be included in the mRNA-1010 group as the actual treatment received for safety and reactogenicity analyses.

All analyses and data summaries/displays will be provided by vaccination group using the appropriate analysis population unless otherwise specified. Summaries may also pool all vaccination groups together (i.e., total group).

6.1.7. Analysis Periods

The following analysis periods and vaccination groups will be used for efficacy analyses:

Vaccination Group	Description	Analysis Period for Efficacy
mRNA-1010 CCI µg	Participants randomized to mRNA-1010 CCI µg	From randomization to the earliest date of study discontinuation, study

Fluarix Quadrivalent [redacted] µg	Participants randomized to active comparator (Fluarix quadrivalent [redacted] µg)	completion, death, or data cutoff date for efficacy

The analysis period and vaccination groups for Safety analyses are summarized below:

Vaccination Group	Description	Analysis Period for Safety
mRNA-1010 [redacted] µg	Participants received mRNA-1010 [redacted] µg	From the day of vaccination (Day 1) to the earliest date of study discontinuation, study completion, death, or data cutoff date for safety
Fluarix Quadrivalent [redacted] µg	Participants received active comparator (Fluarix quadrivalent [redacted] µg)	

The above safety analysis period will be used to summarize unsolicited treatment-emergent adverse events (TEAEs), MAAEs, SAEs, AESIs, and AEs leading to discontinuation throughout the study.

The period up to 7 days after injection, that starts at the day of injection and continues through 6 subsequent days, will be used for analyses of solicited ARs.

The period up to 28 days after injection, that starts at the day of injection and continues through 27 subsequent days, will be used as the primary analysis period for safety analyses including unsolicited AEs, except for solicited ARs.

6.1.8. Subgroups

Table 2: Subgroup Categories

Subgroup Variable	Category
Age Group 1 (per CRF)	≥ 50 to < 65 years ≥ 65 years
Age Group 2	≥ 50 to < 65 years ≥ 65 to < 75 years ≥ 75 years
Prior Influenza Vaccine Status (per CRF)	Received Not received

Sex	Male Female
Race	White Black or African American Asian Other (American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, Unknown, Not reported and other races)
Ethnicity	Hispanic or Latino Not Hispanic or Latino
Region	North America (US and Canada) Rest of World (Germany, United Kingdom, Spain, Denmark, Taiwan, Bulgaria, Poland, and Estonia)

6.2. Background Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following analysis sets (as defined in Section 5) will be summarized based on the Randomization Set:

- Randomization Set
- Full Analysis Set
- Modified Intent-to-Treat Set
- Per-Protocol Set
- Solicited Safety Set
- Safety Set

The denominators for percentages will be based on participants in the Randomization Set.

Summaries of reasons for exclusion from the PP Set and for exclusion from the mITT Set will be provided for excluded participants from the FAS.

A listing of analysis sets by participant will be provided based on the Randomization Set.

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

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

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

For screen failure participants, age (years), sex, race, ethnicity, screen failure reason, and other reason specified will be presented in a listing.

A separate summary table will include the number and percentage of randomized participants by vaccination group and overall with respect to each of the following groups: by stratification factor at randomization (i.e., ≥ 50 to < 65 years and received influenza vaccine in the previous season, ≥ 50 to < 65 years and did not receive influenza vaccine in the previous season, ≥ 65 years and received influenza vaccine in the previous season, or ≥ 65 years and did not receive influenza vaccine in the previous season) and by each of the two stratification factors at randomization separately (≥ 50 to < 65 years vs. ≥ 65 years; received vs. not received) based on the Randomization Set.

The number and percentage of participants in each of the following disposition categories will be summarized based on the Randomization Set:

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

Participants in the Randomization Set with any inclusion and exclusion criteria violation will be provided in a listing.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2).

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

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

The summaries will be provided separately based on the Randomization Set, Safety Set, mITT Set, and PP Set.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

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

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODD) version March 2022. The summary of medications will be based on the Safety Set. Imputation rules for missing and partial dates for medications and non-study vaccinations are detailed in Appendix C. Categorization of prior and concomitant medication is summarized in Table 7.

An overall summary of medications and non-study vaccinations, including the number and percentage of participants who take the following, will be presented by vaccination group:

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

The number and percentage of participants with at least one concomitant medication will be summarized by preferred term and vaccination group. Preferred terms will be displayed in descending order of frequency of the mRNA-1010 treatment group. Prior medications, concomitant medications and non-study vaccinations will be presented in a listing. Concomitant procedures will also be presented in a listing.

6.2.5. Protocol Deviations

The study protocol deviations will be reviewed on a regular basis and categorized as "Significant" and "Non-significant" based on the impacts on study results. Significant protocol deviations are a subset of protocol deviations that may significantly impact the

completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Significant protocol deviations rules will be developed and finalized before database lock by the study team.

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

Selected significant protocol deviations impact critical or efficacy study data, such as disease or therapeutic intervention, and participants with such deviations will be excluded from the PP Set for efficacy analyses; such significant protocol deviations will be determined and documented by Sponsor prior to database lock and unblinding. The reasons for exclusion from the PP Set for efficacy will be summarized.

6.2.6. COVID-19 Impact

The Coronavirus Disease 2019 (COVID-19) impact data will be listed for the Randomization Set and it will include which visit(s)/assessment(s) has (have) been missed due to COVID-19, along with the specific relationship to COVID-19.

6.3. Efficacy Analysis

Efficacy analyses will be performed using the PP and mITT Sets, and participants will be included in the vaccination group to which they are randomized.

A sequential/hierarchical testing procedure will be used to control Type I error rate over the primary efficacy endpoint and key secondary endpoints.

6.3.1. Analysis of the Primary Efficacy Endpoint

The overall Type I error rate for the primary endpoint at the IA is strictly controlled at 2.5% (one-sided) based on the Lan DeMets Pocock approximation spending function. Statistical significance of the primary efficacy endpoint for the primary objective can be achieved at either the IA, or at the final analysis.

6.3.1.1. Primary Efficacy Endpoint Definition/Derivation

The primary efficacy endpoint is the rVE of mRNA-1010 as compared to the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination and up to Day 181 (Month 6) or the end of the influenza season, whichever occurs later, caused by any seasonal influenza A or B virus strains regardless of antigenic match to strains selected for the seasonal vaccine.

The derivation rules to identify the first episode of RT-PCR confirmed protocol-defined ILI (see the definition in Section 3.1.2) are given below:

- CCI
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]

The start date is the earliest date of the ILI symptom onsets (within 7 days prior to or on the same day as the positive RT-PCR date).

- If multiple episodes are identified, the first episode of RT-PCR confirmed ILI is the one with the earliest start date.

The time to the first episode of RT-PCR confirmed protocol-defined ILI, in days, will be calculated as: Start date of the first RT-PCR confirmed protocol-defined ILI – Date of randomization +1.

Cases will be counted for the primary efficacy endpoint when the first episode of RT-PCR confirmed protocol-defined ILI starts 14 days after the vaccination and up to Day 181/ Month 6 or end of influenza season whichever ends later, i.e.,

Vaccination date + 14 ≤ Start date of the first RT-PCR confirmed protocol-defined ILI ≤ Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

6.3.1.2. Analysis of the Primary Efficacy Endpoint

6.3.1.2.1. Primary Analysis for Noninferiority

The primary analysis for NI will first be performed based on the PP Set. The NI hypotheses testing is presented in Section 4.2.1.

To assess the efficacy endpoint for the primary objective, preventing the first occurrence of RT-PCR confirmed protocol-defined ILI within the period of 14 days post study intervention through the end of the influenza season, Cox proportional hazards regression model will be used to estimate HR. The rVE, i.e., 1-HR (mRNA-1010 vs. active comparator) will be estimated along with the 2-sided 95% confidence interval (CI) and one-sided p-value for testing H_0^1: rVE ≤ -10%.

The number and percentage of participants who had a case for the primary efficacy endpoint will be summarized by vaccination group. The symptoms associated with the first RT-PCR confirmed protocol-defined ILI will be summarized by number and percentage of participants with each symptom by vaccination group.

A stratified Cox proportional hazard model including study vaccination group as a fixed effect will be used to estimate the HR (mRNA-1010 vs. active comparator) based on the PP Set. The stratification factors at randomization, i.e. age group (≥ 50 to < 65 years or ≥ 65

years) and influenza vaccine status in the previous season (received or not received), will be applied as the strata variables. Efron's method will be used to handle ties. The rVE will be estimated along with the two-sided 95% CI and one-sided p-value for testing H_0^1: rVE ≤ –10% (inferior).

Potential intercurrent events may include:

1. Early discontinuation or death unrelated to influenza; or
2. Early ILI up to 14 days after study vaccination.

In the estimand of the primary endpoint, a hypothetical strategy will be used to address the intercurrent events in the primary analysis based on the PP Set. The censoring rules for the occurrence of ILIs are presented in Appendix I.

Participants without RT-PCR confirmed protocol-defined ILI will be censored at Day 181 (Month 6) or the end of the influenza season (whichever occurs later), or at the data cutoff date for interim analysis, or at the date of early discontinuation or death unrelated to influenza, whichever is earliest. Participants with early RT-PCR confirmed protocol-defined ILI up to 14 days after the study vaccination (i.e., start date of the RT-PCR confirmed ILI ≤ vaccination date +13) will be censored at the start date of the early RT-PCR confirmed protocol-defined ILI.

The trial will be considered to meet the primary efficacy objective by demonstrating NI of mRNA-1010 to the active comparator if the one-sided p-value for rejecting H_0^1: HR ≥ 1.1 (equivalently, H_0^1: rVE ≤ –10%) is less than the nominal alpha based on the Lan-DeMets Pocock approximation spending function, based on the PP Set. The nominal one-sided alpha level will be 2.07% at IA, and 1.2% at the final analysis, respectively, if the IA is conducted when exactly 75% of the total number of cases are observed.

As sensitivity analyses, the primary endpoint analysis for NI will be repeated on the mITT Set using the same methods as described above. The NI analysis of the primary efficacy endpoint will also be performed using the actual stratification factors (CRF derived) on the PPS Set.

Thirdly, the NI analysis will be repeated on the PP Set with co-infected cases excluded from the analyses:

- 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 two swabs collected within 3 days.

6.3.1.2.2. Primary Analysis for Superiority

If the NI of mRNA-1010 vs. active comparator is demonstrated using the PP Set, superiority of mRNA-1010 vs. active comparator will be evaluated using the same primary endpoint based on the mITT Set, either at IA or at the final analysis.

Superiority of mRNA-1010 vs. the active comparator on the primary efficacy endpoint will be concluded if the one-sided p-value for rejecting H_0^2: HR ≥ 1 (equivalently, H_0^2: rVE $\leq$ 0%) is less than the nominal alpha based on the Lan-DeMets Pocock approximation spending function, based on the mITT Set. For this superiority testing, the nominal one-sided alpha level will be 2.07% at IA, and 1.20% at the final analysis, respectively, if the IA is conducted when exactly 75% of total number of cases are observed.

As for the primary NI analysis, the following sensitivity analyses for the primary superiority analysis will be conducted: 1) the superiority analysis will be repeated on the PP Set using the same methods as described above; 2) the superiority analysis of the primary efficacy endpoint will also be performed using the actual stratification factors (CRF-derived) on the mITT Set; 3) the superiority analyses will be performed on the mITT Set by excluding RT-PCR confirmed protocol-defined ILI co-infected with other respiratory viruses as confirmed by RT-PCR respiratory test panel (see Section 6.3.1.2.1).

6.3.1.2.3. Supportive Analyses

As a supportive analysis, rVE will be estimated by one minus the ratio of incidence rates (mRNA-1010 vs. active comparator) multiplied by 100%:

$$rVE = 100 \times (1 - \text{ratio of incidence rates adjusting for person-time}) \%$$

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.

For each participant, the person-time is calculated as the time (days) from randomization to the date of the first episode for participants with a case, and the time (days) from randomization to the date of censoring for participants without a case (or who are censored). 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-seasons 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 (i.e., first episode of RT-PCR confirmed protocol-defined ILI at least 14 days post vaccination and up to Day 181 (Month 6) or end of the influenza season, whichever occurs later) divided by the total person-season in each vaccination group multiplied by 1000. The same censoring rules as described for the primary analyses will be followed.

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

A stratified log-rank test will be performed to assess the time to first episode of RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination up to Day 181 or at the end of the influenza season.

A Kaplan-Meier curve will be used to plot the estimated cumulative incidence rates over time by vaccination group. Cases of RT-PCR confirmed protocol-defined ILI will be counted starting 14 days post vaccination up to Day 181 or at the end of the influenza season, whichever occurs later. The same censoring rules as described for the primary analyses will be followed.

In addition, supportive analyses will be conducted using similar stratified Cox proportional hazard analyses to estimate the rVEs, defined as the percent reductions in the hazards (mRNA-1010 vs. active comparator), i.e. rVE = 100 x (1 – HR) %, together with the 95% Cis, to prevent the occurrences of the following events:

1. RT-PCR confirmed protocol-defined ILIs caused by influenza A by different subtype:
   - RT-PCR confirmed protocol-defined ILIs caused by influenza subtype A/H1 per RT-PCR starting 14 days post vaccination up to Day 181 or at the end of the influenza season, whichever occurs later;
   - RT-PCR confirmed protocol-defined ILIs caused by influenza subtype A/H3 per RT-PCR starting 14 days post vaccination up to Day 181 or at the end of the influenza season, whichever occurs later;
   - RT-PCR confirmed protocol-defined ILIs caused by influenza A per RT-PCR with unknown subtype starting 14 days post vaccination up to Day 181 or at the end of the influenza season, whichever occurs later.

   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 subtype – Date of randomization +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 subtype is different from the one being analyzed, the participant will be censored at the start date of the confirmed ILI case.

2. Positive RT-PCR cases regardless of ILI symptoms, starting 14 days post vaccination up to Day 181 or at the end of the influenza season, whichever occurs later.

For this analysis, the time to the first event will be calculated as: The first positive RT-PCR date – Date of randomization +1. Similar censoring rules as for the primary efficacy endpoint will be applied.

Supportive analyses will be performed in the PPS set, and in the mITT set if the NI test is successful.

6.3.1.2.4. Subgroup Analyses

To assess consistency of rVE across subgroups, the primary efficacy endpoint will be analyzed in selected subgroups based on the PP Set, using similar methods as described for the primary analysis. The estimated rVE and 95% CI will be provided within each category of the planned subgroups (see Table 2 for subgroups).

If the number of participants in a particular subgroup is less than 15% of the enrollment sample size, then the subgroup may be combined with other subgroups for analyses. The subgroup analyses will not provide inference for the interactions between subgroups.

Forest plots will be provided for rVE and its 95% CI for each subgroup based on the PP Set.

The above subgroup analyses will be repeated on the mITT Set if NI is demonstrated.

6.3.2. Analysis of the Key Secondary Efficacy Endpoints

A sequential/hierarchical statistical multiple testing procedure will be used to control the overall Type 1 error rate over the primary efficacy endpoint and key secondary efficacy endpoints.

Key secondary efficacy endpoints will only be tested for NI and superiority at the final analysis using one-sided 2.5% Type I error rate when the primary efficacy endpoint achieves statistical significance. See Section 6.6 for the multiplicity adjustments among the primary efficacy endpoint and the key secondary efficacy endpoints.

6.3.2.1. Derivation of Cases for Key Secondary Efficacy Endpoints

The first key secondary efficacy endpoint is the rVE of mRNA-1010 vs. the active comparator in preventing the first occurrence of RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A or B virus strains with similarity to the vaccine strains selected for the seasonal influenza vaccine.

The second key secondary efficacy endpoint is the rVE of mRNA-1010 vs. the active comparator in preventing the first occurrence of RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A or B virus strains antigenically matched to the vaccine strains selected for the seasonal influenza vaccine.

Following a positive RT-PCR result obtained by the central laboratory, the antigenicity test on cultured laboratory isolates and sequencing of HA region will be performed on the NP-swab sample stored at the central laboratory.

The derivation rules for the first RT-PCR confirmed protocol-defined ILI caused by influenza A or B virus strains with similarity to selected vaccine strains are as follows:

- Must be the first RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1)
- Similarity is confirmed by culture antigenic test and/or genetic sequencing, following the rules specified in Table 3 below.

The derivation rules for the first RT-PCR confirmed protocol-defined ILI caused by influenza A or B virus strains antigenically matched to selected vaccine strains are as follows:

- Must be the first RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1)
- Antigenic match is confirmed by culture antigenic test with more details specified in Table 3 below.

Table 3: 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	Matched and Similar	Matched and Similar
	Not Matched	Not Matched; Not Similar	Not Matched; Not Similar	Not Matched; Not Similar

	Unknown/Not Reportable	Similar but Unknown Antigenically	Not Similar and Unknown Antigenically	Unknown for Both

When deriving similarity, the culture result (if available) will take precedence over the sequencing result. The sequencing test provides additional information when the culture result is unavailable.

After the identification of a RT-PCR confirmed protocol-defined ILI, the results from the subsequent viral culture antigenic test and/or the genomic sequencing test on the NP-swab sample may be unavailable to confirm antigenic match or similarity to the selected vaccine strains. The main reasons include 1) damaged/lost sample; 2) unsuccessful amplification and/or culturing in laboratory processing; and 3) tests not done due to a local certified laboratory being used.

In the third case (a local certified laboratory test is used for RT-PCR confirmation), an NP-swab sample may be collected and processed by the central laboratory at a later time. If another positive RT-PCR test exists within 7 days of the confirming positive RT-PCR date and subsequent antigenic test and/or genomic sequencing test results are available, then the information from this test can be used to derive the similarity and antigenic match, following the same logic described above.

If a positive RT-PCR test does not exist to provide supplemental information, then the antigenic match and/or similarity results will be considered missing.

The time to the first identified episode for the key secondary efficacy endpoints, in days, will be calculated as: Start date of the first identified episode – Date of randomization + 1.

Cases will be counted for each of the two key secondary efficacy endpoints when the first identified episode starts 14 days after the vaccination and up to Day 181/ Month 6 or at the end of the influenza season whichever ends later. i.e.

$$\text{Vaccination date} + 14 \leq \text{Start date of the first identified episode} \leq \text{Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.}$$

6.3.2.2. Analysis of the Key Secondary Efficacy Endpoints

The same primary, sensitivity, and supportive analysis methods as described for the primary efficacy endpoint (Section 6.3.1.2) will be applied to the key secondary efficacy endpoints based on the PP and mITT Sets, unless otherwise specified.

As for the primary efficacy endpoint, potential intercurrent events for key secondary efficacy endpoints may include:

1. Early discontinuation or death unrelated to influenza; or
2. Early ILI up to 14 days after study vaccination.

The same intercurrent event handling approach used for the primary efficacy endpoints will be used to address the intercurrent events for the analysis of key secondary efficacy endpoints.

Similar censoring rules as for the primary efficacy endpoint will be applied. Participants without RT-PCR confirmed protocol-defined ILI with similarity to selected influenza A or B virus strains for the seasonal influenza vaccine will be censored at Day 181 (Month 6) or at the end of the influenza season (whichever occurs later), or at the date of early discontinuation or death unrelated to influenza, whichever is earliest. Participants with early RT-PCR confirmed protocol-defined ILI up to 14 days after the study vaccination will be censored at the start date of the earliest RT-PCR confirmed protocol-defined ILI.

Participants without RT-PCR confirmed protocol-defined ILI with antigenically matched to selected influenza A or B virus strains for the seasonal influenza vaccine will be censored at Day 181 (Month 6) or at the end of the influenza season (whichever occurs later), or at the date of early discontinuation or death unrelated to influenza, whichever is earliest. Participants with early RT-PCR confirmed protocol-defined ILI up to 14 days after the study vaccination (start date of the RT-PCR confirmed ILI $\leq$ vaccination date +13) will be censored at the start date of the earliest RT-PCR confirmed protocol-defined ILI.

In addition, after he first RT-PCR confirmed ILI is confirmed, the antigenic match and/or similarity (see Section 6.3.2.1) is negative or the result is missing, the observation will be censored at the ILI start date for the corresponding key secondary efficacy endpoints.

The following analyses will be conducted at the final analysis for each of the key secondary efficacy endpoints.

6.3.2.2.1. Analysis for Noninferiority

Relative vaccine efficacy will be estimated using a stratified Cox proportional hazard model including study vaccination group as a fixed effect to estimate the HR (mRNA-1010 vs. active comparator) at a one-sided 2.5% significance level based on the PP Set. The stratification factors at randomization (Section 4.4) will be applied as the strata variables. Efron's method will be used to handle ties. The rVE will be estimated along with the two-sided 95% CI and one-sided p-value for testing H_0^1: $rVE \leq -10\%$ (inferior).

Noninferiority will be demonstrated if the one-sided p-value for rejecting H_0^1: $HR \geq 1.1$ (equivalently, H_0^1: $rVE \leq -10\%$) is less than 2.5%, on the PP Set at the final analysis.

As a sensitivity analysis, the analysis of the key secondary efficacy endpoints for NI will be repeated on the mITT Set. In addition, another sensitivity analysis for the NI of the key secondary efficacy endpoints will be performed using the actual stratification factors (CRF derived) on the PPS Set.

6.3.2.2.2. Analysis for Superiority

If the NI of mRNA-1010 vs. active comparator is demonstrated using the PP Set, superiority of mRNA-1010 vs. active comparator will be evaluated using the same key efficacy endpoint on the mITT Set, at the final analysis.

Superiority will be demonstrated if the one-sided p-value for rejecting H_0^2: $HR \geq 1$ (equivalently, H_0^2: $rVE \leq 0\%$) is less than 2.5%, on the mITT Set.

As a sensitivity analysis, the analysis of the key secondary efficacy endpoints for superiority will be repeated on the PP Set. In addition, another sensitivity analysis for the superiority of the key secondary efficacy endpoints will be performed using the actual stratification factors (CRF derived) on the mITT Set.

6.3.2.2.3. Supportive Analyses

The same method used for the primary endpoint based on the incidence rate and stratified log rank test will be performed on the mITT set as a supportive analysis if the NI for the corresponding key secondary endpoint(s) is demonstrated.

6.3.2.2.4. Subgroup Analysis

Similar subgroup analysis for NI as used for the primary endpoint may be performed on the PP Set if sufficient case numbers of the key secondary endpoints have been observed. Subgroup analysis may be performed for the superiority test on mITT Set if the NI for the corresponding key secondary endpoint is demonstrated.

6.3.3. Analysis of the Other Secondary Efficacy Endpoints

6.3.1.1. Derivation of Cases for Other Secondary Efficacy Endpoints

6.3.1.2. RT-PCR Confirmed US CDC-defined ILI

The secondary efficacy endpoints for RT-PCR confirmed US CDC-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of influenza season are as follows:

- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by any influenza A or B strains regardless of antigenic match.
- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A or B virus strains with similarity to vaccine strains.
- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed US CDC-defined ILI starting 14 days post

vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A or B virus strains that are antigenically matched to vaccine strains.

The first RT-PCR confirmed US CDC-defined ILI is derived as the first RT-PCR confirmed protocol-defined ILI case (see derivation rules in Section 6.3.1.1) which also meets the US CDC-defined ILI definition: The presence of temperature ≥ 37.8 °C [≥100°F], accompanied by at least one of the respiratory illness symptoms (cough and/or sore throat).

The confirmations of similarity and antigenic match follow those for the key secondary efficacy endpoints as described in Section 6.3.2.1 and Table 3.

The time to first identified episode for the secondary efficacy endpoints, in days, will be calculated as: Start date of the first identified episode – Date of randomization +1.

Cases will be counted for the secondary efficacy endpoints when the first identified episode for the other secondary endpoints starts 14 days after the vaccination and up to Day 181 (Month 6) or at the end of the influenza season whichever occurs later, i.e.,

Vaccination date + 14 ≤ Start date of the first episode for the secondary efficacy endpoint ≤ Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

6.3.1.3. Culture-Confirmed Protocol-Defined ILI

The secondary efficacy endpoint for culture-confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 or at the end of the influenza season are as follows:

- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of culture-confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by any influenza A or B strains.

The derivation rules for the first culture-confirmed protocol-defined ILI caused by any influenza A or B virus strains (see definition in Section 3.2.2) are as follows:

- Must be the first RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1)

- Must be confirmed by a positive result for influenza infection by viral culture using the stored NP-swab sample

As for the key secondary efficacy endpoints, when a local certified laboratory is used for the RT-PCR test, the viral culture test cannot be performed on the NP swab sample. If another qualified positive RT-PCR test with subsequent viral culture test result (positive or negative) is available, then the same search criteria (positive RT-PCR dates within 7 days) will be implemented.

The time-to-first identified culture-confirmed protocol-defined ILI, in days, will be calculated as: Start date of the first identified episode – Date of randomization + 1.
Cases will be counted when the first identified episode of culture-confirmed protocol-defined ILI starts 14 days after the vaccination and up to Day 181 (Month 6) or at the end of the influenza season whichever occurs later, i.e.,

Vaccination date + 14 ≤ Start date of the first culture-confirmed protocol-defined ILI ≤ Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

6.3.1.4. Culture-Confirmed US CDC-Defined ILI

The secondary efficacy endpoint for culture-confirmed US CDC-defined ILI starting 14 days post vaccination through Day 181 or at the end of the influenza season are as follows:

- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of culture-confirmed US CDC-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by any influenza A or B strains.

A culture-confirmed US CDC-defined ILI case is defined as a positive result for influenza infection by viral culture following a positive result for influenza infection by RT-PCR, together with eligible symptoms (Section 3.2.2).

The derivation rules for the first culture-confirmed US CDC-defined ILI caused by any influenza A or B virus strains are as follows:

- Must be the first RT-PCR confirmed US CDC-defined ILI (Section 6.3.2.3.1)

- Must be confirmed by a positive result for influenza infection by viral culture using the stored NP-swab sample

As for the key secondary efficacy endpoints, when a local certified laboratory is used for the RT-PCR test without a viral culture on the NP swab sample, another qualified positive RT-PCR test with subsequent viral culture antigenic match result (positive or negative) can be used. The same search criteria (positive RT-PCR dates within 7 days) will be implemented.

The time to first identified culture-confirmed US CDC-defined ILI, in days, will be calculated as: Start date of the first culture-confirmed US CDC-defined ILI – Date of randomization + 1.

Cases will be counted when the first identified episode of culture-confirmed US CDC-defined ILI starts 14 days after the vaccination and up to Day 181 (Month 6) or end of influenza season whichever occurs later, i.e.,

Vaccination date + 14 ≤ Start date of the first culture-confirmed US CDC-defined ILI ≤ Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

6.3.1.5. RT-PCR Confirmed Protocol-defined ILI Caused by Specific Influenza Strains

The other secondary endpoints defined in Section 3.2.2 will be analyzed as follows:

- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A virus strain that is antigenically matched to the selected vaccine strain H1N1.
- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A virus strain that is antigenically matched to the selected vaccine strain H3N2.

- rVE of mRNA-1010 vs. the active comparator to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by influenza A virus strains that are antigenically matched to the selected vaccine strains H1N1 and/or H3N2.

The first RT-PCR confirmed protocol-defined ILI caused by influenza A virus strain that is antigenically matched to the H1N1 strain contained in the vaccine:

- Must be the first RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1),
- Antigenic match to the A/H1N1 strain contained in the vaccine must be confirmed using cultured viral isolate from the same NP swab sample by antigenicity testing with strain-specific reference sera.

Similarly, the first RT-PCR confirmed protocol-defined ILI caused by influenza A virus strain that is antigenically matched to the H3N2 strain contained in the vaccine are derived as:

- Must be the first RT-PCR confirmed protocol-defined ILI (Section 6.3.1.1),
- Antigenic match to the A/H3N2 strain contained in the vaccine must be confirmed using cultured viral isolate from the same NP swab sample by antigenicity testing with strain-specific reference sera.

The first RT-PCR confirmed protocol-defined ILI caused by influenza A virus strains that are antigenically matched to the selected vaccine strains H1N1 and/or H3N2 contained in the selected vaccine is derived similarly.

As for the key secondary efficacy endpoints, when a local certified laboratory is used for the RT-PCR test without a viral culture on the NP swab sample, then another qualified positive RT-PCR test with subsequent viral culture antigenic match result (positive or negative) can be used. The same search criteria (positive RT-PCR dates within 7 days) will be implemented.

The time to the first identified episode for each of these secondary efficacy endpoints, in days, will be calculated as: Start date of the first identified episode – Date of randomization + 1.

A participant will be counted as a culture-confirmed US CDC-defined ILI case caused by a specific influenza strain if the first identified episode for each of these secondary efficacy endpoints starts 14 days after the vaccination and up to Day 181 (Month 6) or at the end of the influenza season whichever occurs later, i.e.,

Vaccination date + 14 ≤ Start date of the first identified episode
≤ Date of Day 181/ Month 6 or at the end of the influenza season, whichever occurs later.

6.3.1.6. Hospitalizations Associated with RT-PCR Confirmed Protocol-Defined ILI

This secondary efficacy endpoint is the rVE of mRNA-1010 vs. the active comparator in preventing hospitalizations associated with RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or at the end of the influenza season, whichever occurs later, caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine.

Cases of hospitalizations associated with a protocol-defined ILI will be identified in the Adverse Events Healthcare Encounter eCRF page if the reason for the hospitalization is assessed to be associated with a protocol-defined ILI by the investigator. These cases will be adjudicated by a blinded medical team before database lock and will be verified for confirmation by a positive RT-PCR test.

Participants with at least one hospitalization associated with a RT-PCR confirmed ILI that starts 14 days after the vaccination and up to Day 181 (Month 6) or at the end of the influenza season whichever occurs later will be summarized based on the PP Set.

6.3.1.7. Analysis of Other Secondary Efficacy Endpoints

For each of the other secondary efficacy endpoints discussed in Section 6.3.2.3.1 – 6.3.2.3.4, a stratified Cox proportional hazards model will be used to estimate the HR. Relative vaccine efficacy will be estimated along with two-sided 95% CI based on the PP and mITT Sets.

Intercurrent events, missing data, and censoring rules will be similar to those for the primary and key secondary efficacy endpoints, where applicable. After the first RT-PCR confirmed protocol-defined ILI is identified, if any additional condition required for the other efficacy endpoint is not met or cannot be determined, the observation will be censored at the ILI start date for the corresponding other secondary efficacy endpoints.

The other secondary efficacy endpoint discussed in Section 6.3.2.3.5 will be analyzed as follows:

- rVE of mRNA-1010 vs. the active comparator in preventing hospitalizations associated with RT-PCR confirmed protocol-defined ILI starting 14 days post vaccination through Day 181 (Month 6) or the end of the influenza season, whichever occurs later, caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine

The number and percentage of participants with at least one case will be summarized by vaccination group.

The rVE will be estimated by one minus the ratio of observed incidence rates (mRNA-1010 vs. active comparator) multiplied by 100%:

$$rVE = 100 \times (1-[(C_{mRNA}/N_{mRNA}) / (C_{control}/N_{control})]) \%,$$

where C_{mRNA} and $C_{control}$ are the number of cases per the hospitalizations associated with RT-PCR confirmed protocol-defined ILI efficacy endpoint definition in the mRNA-1010 group and the active comparator group respectively, and N_{mRNA} and $N_{control}$ are the number of participants in the mRNA-1010 group and the active comparator group, respectively.

A 2-sided 95% CI for rVE will be calculated based on Farrington and Manning's score method (Farrington and Manning 1990) based on the PP and mITT Sets.

The above analyses of secondary efficacy endpoints are not controlled for multiplicity.

6.4. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the PP Immunogenicity Subset. For all summary tables, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

For each of the four strains, the GMT of HAI titers with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale. The GMFR of HAI titers with corresponding 95% CI at Day 29 over baseline will also be provided. Descriptive summary statistics will also be provided, including n, median, minimum, and maximum will be provided.

An analysis of covariance (ANCOVA) model will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The geometric least square mean (GLSM), and its corresponding 95% CI results on the log-transformed scale estimated from the model will be back-transformed to obtain these estimates on the original scale, as an estimate of the GMT. GMR, estimated by the ratio of GLSM and the corresponding two-sided 95% CI will be provided to assess the difference in immune response between the mRNA-1010 compared to the active comparator group at Day 29.

For each strain, seroconversion is defined as 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 four-fold rise in post-vaccination HAI antibody titer.

The number and percentage of participants with seroconversion due to vaccination will be provided with two-sided 95% CI using the Clopper-Pearson method at Day 29. To compare the seroconversion rates between the vaccination groups, the Miettinen-Nurminen method will be used to calculate the 95% CI for the difference in seroconversion rates. The seroconversion rate difference with the corresponding 95% CI at Day 29 will be provided for each strain.

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

The above immunogenicity analyses will be repeated using the Immunogenicity Subset as a sensitivity analysis.

Subgroup analyses will be performed in the Per-Protocol Immunogenicity Subset for the following subgroups: Age Group 1, Age Group 2, Prior Influenza Vaccine Status, Sex, Race, and Ethnicity (Section 6.1.8). Subgroups with fewer than 30 participants in the analysis set may be combined in other subgroups.

6.5. Planned Analyses

There is one planned IA with data cut-off around the middle of February 2023 regardless of number of influenza cases accrued for the primary NI hypothesis to be tested to support the primary objective. The intent of the IA is for early detection of reliable evidence that rVE of mRNA-1010 is noninferior to the active comparator. The Lan-DeMets Pocock boundaries are used for calculating efficacy boundaries and to preserve the (1-sided) 2.5% Type I error rate over the IA and the final analysis (when the target number of cases have been observed), relative to the hypothesis:

H_0^1: HR ≥ 1.1 (equivalently, rVE ≤ - 10%).

If NI is demonstrated at an IA, the subsequent final analysis will be considered supportive in nature for the NI claim. The DSMB will review the IA results and make recommendations to the Sponsor in terms of study results reporting and unblinding based on the boundaries of early efficacy as described in this section.

In summary, one IA for the primary efficacy endpoints and a final efficacy analysis are planned in this study (Table 4). An EoS analysis may be performed in this study as described below.

- IA for the primary efficacy endpoint will be performed with data cut-off around the middle of February 2023 when it is projected that approximately 75% of the total cases (274 RT-PCR confirmed protocol-defined ILI cases across both treatment groups) would be observed in the PP Set. In the case that fewer cases are observed by middle of February, the IA will continue to be conducted during this timeframe due to seasonality considerations. The nominal alpha level to be spent at the IA and final analysis will be adjusted accordingly. The DSMB will review the unblinded IA results.
- The final efficacy analysis will be performed when approximately 365 cases across both treatment groups have been observed in the PP set.
- The EoS analysis may be performed when all study participants have completed the final visit on Day 361 (Month 12) or have withdrawn from the study. The study database will be cleaned and locked, and the study will be unblinded.

The RT-PCR confirmed ILI cases are counted when the first episode starts 14 days after the vaccination and up to Day 181/ Month 6 or at the end of the influenza season whichever ends later.

Table 4: Planned Analyses and Hypothesis Testing for the Primary Efficacy Endpoint

Planned Analysis	Noninferiority testing on PP Set	Superiority testing on mITT Set
IA (75%)	274 cases	290 cases
Final Analysis (100%)	365 cases	386 cases

Subsequent final analysis is of a supportive nature if success is achieved at the IA.

6.5.1. Interim Analysis

There is one planned IA at 75% of total target cases across the 2 treatment groups and a final analysis for the first null hypothesis to be tested to support the primary objective. The main intent of the IA is for early detection of reliable evidence that rVE of mRNA-1010 is noninferior to the active comparator. The Lan-DeMets Pocock approximation spending function is used for calculating efficacy boundaries and to preserve the (one-sided) 2.5% Type I error rate over the IAs and the final analysis (when the target number of cases have been observed).

The NI hypotheses are as follows:

Null hypothesis: H_0^1: rVE $\leq -10\%$ (inferior)

Alternative hypothesis: H_a^1: rVE $> -10\%$ (non-inferior)

Equivalently, the NI hypotheses are:

H_0^1: HR ≥ 1.1 (inferior)

H_a^1: HR < 1.1 (non-inferior)

If NI is demonstrated at an IA, the subsequent analyses will be considered supportive in nature for the NI claim. The DSMB will review the IA results and make recommendations to the Sponsor in terms of study results reporting and unblinding based on the boundaries of early efficacy as described in this section, safety data, and data external to this study.

Table 5 summarizes the timing, number of cases, and decision guidance at each IA and final analysis.

Table 5: Interim Boundaries Using Lan-DeMets Pocock Spending Function, Calculation Based on the PP Set for the Endpoint Supporting the Primary Objective

Information Fraction (% of total #cases)	Number of Cases	Nominal Alpha (1-sided) ±	Efficacy Boundary Rejecting H_0: rVE ≤ -10%	Cumulative Probability (Crossing Efficacy Boundary if the True rVE = 25%)
IA (75%)	274	2.07%	rVE ≥ 14.0% (HR ≤ 0.860)	78.9%
Final Analysis (100%)	365	1.2%	rVE ≥ 13.2% (HR ≤ 0.868)	95.0%

±: actual nominal alpha may be adjusted based on the actual information fraction at individual IA(s).

The IA will occur with data cut-off around the middle of February in 2023 when approximately 75% of the total cases in the PP Set are expected to be observed. The study will be considered positive (non-inferior) at IA if the one-sided p-value for rejecting HR ≥ 1.1 is less than 2.07% based on the Lan-DeMets Pocock approximation spending function, provided that IA is conducted exactly at the 75% information fraction. The nominal alpha to be spent at the IA and final analysis may be adjusted according to the actual number of cases observed at IA.

If NI is demonstrated at IA, the superiority claim in the same primary endpoint will be evaluated to support the primary objective, i.e., H_0[2]: HR ≥ 1 (equivalently, rVE ≤ 0%). Approximately 290 cases are expected to be observed in the mITT Set at IA. Superiority of mRNA-1010 relative to the active comparator is demonstrated if the one-sided p-value for rejecting HR ≥ 1 (equivalently, rVE ≤ 0%) is less than 2.07% based on the Lan-DeMets Pocock approximation spending function. The nominal alpha to be spent at the IA and final analysis may be adjusted according to the actual number of cases observed at IA.

No formal statistical testing is planned at the IA for key secondary and other secondary efficacy endpoints. However, descriptive summarizations and statistical analyses may be conducted in an exploratory manner to support the primary endpoint.

6.5.2. Final Analysis

If the primary NI objective is not achieved at IA, it will be evaluated again at the final analysis, when approximately 365 cases have been observed in the PP Set. The study will be considered positive (non-inferior) at the final analysis if the one-sided p-value for rejecting HR $\geq$ 1.1 is less than 1.2% based on the Lan-DeMets Pocock approximation spending function.

Similarly, if the primary superiority objective is not achieved at IA, it will be evaluated again using the same primary endpoint at the final analysis, provided that the NI has been demonstrated (either at the IA or at the final analysis). Approximately 386 cases are expected to have been observed in the mITT Set. Superiority of mRNA-1010 relative to the active comparator is demonstrated if the one-sided p-value for rejecting HR $\geq$ 1 is less than 1.2% based on the Lan-DeMets Pocock approximation spending function.

Note that the actual nominal alpha may be adjusted based on the actual information fraction at individual IA.

Following the multiplicity adjustment procedure described in Section 6.6, the NI and superiority testing for the key secondary efficacy endpoints will be performed at the final analysis. Upon successes achieved for the preceding analyses pre-specified in the hierarchical testing sequence (Figure 1), the NI and superiority in the key secondary efficacy endpoints will be demonstrated if the one-sided p-value for each of the hypothesis testing is less than 2.5%.

Analyses of other secondary efficacy endpoints may be conducted to support the primary and key secondary efficacy endpoints. No formal statistical testing is planned for these analyses.

6.5.3. End-of-Study Analysis

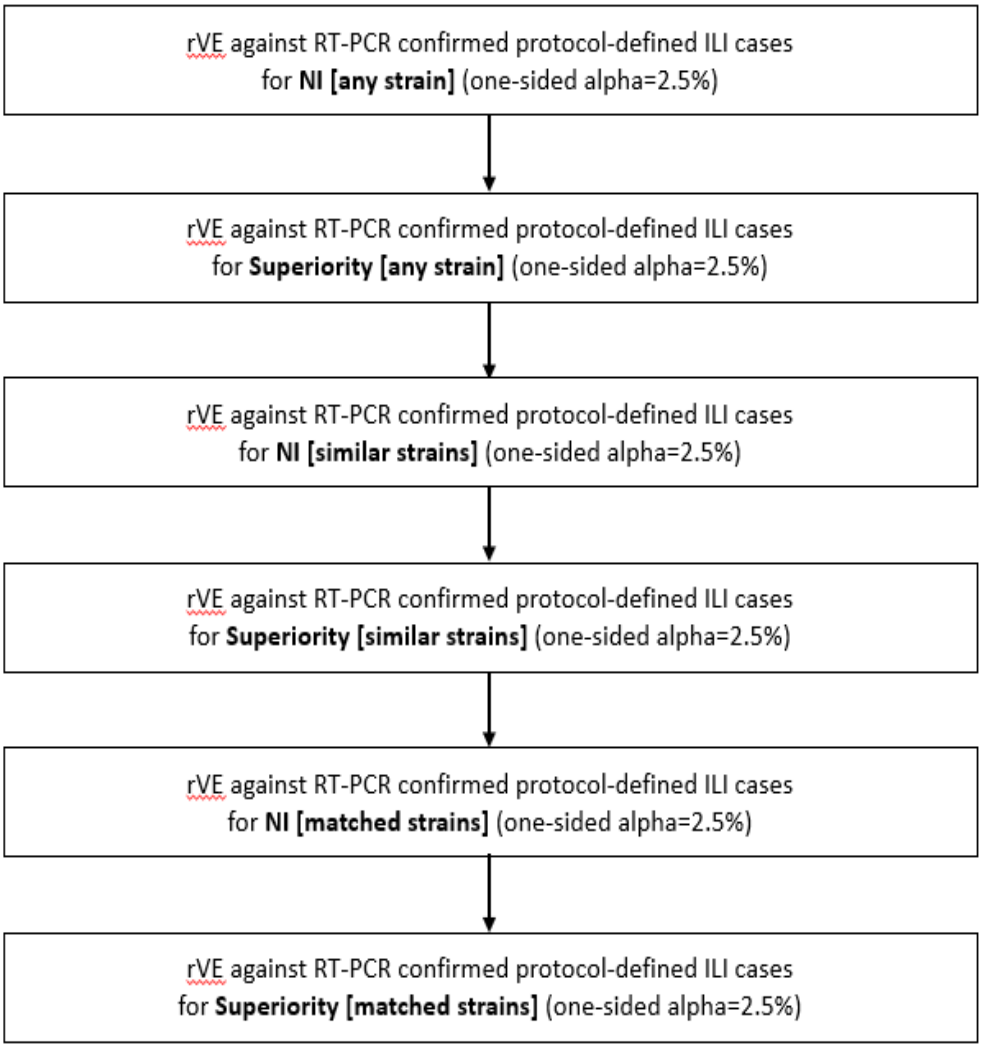
An EoS analysis may be performed at the end of the study when all study participants have completed the final visit on Day 361 (Month 12) or have withdrawn from the study. The study database will be cleaned and locked, and the study will be unblinded. The final analysis and the EoS analysis may be combined if timing allows.

Analyses for the primary, key secondary, and other secondary efficacy endpoints may be re-run as supportive analyses.

6.6. Multiplicity Adjustment

To control the overall one-sided Type I error rate for the study, a hierarchical testing strategy will be used to test the primary and secondary efficacy endpoints (Figure 1).

Figure 1: Testing Sequence of the Primary and Secondary Endpoints



Noninferiority of mRNA-1010 vs. the active comparator on the primary efficacy endpoint will be declared if the one-sided p-value for rejecting HR $\geq$ 1.1 is less than the nominal alpha based on the Lan-DeMets Pocock approximation spending function, based on the PP Set. The nominal alpha levels (one-sided) are 2.07%, and 1.2% at the IA and final analysis,

respectively, if the IA is conducted when 75% of total target cases are accumulated across the 2 groups.

If the NI criteria is met for the primary efficacy endpoint, superiority of mRNA-1010 relative to the active comparator will be tested on the mITT Set. The superiority of rVE will be demonstrated if the one-sided p-value for rejecting HR ≥ 1 is less than the nominal alpha based on the Lan-DeMets Pocock approximation spending function, based on the mITT Set. For this superiority testing, the nominal one-sided alpha level will be 2.07% and 1.2% at the planned IA and final analysis, respectively, if the IA is conducted when 75% of total target cases are accumulated across the two treatment groups.

If the above superiority is demonstrated, then the following secondary efficacy endpoints will be evaluated for NI and superiority in the order outlined in Figure 1 at the final analysis using a one-sided 2.5% Type I error rate:

- rVE of mRNA-1010 vs. the active comparator against the first episode of RT-PCR confirmed protocol-defined ILI caused by influenza A or B virus strains with similarity to the seasonal influenza vaccine strains.
- rVE of mRNA-1010 vs. the active comparator against the first episode of RT-PCR confirmed protocol-defined ILI caused by influenza A or B virus strains antigenically matched to the seasonal influenza vaccine strains.

The testing sequence can only continue to the next level if all tests at the higher level achieve statistical significance at the 2.5% alpha level. If a test at the higher level fails to demonstrate statistical significance, then the testing sequence will stop, and all testing thereafter will not be conducted.

Analyses of other remaining secondary efficacy endpoints are not controlled for multiplicity.

6.7. Safety Analysis

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

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

When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE/AR or a continuing AE/AR will be counted once. AE/AR data will be summarized 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 internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1010 vaccination group within each SOC.

6.7.1. Solicited Adverse Reactions

Solicited ARs are a subset of AEs in which there is a reasonable possibility that the IP caused the AE. These AEs consist of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration.

The solicited ARs are recorded by the participant in the eDiary. The eDiary will solicit daily participant reporting of occurrence and intensity of ARs using a structured checklist from Day 1 through Day 7 after the IP injection (i.e., the day of injection and 6 subsequent days).

If any solicited ARs reported during the 7-day follow-up post injection are not captured in the eDiary, then they should be reported in the Reactogenicity eCRF.

Solicited ARs reported in both the eCRF and eDiary will be included in the evaluation of solicited ARs.

If an event starts during the solicited period (i.e., from Day 1 through Day 7 after the IP injection), but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event on the Reactogenicity page of the eCRF.

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

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

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

The following local ARs will be recorded daily by the participants in the eDiary:

- Injection site pain
- Injection site erythema (redness)
- Injection site swelling/induration (hardness)
- Axillary (underarm) swelling or tenderness ipsilateral to the side of injection

The following systemic ARs will be recorded daily by the participants in the eDiary:

- Headache
- Fatigue
- Myalgia (muscle aches all over the body)
- Arthralgia (aches in several joints)
- Nausea/vomiting
- Chills
- Fever (an oral temperature greater than or equal to 38.0°C/100.4°F)

The solicited ARs will be graded based on the grading scales presented in Appendix F, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

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

Analyses of solicited ARs will be provided by vaccination group based on the Solicited Safety Set, unless otherwise specified.

The number and percentage of participants with any solicited local ARs, solicited systemic ARs, and any solicited ARs during the 7-day follow-up period after vaccination will be summarized, along with the number of events under each category. A two-sided 95% exact CI using the Clopper-Pearson method will be provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The number and percentage of participants who reported each individual solicited local AR (with a toxicity grade of Grade 1 or greater) and solicited systemic AR (with a toxicity grade of Grade 1 or greater) during the 7-day follow-up period after vaccination will be provided by toxicity grade.

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

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, regardless of whether it is intermittent, continued, or continued beyond 7 days.

Separate bar charts will be provided for the summary of local and systemic solicited adverse reactions within 7 days after vaccination

All solicited ARs that continue beyond 7 days post-injection will be summarized.

All delayed ARs with first onset day after 7 days post-injection will also be summarized.

The above analyses of solicited ARs will be provided for the following subgroups (Table 2):

- Age group 1: ≥ 50 to < 65 years or ≥ 65 years
- Age group 2: ≥ 50 to < 65 years, ≥ 65 to < 75 years, or ≥ 75 years
- Sex: Female or Male
- Race: White, Black or African American, Asian, or Other

These summaries may be provided for additional subgroups of selected baseline characteristics.

6.7.2. Unsolicited Treatment-emergent Adverse Events

A TEAE is defined as any event that is not present before exposure to the study intervention or any event already present that worsens in intensity or frequency after exposure. Worsening of a pre-existing condition after vaccination will be reported as a new AE.

AEs will also be evaluated by the investigator for the coexistence of MAAEs and/or AESIs. A MAAE is an AE that leads to an unscheduled or scheduled visit to a healthcare practitioner. AESIs for this study are pre-defined in the protocol (Table 12) including thrombocytopenia, neurologic diseases, anaphylaxis, and myocarditis/pericarditis.

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

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by vaccination group.

All summary tables for unsolicited AEs will be presented by SOC and PT or by PT only for TEAEs with counts of participants included. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1010 group and

then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

Unsolicited TEAEs occurring up to 28 days after IP injection and occurring throughout the study (up to Day 361/EoS) Will be summarized.

In addition, the number of participants with occurrences of selected TEAEs of clinical interest identified by standardized MedDRA queries (SMQ) will be summarized. SMQ will be summarized by PT, if applicable. Detailed descriptions of SMQ are presented in Table 15 and Table 16.

Percentages will be based upon the number of participants in the Safety Set within each treatment group.

6.7.1.1. Overview of Unsolicited TEAEs

An overall summary of unsolicited TEAEs occurring up to 28 days after IP injection including the number and percentage of participants, along with the number of events, by vaccination group who experience the following will be presented:

- Any unsolicited TEAEs
- Any unsolicited treatment-related TEAEs
- Any serious TEAEs
- Any treatment-related serious TEAEs
- Any unsolicited severe TEAEs
- Any unsolicited treatment-related severe TEAEs
- Any unsolicited treatment-emergent MAAEs
- Any unsolicited treatment-related treatment-emergent MAAEs

- Any unsolicited treatment emergent AESIs
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited TEAEs that are fatal

In addition, separate listings containing individual participant AE data for unsolicited AEs, unsolicited serious AEs, unsolicited severe AEs, unsolicited MAAEs, unsolicited AESIs as assessed by investigator, unsolicited AEs leading to discontinuation from participation in the study, and unsolicited adverse events leading to death will be produced. A separate listing of deaths will also include the cause of death.

6.7.1.2. TEAEs by System Organ Class and Preferred Term

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

- Any unsolicited TEAEs
- Any unsolicited treatment-related TEAEs
- Any serious TEAEs
- Any treatment-related serious TEAEs
- Any unsolicited severe TEAEs
- Any unsolicited treatment-related severe TEAEs
- Any unsolicited treatment-emergent MAAEs
- Any unsolicited treatment-related treatment-emergent MAAEs
- Any unsolicited treatment emergent AESIs
- Any unsolicited TEAEs leading to discontinuation from participation in the study.

Unsolicited TEAEs and unsolicited treatment-related TEAEs will be summarized by SOC and PT for TEAEs with occurrence in ≥ 1% of participants in any vaccination group based

on PT and presented by SOC and PT and maximum severity using frequency counts and percentages.

Summary tables for all unsolicited SAEs, AESIs, MAAEs, AEs leading to discontinuation from the study, and AEs leading to death occurring throughout the study (up to Day 361 (Month 12)/EoS) will be provided by SOC and PT as applicable.

6.7.1.3. TEAEs by Preferred Term

A summary table of all unsolicited TEAEs will be provided by PT in descending order of frequency in the mRNA-1010 group.

6.7.1.4. TEAEs by Severity

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

- All unsolicited TEAEs
- All unsolicited treatment-related TEAEs

6.7.1.5. Subgroup Analysis of TEAEs

An overall summary of unsolicited TEAEs occurring up to 28 days after IP injection will be conducted for each of the following subgroups (Table 2) based on Section 6.7.2.1.

- Age group 1: ≥ 50 to < 65 years or ≥ 65 years
- Age group 2: ≥ 50 to < 65 years, ≥ 65 to < 75 years, or ≥ 75 years
- Sex: Female or Male
- Race: White, Black or African American, Asian, or Other

Summary tables for unsolicited TEAEs, treatment-related TEAEs, and SAEs occurring up to 28 days after IP injection will be presented by SOC and PT for each subgroup.

6.7.1.6. Death

The total number of deaths due to any cause and time of death from the injection (numeric and by time point window) will be summarized.

6.7.3. Other Safety Data

6.7.1.1. Vital Sign Measurements

On Day 1, vital sign measurements will be collected once prior to vaccination and approximately 30 minutes after vaccination (prior to discharge of the participant). Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.

Vital sign measurements will include the following:

- Systolic and diastolic blood pressures
- Heart rate
- Respiratory rate
- Body temperature

The vital sign measurements will be presented in a data listing. The toxicity grade will also be included in the data listing.

Vital signs meeting the toxicity grading criteria for Grade 3 or higher as presented in Appendix H will be listed separately.

Observed values and changes from pre-injection (baseline) to post-injection at Day 1 for all vital sign measurements will be summarized by vaccination group.

Shift from pre-injection to post-injection results in vital sign toxicity grades at Day 1 will also be summarized by vaccination group.

6.7.1.2. Pregnancy Test

Pregnancy test results will be presented in a listing.

6.7.4. COVID impact

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

6.8. Data Safety Monitoring Board

A DSMB will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise

to allow for the ongoing review of safety data from this study population. Safety data will be reviewed according to intervals defined in the DSMB charter and will also occur as needed.

The DSMB will review the IA results and make recommendations to the Sponsor in terms of study results reporting and unblinding based on the boundaries of early efficacy as described in this SAP.

The Sponsor may also request that the DSMB conduct ad hoc reviews of safety events from this study. The DSMB composition, its remit, and frequency of data review will be further defined in the DSMB charter.

7. Changes from Planned Analyses in Protocol

No changes have been made to those analyses planned in the protocol.

8. References

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

Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Statist. Med. 1990;9(12):1447–1454.

9. List of Appendices

9.1. Appendix A Schedule of Events

Table 6: Schedule of Events

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C[1]/SC**	**SC**	**SC**	**SC**	**SC**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**M9**	**M12**	**Up to M12**
Study Visit	**Screening[2]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181**	**D271**	**D361/EoS**	**USV**
Window Allowance (Days)	**-28**	**N/A**	**±2**	**-7 to +3**	**±5**	**±14**	**±14**	**±14**	**N/A**
Informed consent form, demographics, vaccination and, medical history[3]	X								
Inclusion/exclusion criteria	X	X							
Physical examination[4]	X								
Vital signs[5]	X	X							
Pregnancy testing[6]	X	X							
Randomization		X							
Blood collection for immune response biomarkers subset and/or transcriptomics (optional) subset[7]		X		X					
Blood collection for future research sample (optional)[8]		X							
Study vaccination (including 30-minute post-dosing observation period)[9]		X							
Collection of EFS[10]		X							
NP swab for virus detection[11]									X
Follow-up safety call			X	X[12]	X	X	X	X	
eDiary activation for recording solicited ARs (7 days)[13]		X							

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C[1]/SC**	**SC**	**SC**	**SC**	**SC**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**M9**	**M12**	**Up to M12**
Study Visit	**Screening[2]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181**	**D271**	**D361/EoS**	**USV**
Window Allowance (Days)	**-28**	**N/A**	**±2**	**-7 to +3**	**±5**	**±14**	**±14**	**±14**	**N/A**
Review of eDiary for solicited ARs			X						
Symptom Reporting eDiary activation[14]		X							
Symptom Reporting eDiary for collection of symptoms of ILI[15]		Twice weekly from Day 1 to Day 181					Once weekly from Day 182 to Day 361		
Review of Symptom Reporting eDiary		Review participant recorded ILI starting on Day 1 through Day 361 (Month 12)/EoS							
Telephone/electronic contacts to remind participants of ILI eDiary reporting[16]		Once weekly from Day 1 to Day 181					Every 2 weeks from Day 182 to Day 361		
eDiary collection of EQ-5D-5L[17]		X			X	X	X	X	X
eDiary collection of WPAI:ILI			eDiary prompts[18]						
Recording of unsolicited AEs		X	X	X					
Recording of any SAEs, AESIs, and MAAEs, as well as AEs that led to discontinuation and relevant concomitant medications/procedures[19]		X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[20]		X	X	X	X	X	X	X	
Recording of hospitalizations and outpatient treatment related to or for the treatment of the MAAE or SAE[20]		X	X	X	X	X	X	X	X
Study completion								X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic; COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report form; eDiary = electronic diary; EFS = Edmonton Frail Scale; EoS = end of study; EQ-5D-5L = EuroQol 5-dimension 5-levels; EQ-VAS = EuroQol visual analogue scale; HRQoL = health-related quality of life; ILI = influenza like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (or contact by electronic means); USV = unscheduled visit; WPAI:ILI = Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (FDA 2020), investigators may convert clinic visits to telemedicine visits with the approval of the Sponsor.

1. Day 29 clinic visit is only required for participants in the immune response biomarker subset.
2. The Screening visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
3. Verbal medical history is acceptable.
4. A full physical examination, including height and weight, will be performed at the Screening visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as a MAAE.
5. Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
6. A point-of-care urine pregnancy test will be performed at the Screening visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening visit. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle-stimulating hormone level may be measured at the Screening visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
7. In a subset of participants, samples will be collected for future immune response biomarkers assessment. Of the people who participate in the subset, an additional blood sample collection for transcriptomics will be optional. Samples on Day 1 must be collected prior to receipt of vaccination.
8. Sample collection for future research sample including genomics is optional. Samples on Day 1 must be collected prior to receipt of vaccination.
9. All participants will be randomized to receive a single IM injection.
10. Assessment of EFS will only be performed for participants aged 65 years and older.
11. The NP swab specimen(s) for pathogens, including influenza virus and other respiratory pathogens (e.g., SARS-CoV-2) will be collected anytime from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined ILI per the ILI Case Definitions. If participants experience ILI symptoms, they will be instructed to contact the clinic and have an NP swab collected for testing within 72 hours. NP swabs should be collected prior to any antiviral therapy, if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the eCRF.
12. Only for those participants not in the immune response biomarker subset who otherwise would have a clinic visit this day.
13. The eDiary entries will be recorded at approximately 30 minutes after injection while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and the subsequent 6 days following injection.
14. The Symptom Reporting eDiary will be activated for collection of ILI symptoms starting at Day 1 and lasting until Day 361 (Month 12)/EoS.
15. Participants will be instructed to report via Symptom Reporting eDiary or telephone calls whether ILI symptoms have been experienced. If participants experience ILI symptoms, they will be instructed to contact the clinic and have an NP swab collected for testing within 72 hours. NP swabs should be collected prior to any antiviral therapy, if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit.
16. Telephone/electronic contacts are to remind participants of ILI eDiary reporting, not to capture AEs.
17. For participants reporting symptoms of ILI, the EQ-5D-5L responses will be collected using the eDiary on the day of the symptoms reporting (+1 day) and 5 days (+1 day) later.

18. For participants reporting symptoms of ILI, the WPAI over the previous 7 days will be collected using the eDiary at 5 days (+1 day) following the start of ILI symptoms reporting.
19. Trained study personnel or designee will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, and information on concomitant medications associated with those events. All concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 361 (Month 12)/EoS.
20. All concomitant medications and non-study vaccinations will be recorded through 28 days after study intervention (including receipt of any authorized or investigational COVID-19 vaccine). Additionally, certain concomitant medications will be recorded through Day 361/EoS.

9.2. Appendix B Standards for Variable Display in Tables, Figures and Listings (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 SD will be presented to two decimal places more than the original results; and the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to one decimal place unless otherwise stated.

9.3. Analysis Visit Windows for Immunogenicity Analysis

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

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

Step 2: If the immunogenicity assessments are not collected at the scheduled visit, any assessments collected at unscheduled visits will be used using the analysis visit windows described in Table 7 below.

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

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

Table 7: Analysis Visit Windowing

Visit	Target Study Day	Visit Window in Study Day
Immunogenicity		
Day 1	1 (Date of Injection)	1, Pre-vaccination
Day 29	29	[2, 105]

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

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

1. **Missing or partially missing medication start date**

- If only day is missing, use the first day of the month, unless the start month and year of the medication coincide with the start month and year of the IP injection:
    - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of IP injection.
    - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the month or the date of IP injection - 1.
    - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of IP injection or is missing, then use the date of IP injection.
- If day and month are both missing, use the first day of the year, unless the start year of the medication coincide with the start year of the IP injection:
    - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of IP injection.

- If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the year or the date of IP injection -1.
- If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of IP injection or is missing, then use the date of IP injection.

- If day, month, and year are all missing, the date will not be imputed, but will use the following rules for purposes of determining the status as prior and/or concomitant.
  - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then the medication will be treated as having begun after IP injection;
  - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), or if the mark is missing, then the medication will be treated as a prior medication (and as a concomitant medication unless the stop date indicates the medication was stopped prior to IP injection).

2. **Missing or partially missing medication stop date**:

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

In summary, the prior and concomitant categorization of a medication is described in the table below.

Table 8: Prior and Concomitant Categorization of Medications and Non-Study Vaccinations

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

P = Prior; C = Concomitant
[1] includes medications with completely missing end date
[2] includes medications with completely missing start date, unless marked as not administered as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No")

9.5. Appendix D Imputation Rules for Missing Dates of AEs

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

1. Missing or partially missing 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 IP injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the IP injection. In this case, use the date of IP injection.
   - 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 IP injection or is missing/partial AND the start year of the AE coincides with the start year of the IP injection. In this case, use the date of IP injection.
   - If day, month, and year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of IP injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partially missing end dates will not be imputed.

9.6. Appendix E Estimands and Estimand Specifications

Table 9: Intercurrent Event Types

Label	Intercurrent Event Type	Comment
IcEv1 (early discontinuation or death without confirmation of cases, i.e., unrelated death)	Unrelated death without documented influenza	Participants in PP Set who withdraw consent or die due to reasons unrelated to influenza will be included in primary efficacy analysis.
IcEv2 (early infection)	Infection starting up to 14 days after the study intervention	Participants in PP Set who experience an early influenza infection up to 14 days after the IP will be included in primary efficacy analysis.
Abbreviation: IcEv: intercurrent event, PP: per-protocol.		

Table 10: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for Per-Protocol Analysis

Objective: To demonstrate the efficacy of mRNA-1010 to prevent influenza	
Estimand Description	rVE will be measured using 1 – HR (mRNA-1010/ Fluarix) from 14 days after study intervention. A hypothetical strategy will be used for early discontinuation (e.g., withdrawal consent, deaths unrelated to influenza) or early infection in participants in the PP Set.
Target Population	Adults aged 50 years and older
Variable/Endpoint	Time-to-first episode of RT-PCR confirmed protocol-defined ILI: • For participants who experience at least one RT-PCR confirmed protocol-defined ILI, this will be the number of days from the date of randomization to the earliest start date of RT-PCR confirmed protocol-defined ILI. If the earliest start date is < 14 days following randomization, the value will be censored. • For participants who do not experience RT-PCR confirmed protocol-defined ILI, this will be the number of days from the date of randomization to the earliest date of: o early discontinuation or death unrelated to influenza o Day 181/Month 6 or the end of the influenza season (whichever occurs later). All values for or participants who do not experience RT-PCR confirmed protocol-defined ILI will be censored.
Treatment Condition(s)	Test: mRNA-1010 Reference: Active Comparator (Fluarix®)
Estimand Label	**Estimand 1**
Population-Level Summary	rVE defined as 1 - HR of mRNA-1010/active comparator

Intercurrent Event Strategy	
IcEv1 (Early discontinuation or unrelated death):	Hypothetical
IcEv2 (Early infection):	Hypothetical
Rationale for Strategy(s)	Hypothetical: early discontinuation (including unrelated death) censored at time of discontinuation (or at time of death), and early case will be censored at the time of initial onset, handled with independent censoring.

9.7. Appendix F Solicited Adverse Reactions and Grades

Table 11: Solicited Adverse Reactions and Grades

Reaction	Grade 1	Grade 2	Grade 3	Grade 4[1]
Injection site pain	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room (ER) visit or hospitalization
Injection site erythema (redness)	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 - 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*	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Headache	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization

Reaction	Grade 1	Grade 2	Grade 3	Grade 4[1]
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Nausea/vomiting	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Fever (oral)	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

Abbreviation: ER = Emergency room.
Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event reported on the AE page will be determined per assessment by the Investigator.
[1] Grading of Grade 4 events will be determined per Investigator and assessment is recorded on the reactogenicity event page in the electronic case report form.
Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

9.8. Appendix G Adverse Events of Special Interest Terms

Table 12: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per protocol (Section **Error! R eference source not found.**) • Follow reporting procedures in the protocol (Section **Error! Reference source not found.**)
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

Abbreviation: HELLP = hemolysis, elevated liver enzymes, and low platelet count.

9.9. Appendix H Severity Grading of Vital Sign Abnormalities

Table 13: Severity Grading of Vital Sign Abnormalities

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

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

9.10. Appendix I Censoring Rules for Efficacy Endpoint Cases

Table 14: Censoring Rules for the Primary Efficacy Endpoint and Secondary Efficacy Endpoints Cases

Situation	Censoring Approach
Without Efficacy Endpoint Case	Censored at Day 181/Month 6 or at the end of the influenza season, whichever occurs later; or at the data cutoff date for interim analyses.
Early discontinuation or death unrelated to influenza	Censored at date of discontinuation/death
Early ILI up to 14 days after study vaccination	Censored at date of documented case
(Secondary endpoints only) Unknown or undetermined antigenic match or similarity status for an RT-PCR confirmed ILI due to missing data.	Censored at the ILI start date
Secondary endpoints including RT-PCR confirmed US CDC-defined ILI, culture-confirmed protocol-defined ILI, and culture-confirmed US CDC-defined ILI endpoints: In the case that no events satisfy the definition for the particular endpoint, but RT-PSR confirmed protocol-defined ILI occurred.	Censored at the first RT-PCR confirmed protocol-defined ILI start date (regardless of whether or not ≥14 days post-vaccination)

9.11. Appendix J Definition of TEAE of Special Interest by SMQ

Table 15: TEAE of Special Interest by SMQ

TEAE of Special Interest	Type of MedDRA Query	Broad or Narrow Search	SMQ Search Criteria
Hypersensitivity	SMQ	Broad/Narrow	Specified PT terms
Angioedema	SMQ	Broad/Narrow	Specified PT terms
Anaphylactic Reaction	SMQ	Broad/Narrow	Specified PT terms and algorithmic approach specified in Table 18.
Autoimmune Disorder	SMQ	Broad/Narrow	Specified PT terms

Table 16: Algorithmic Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

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

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

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

C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling
C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria
C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest
D	Broad	Cardiovascular insufficiency

D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension