ModernaTX, Inc.

Protocol mRNA-1010-P303

A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older

Statistical Analysis Plan

SAP Version 2.0

Version Date of SAP: 03-APR-2024

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BMI	Body Mass Index
CEAC	Cardiac Event Adjudication Committee
CDC	Centers For Disease Control and Prevention
CI	Confidence Interval
CRO	Contract Research Organization
CSP	Clinical Study Protocol
DCO	Data Cut-off
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eDiary	electronic Diary
EoS	End of Study
FAS	Full Analysis Set
GLSM	Geometric Least Square Mean
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
ILI	Influenza-Like Illness
IM	Intramuscular
IP	Investigational Product
IRT	Interactive Response Technology
IST	Internal Safety Team
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event

max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MN	Microneutralization
mRNA	messenger Ribonucleic Acid
nAbs	neutralizing Antibodies
NH	Northern Hemisphere
NP	Nasopharyngeal
PP	Per-Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
RT-PCR	Real Time Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Seroconversion Rate
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	WHO Drug Dictionary

DOCUMENT HISTORY

Version	Date	Description of major modifications
1.0	16MAY2023	Original version per the study protocol dated on 28FEB2023
2.0	03APR2024	Added Part B and Part C per Protocol Amendment 2 dated on 11DEC2023

1. Introduction

This SAP, which describes the planned analyses for Study mRNA-1010-P303, is based on the most recent approved study protocol amendment 2, dated 11 December 2023, and the most recent approved eCRF, dated 22 February 2024.

In addition to the information presented in the statistical analyses section of the protocol (Section 9.5), which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

The Sponsor is conducting this Phase 3 study (mRNA-1010-P303) of its seasonal influenza mRNA vaccine (mRNA-1010) in 3 parts (Part A, Part B, and Part C). Each part will be described separately in this SAP.

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

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

2. Part A

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to evaluate:

- The humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29.
- The reactogenicity and safety of mRNA-1010.

2.1.2. Secondary Objectives

The secondary objective is:

- To further evaluate the humoral immunogenicity of mRNA-1010 against 4 vaccine-matched influenza virus A and B strains at Day 29.

2.1.3. Exploratory Objectives (May be Performed)

The following exploratory objectives may be performed:

- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of Fluarix Quadrivalent against 4 vaccine-matched influenza virus A and B strains at Day 181/EoS.
- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of Fluarix Quadrivalent against vaccine-matched or vaccine-mismatched A and B strains, including the use of alternative methods.
- To assess the occurrence of clinical influenza in study participants and characterize their immune response to infection and viral isolates.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary objectives will be evaluated by the following endpoints:

- Immunogenicity endpoints:

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

GMT and rate of seroconversion will be evaluated for each individual A and B strain (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). Therefore, there will be eight co-primary immunogenicity endpoints in the study.

- Reactogenicity and safety endpoints:
  - Solicited local and systemic ARs through 7 days after study intervention dosing.
  - Unsolicited AEs through 28 days after study intervention dosing.
  - MAAEs from Day 1 to Day 181/EoS.
  - AESI from Day 1 to Day 181/EoS.
  - SAEs from Day 1 to Day 181/EoS.
  - AE leading to discontinuation from study participation from Day 1 to Day 181/EoS.

2.2.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- The proportion of participants with HAI titer ≥1:40 at Day 29.
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.

2.2.3. Exploratory Endpoints

The exploratory objectives may be evaluated by the following endpoints:

- GMT at Day 181 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
- GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).
- GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine mismatched strains on Day 29 compared with Day 1 (Baseline).
- Frequency of RT-PCR confirmed protocol-defined ILI and assessment of immune responses in participants with the RT-PCR-confirmed ILI.

2.3. Study Design

2.3.1. Overall Study Design

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

mRNA-1010 to be tested contains 4 mRNAs in an equivalent mRNA mass ratio that encode membrane-bound HA of the 4 different influenza strains recommended by WHO for 2022-2023 NH cell- or recombinant-based vaccines. Fluarix Quadrivalent contains 4 HAs of the 4 different influenza strains recommended by the WHO for 2022-2023 NH egg-based vaccines.

Medically stable adults, aged 18 years and older, will be screened and enrolled. Approximately 2400 participants will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA 1010 or a single dose of Fluarix Quadrivalent (Table 1).

Table 1 Treatment Groups and Dose Levels (Part A)

Treatment Group	Study Intervention Received	mRNA/Antigen HA (each) (µg)	Total Dose (µg)	Number of Participants
1	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	1200
2	Fluarix Quadrivalent	15 (of protein)	60 (of protein)	1200

Abbreviations: HA=hemagglutinin; mRNA=messenger ribonucleic acid

Clinic/in-person visits will consist of a Screening Visit (up to 28 days before the Day 1 visit and may be performed over multiple visits if within the 28-day screening window), a dosing visit on Day 1 (Baseline; may be on the same day as the Screening Visit), a visit on Day 29 (Month 1), and a subsequent visit on Day 181 (Month 6)/EoS with up to 7 months of study participation for each participant. There will also be contacts by electronic means or telephone calls on Day 8 and Day 91 (Month 3).

2.3.2. Statistical Hypotheses

The following null hypothesis will be tested:

H_0: Immunogenicity response to mRNA-1010, as measured by GMT and seroconversion rate at Day 29 using HAI assay, is inferior compared to that in participants who received Fluarix Quadrivalent for each of the 4 vaccine-matched influenza virus A and B strains.

Each of the eight coprimary immunogenicity endpoints will be evaluated for noninferiority of mRNA-1010 versus Fluarix Quadrivalent at a 2-sided alpha of 0.05 level. The study is considered as a success if all the eight coprimary immunogenicity endpoints meet the noninferiority criteria.

- For each of the 4 vaccine-matched strains, the noninferiority in GMT in participants who received mRNA-1010 compared to that of participants who received Fluarix Quadrivalent will be demonstrated by the lower bound of the 95% CI of the GMR ruling out 0.667 (lower bound >0.667) using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of HAI titer in those receiving mRNA-1010 compared with the GMT of those receiving Fluarix Quadrivalent.
- For each of the 4 vaccine-matched strains, the noninferiority in seroconversion rate in the mRNA-1010 group compared to that of Fluarix Quadrivalent group will be demonstrated by the lower bound of the 95% CI of the seroconversion rate difference (mRNA-1010 versus Fluarix Quadrivalent) ruling out −10% (lower bound > −10%) using a noninferiority margin of 10%.

2.3.3. Sample Size and Power

Assuming approximately 15% of 2400 randomized participants will be excluded from the PP Immunogenicity Set, with approximately 2040 participants in the PP Immunogenicity Set (1:1 ratio; approximately 1020 participants in each treatment group), the study has at least 98% power to demonstrate noninferiority of the immune response for all 4 strains, as measured by the GMT in participants receiving mRNA-1010 compared with that in the Fluarix Quadrivalent group, at a 2-sided alpha of 0.05 level, assuming an underlying GMR of 0.9 in all 4 strains and a noninferiority margin of 1.5. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

The study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by seroconversion rate in the mRNA-1010 group compared with that in the

Fluarix Quadrivalent group, at a 2-sided alpha of 0.05 level, assuming a seroconversion rate of 69% in influenza A strains and 59% in influenza B strains, respectively, in the mRNA-1010 group (a true rate difference is −1% compared to the Fluarix Quadrivalent group), and a noninferiority margin of 10%.

The overall power considering meeting the primary objective to evaluate the immune response for all the 4 influenza virus strains is approximately 93%.

2.3.4. Randomization

Randomization will be performed using an IRT. Approximately 2400 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of Fluarix Quadrivalent (Table 1). Randomization will be stratified by age categories (18 to <50 years old, ≥50 to <65 years old, or ≥65 years old) and influenza vaccine status in the prior 12 months (received or not received). Approximately 50% of participants (1200) enrolled will be ≥50 years old, including approximately 20% (480) who will be ≥65 years old. The Sponsor anticipates approximately 200 participants enrolled in the ≥65 years old age group will be ≥75 years old.

2.3.5. Blinding and Unblinding

The following blinding and responsibility for analyses apply to Part A, Part B, and Part C:

This is an observer-blind study. The investigators, 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 numbers) will be assigned to study intervention accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than 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 participants or the blinded clinic staff involved in the conduct of the study unless this information is necessary in the case of an emergency.

- Unblinded clinic staff 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 statistical and programming team will perform the preplanned primary analysis (see Section 2.5.7). Sponsor team members will be prespecified to be unblinded to the primary analysis and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants.
- The IST may review data, as appropriate, to safeguard the interests of participants and to help ensure the integrity of the study.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the study intervention in a secure location that is not accessible or visible to other clinic staff. An opaque sleeve over the syringe used for study intervention dosing will maintain the blind at the time of study intervention dosing, as the doses containing mRNA-1010 will look different from those of Fluarix Quadrivalent. Only delegated unblinded clinic staff will conduct the study intervention dosing procedure. Once the study intervention dosing is completed, only the blinded clinic staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

2.4. Analysis Sets

The analysis sets are defined in Table 2.

Table 2 Populations for Analysis

The following analysis populations apply to Part A, Part B, and Part C, unless otherwise specified:

Population	Description

Randomization Set	All participants who are randomly assigned to the treatment, regardless of the participants' treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.
Full Analysis Set	All participants in Randomization Set who received any study vaccination. Participants will be analyzed according to the treatment group to which they were randomized.
Immunogenicity Set	All participants in the FAS who have baseline and Day 29 antibody assessment via HAI assay. Participants will be analyzed according to the treatment group to which they were randomized.
PP Immunogenicity Set	The PP Immunogenicity Set includes all participants in the Immunogenicity Set who received the planned dose of study intervention, complied with the immunogenicity testing schedule for baseline and Day 29 *, and had no significant protocol deviations that impact key or critical data. Participants with RT-PCR-confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity Set (Part A only). The PP Immunogenicity Set will be used for all analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the treatment group to which they were randomized.
Solicited Safety Set	All participants in the FAS who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs, and participants will be included in the treatment group corresponding to the study intervention that they actually received.
Safety Set	All participants in the FAS. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the treatment group corresponding to the study intervention that they actually received.

Abbreviations: AR=adverse reaction; FAS=Full Analysis Set; HAI=hemagglutinin inhibition; PP=per protocol; RT-PCR=reverse transcription polymerase chain reaction.
* Complied with the immunogenicity testing schedule for baseline and Day 29 is defined as having immunogenicity samples collected before the IP administration and between Day 22 and Day 43 (i.e., -7/+14 days of Day 29).

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

Table 3 Major Dosing Errors for Participants Randomized into mRNA-1010 (Part A/B/C)

Actual Vaccine Received	Major Dosing Errors
mRNA-1010 ≤37.5 µg	Yes
mRNA-1010 >37.5 µg – 62.5 µg	No
mRNA-1010 >62.5 µg	Yes
Any Fluarix Quadrivalent or Fluzone HD Quadrivalent	Yes

Table 4 Major Dosing Errors for Participants Randomized into Fluarix Quadrivalent (Part A/B)

Actual Vaccine Received	Major Dosing Errors
Fluarix Quadrivalent ≤45 µg	Yes
Fluarix Quadrivalent >45 µg – 75 µg	No
Fluarix Quadrivalent >75 µg	Yes
Any Fluzone HD Quadrivalent or mRNA-1010	Yes

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

- mRNA-1010 50 µg group: If the received dose of mRNA-1010 is >0 µg, and Fluzone and Fluarix Quadrivalent are 0 ug.
- Fluarix Quadrivalent 60 µg group: If the received dose of Fluarix Quadrivalent is >0 µg, and Fluzone and mRNA-1010 are 0 µg.

2.5. Statistical Analysis

2.5.1. General Considerations

SoA is presented in Section 7.1.1.

The following general consideration for analysis applies to Part A, Part B, and Part C, unless otherwise specified:

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

Categorical variables will be summarized using counts and percentages. For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards, see Section 7.2.

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

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

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

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1010 50 µg (for Part A, Part B, and Part C)

- Fluarix Quadrivalent 60 µg (for Part A and Part B), or Fluzone HD Quadrivalent 240 µg (for Part C)

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

Study day relative to injection will be calculated as below:

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

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

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

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Section 7.3.

Analysis Periods:

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

- 7 days post-vaccination: this period includes the day of vaccination and 6 subsequent days. This analysis period will be used for solicited local/systemic ARs and SAEs that occur during this time.
- Up to 28 days post-vaccination: this period starts from the day of vaccination and spans 28 days to include the day of vaccination and 27 subsequent days. This analysis period will be used for unsolicited AE, except for solicited AR, unless specified otherwise.

- Up to data cutoff date: this period starts from day of vaccination and continues through the data cutoff date applied at planned analyses as specified in Section 2.5.7.
- Overall study period/Throughout the study: this period starts on Day 1 and continues through the earliest of the following: study completion, discontinuation from the study, or death.

For the Day 29 primary analysis, the analysis will include all participants' immunogenicity data and safety data collected up to a DCO Date. DCO determination will be based on the Day 29 visit date of the last dosed participant in the Part, the needed time for data entering (which may be a few additional days), and the actual DCO date will be provided by the Clinical Operation of the study.

Incomplete/Missing Data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Section 7.4.
- Imputation rules for missing AE dates are provided in Section 7.4.
- For summarizations of GMTs, antibody titers reported as below LLOQ will be replaced by 0.5 x LLOQ. Values that are greater than ULOQ will be converted to the ULOQ.
- Other incomplete/missing data will not be imputed, unless otherwise specified.

Subgroups:

Table 5 Definition for Subgroups (Part A)

Subgroup Variable *	**Categories**
Age Group 1	≥18 to <50 years old ≥50 to <65 years old ≥65 years old
Age Group 2	≥18 to <50 years old ≥50 to <65 years old ≥65 to <75 years old ≥75 years old
Flu Vaccine Status in the past 5 to 12 months (only for immunogenicity analyses)	Yes No

Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
Sex	Male Female
BMI (only for immunogenicity analyses)	<30 kg/m^2 ≥30 kg/m^2

*Subgroup derivations will be based on the information from eCRF.

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

2.5.2. Background Characteristics

The following background characteristics summaries apply to Part A, Part B, and Part C, unless otherwise specified.

2.5.2.1. Participant Disposition

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

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

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

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

- Received injection
- Completed the study

- Prematurely discontinued the study and the reason for discontinuation

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

The number and percentage of participants in the following categories (analysis sets defined in Section 2.4) will be summarized as defined in Section 2.5.1 (for general consideration) based on the

Randomization Set:

- Randomization Set
- Full Analysis Set
- Immunogenicity Set
- PP Immunogenicity Set
- Safety Set
- Solicited Safety Set

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

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

2.5.2.2. Demographics and Baseline Characteristics

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

- Age
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

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

- Age group 1 (18 to <50 years old, ≥50 to <65 years old, or ≥65 years old)
- Age group 2 (18 to <50 years old, ≥50 to <65 years old, ≥65 to <75 years old, or ≥75 years old)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Previous Year's Flu Vaccine Status (Received/Not received any seasonal flu vaccine anytime in the past 5 to 12 months)

The summaries will be provided separately for all analysis sets (except Solicited Safety Set) defined in Section 2.4.

2.5.2.3. Medical History

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

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

2.5.2.4. Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and non-study vaccinations will be coded using the WHODD, version Mar 2022. Imputation rules for missing dates of medications and non-study vaccinations are detailed in Section 7.4. The summary of concomitant medications will be based on the Safety Set.

Categorization of prior and concomitant medications are summarized in The following applies to Part A, Part B, and Part C:

Table 13 in Section 7.5. The following applies to Part A, Part B, and Part C.

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

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

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

2.5.2.5. Protocol Deviations

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

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

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

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

2.5.2.6. Study Exposures

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

2.5.3. Immunogenicity Analysis

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

The primary analysis population for immunogenicity will be the PP Immunogenicity Set, unless otherwise specified. The primary objective of this study is to use the immunogenicity response to infer efficacy in participants receiving mRNA-1010, see Section 2.3.2 for statistical hypotheses.

Immune responses, as measured by GMT and seroconversion rate in the mRNA-1010 group based on Day 29 HAI titers, will be compared to that in participants receiving the active comparator for all 4 strains.

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

The primary immunogenicity estimands are presented in detail in Table 17. The Day 29 primary analysis of immunogenicity will be performed after all participants have completed the Day 29 visit.

2.5.3.1. Analysis of Primary Endpoints

- GMT as measured by HAI against 4 vaccine-matched influenza virus A and B strains at Day 29

The GMT will be calculated using the following formula:

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

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

An ANCOVA model will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, treatment group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The GLSM and its corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale, as an estimate of the GMT.

The GMR for mRNA-1010 vs. active comparator, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference and calculated by back-transforming of the difference estimated from the ANCOVA model. The corresponding 2-sided 95% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 group compared to the active comparator group at Day 29. For each strain, the noninferiority of GMT will be considered demonstrated if the lower bound of the 95% CI of the GMR is >0.667 based on a noninferiority margin of 1.5.
Descriptive statistics (n, median, min, max) will also be provided for the GMT of HAI titers with corresponding 95% CI at each timepoint. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMT with corresponding 95% CI will be plotted at each time point respectively.

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

The number and percentage of participants with seroconversion at Day 29 will be provided with 2-sided 95% CI using the Clopper-Pearson method. To compare the seroconversion rates between the treatment groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in seroconversion rates at Day 29. For each strain, the noninferiority of seroconversion rate will be considered demonstrated if the lower bound of the 95% CI of the seroconversion rate difference is > −10% based on a noninferiority margin of 10%.

2.5.3.2. Supplementary Analysis

The primary analyses will be repeated using the Immunogenicity Set as a supplementary analysis.

2.5.3.3. Subgroup Analysis

To assess the consistency of immunogenicity response of mRNA-1010 across subgroups, subgroup analysis of the co-primary endpoints may be conducted by subgroups defined by age group 1, age group 2, previous year's flu vaccine status, race, sex, and BMI category (see Table 5), based on PP Immunogenicity Set. For each subgroup category, the co-primary immunogenicity endpoints will be analyzed using the same statistical methods as for primary analysis. Additional details are documented in Section 2.5.3.1.

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

2.5.3.4. Analysis of Secondary Endpoints

- The proportion of participants with HAI titer ≥1:40 at Day 29

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

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

The GMFR will be calculated using the following formula:

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

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

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

2.5.3.5. Analysis of Exploratory Endpoints

- GMT at Day 181 as measured by HAI

Descriptive statistics (n, median, min, max) will be provided for the GMT of HAI titers with corresponding 95% CI at Day 181. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

- Proportion of participants reaching seroconversion at Day 181 as measured by HAI

The number and percentage of participants with seroconversion at Day 181 will be provided with 2-sided 95% CI using the Clopper-Pearson method.

For GMT and seroconversion at Day 181, the analyses will be based on participants in PP Immunogenicity Set who also had immunogenicity sample(s) collected between Day 167 and Day 195 (i.e., between -/+ 14 days of Day 181).

- GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline)
- GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine mismatched strains on Day 29 compared with Day 1 (Baseline).

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

- Assessment of immune responses in participants with RT-PCR-confirmed protocol-defined ILI.

A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom, or the occurrence of any 2 or more respiratory symptoms, as shown in Table 6.

An RT-PCR confirmed protocol-defined ILI is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local

certified laboratory within 7 days of onset of protocol-defined ILI at any time during the study period.

Table 6 Respiratory and Systemic Symptoms for Protocol-defined ILI (Part A)

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

CCI [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

CCI [redacted]

Descriptive statistics (n, median, min, max) may be provided for GMT with corresponding 95% CI at each time point for participants with RT-PCR-confirmed protocol-defined ILI. Additionally, the number and percentage of participants with seroconversion at each time point may be provided with 2-sided 95% CI using the Clopper-Pearson method for participants with RT-PCR-confirmed protocol-defined ILI.

2.5.4. Multiplicity

The study is considered as a success only if all the eight (8) co-primary immunogenicity endpoints meet the noninferiority criterion. Each of the co-primary immunogenicity endpoints will be tested at 2-sided alpha of 0.05 level.

2.5.5. Safety Analysis

The following safety analyses apply to Part A, Part B, and Part C, unless otherwise specified:

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

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

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

2.5.5.1. Analysis of Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with study intervention dosing. The eDiary will solicit daily participant reporting of ARs using a structured checklist. Participants will record such occurrences in the eDiary on the day of study intervention dosing and 6 subsequent days.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the clinic staff in EDC, where reactogenicity is collected:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (MAAE).
- Solicited local or systemic AR persisting beyond 7 days post study intervention dosing.
- Solicited local or systemic AR that leads to participant discontinuation from study participation.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

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

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

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

after the injection will be provided. The same analysis will be conducted for subgroups defined by age group1, age group 2, race, and sex, see Table 5.

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

The number and percentage of participants with onset of individual solicited AR will be summarized by study day relative to the injection (Day 1 through Day 7). The onset of individual solicited AR is defined as the time point after injection at which the respective solicited AR first occurred. Descriptive statistics will be provided for the duration of solicited ARs (overall, local, and systemic) and each individual solicited AR by vaccination group. The duration of local or systemic solicited ARs, along with the specific individual solicited ARs, will be calculated as: reaction end date – reaction start date +1, no matter it is intermittent or continued or if the solicited AR continues beyond 7 days. All solicited ARs that continue beyond 7 days post-injection will be summarized. All delayed ARs with onset day after 7 days post-injection may also be summarized.

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

2.5.5.2. Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. A TEAE is defined as any event that does not present before exposure to IP or any event already present that worsens in intensity or frequency after exposure.

An MAAE is an AE that leads to an unscheduled or scheduled visit to a healthcare practitioner.

AESIs is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and immediate notification by the

investigator to the Sponsor are required. AESI for this study are pre-defined in the protocol Section 5.4 including thrombocytopenia, new onset of or worsening of the neurologic diseases, anaphylaxis, and myocarditis/pericarditis.

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

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT or by PT only for TEAEs with counts of participants included. Summary tables for unsolicited AEs will be based on treatment-emergent AEs, unless otherwise specified. Listings for unsolicited AEs will be based on treatment-emergent AEs and AEs that occurred before the IP administration and will be flagged.

Unsolicited TEAEs will be summarized up to 28 days after vaccine injection. Treatment-emergent MAAEs, AESIs, SAEs, and AEs leading to discontinuation from study participation will be summarized throughout the study (up to Day 181/EoS).

In addition, number of participants with occurrences of selected TEAEs of clinical interests identified by SMQ will be summarized. SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in The following applies to Part A, Part B, and Part C:

Table 20. Additional SMQs may be summarized, as necessary.

2.5.5.2.1. Overview of Unsolicited AEs

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

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

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

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

2.5.5.2.2. Unsolicited AEs by SOC and PT

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

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

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

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

2.5.5.2.3. Unsolicited AEs by PT

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

- All unsolicited TEAEs
- SMQ

2.5.5.2.4. Unsolicited AEs by Severity

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

- All unsolicited TEAEs
- All unsolicited treatment-related TEAEs

2.5.5.2.5. Independent Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in the protocol Section 5.1.6.2) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

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

2.5.5.2.6. Subgroup Analysis of Unsolicited AEs

Analysis of unsolicited TEAEs will be conducted for subgroups defined in Table 5. Overall summary of the unsolicited TEAEs up to 28 days will be provided for each subgroup. Summary tables for TEAE, treatment-related TEAEs, and SAEs by SOC and PT may also be provided for each subgroup up to 28 days after the vaccine.

2.5.5.3. Death

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

2.5.5.4. Other Safety Data

2.5.5.4.1. Pregnancy

Pregnancy testing is scheduled to occur at the Screening Visit and Day 1. Individuals who have a positive pregnancy test at the Screening Visit and Day 1 must not be enrolled. Additional pregnancy testing may also be performed at any time during the study if required by local regulatory requirements, or at the discretion of the investigator. Pregnancy test results will be listed by participant.

2.5.5.4.2. Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature will be measured at the time points indicated in the SoA (Section 7.1). Abnormal vital sign measurements will be graded per toxicity grading criteria provided in Section 7.7. Vital signs may be collected at other clinic/in-person visits in conjunction with a symptom-directed physical examination. The preferred route of temperature assessment is oral.

Observed value and change from pre-injection (baseline) to post-injection in vital signs will be summarized by vaccination group. Abnormal vital sign measurements will be graded per toxicity grading criteria provided in Section 7.7. A toxicity grade shift table of the vital signs from pre-injection to post-injection will be provided. Additionally, the values that are outside the reference ranges will be flagged in a data listing. Participant with any abnormal vital sign measurement where toxicity grade (Grade 3 or higher) will be listed separately.

2.5.6. Exploratory Analysis

2.5.6.1. Frequency of RT-PCR-Confirmed Protocol-Defined ILI

Number and percentage of participants with RT-PCR confirmed protocol-defined influenza infection (See Section 2.5.3.5) within the period of 14 days post-injection up to EoS will be summarized for the Safety Set. A 2-sided 95% CI using the Clopper-Pearson method will be provided for the percentage of participants with the RT-PCR confirmed influenza infection.

2.5.6.2. Biomarker Analysis

Biomarkers may be evaluated for safety and/or vaccine efficacy using left over samples that include serum collections and NP swab. Transcriptomics or genomics may be evaluated as an optional assessment from participants that consent to providing the samples. Participants who do not wish to have their samples analyzed for transcriptomics may still participate in the study.

The biomarker analysis will not be covered in this plan and will be developed in a separate plan as needed.

2.5.6.3. COVID-19 Impact

For Part A, Part B, and Part C, a listing will be provided for the impact of COVID-19 on the execution of the study.

2.5.7. Planned Analyses

2.5.7.1. Primary Analysis

The primary analysis of immunogenicity and safety will be performed after all participants have completed the Day 29 Visit. All data relevant to the primary study analysis through the Day 29 Visit will be cleaned for the primary analysis (i.e., data that are as clean as possible) and a report may be generated.

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

2.5.7.2. Final Analysis

Final analysis of all immunogenicity and safety data will be performed once all participants complete the Day 181 (Month 6)/EoS Visit.

3. Part B

3.1. Study Objectives

3.1.1. Primary Objectives

The primary objective is to evaluate:

- The humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults 18 to <65 years old.
- The reactogenicity and safety of mRNA-1010.

3.1.2. Secondary Objectives

The secondary objective is to evaluate:

- The immunological response of mRNA-1010 (for superiority) relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza virus A and B strains at Day 29.
- To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza virus A and B strains at Day 29.

3.1.3. Exploratory Objectives (May be Performed)

The following exploratory objectives may be performed:

- To evaluate humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.
- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched or vaccine-mismatched A and B strains.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary objectives will be evaluated by the following endpoints:

- Immunogenicity endpoints:
    - GMT at Day 29 as measured by HAI.
    - Proportion of participants reaching seroconversion at Day 29 as measured by HAI. GMT and rate of seroconversion will be evaluated for each individual A and B strain (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). Therefore, there will be eight co-primary immunogenicity endpoints in the study.
- Reactogenicity and safety endpoints:
    - Frequency and grade of solicited local and systemic reactogenicity ARs during a 7-day follow-up period post-injection.
    - Frequency and severity of any unsolicited AEs during the 28-day follow-up period post-injection.
    - Frequency of any SAEs, MAAEs, and AESIs from Day 1 to Day 181/EoS.

3.2.2. Secondary Endpoints

- GMT at Day 29 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
- The proportion of participants with HAI titer ≥1:40 at Day 29.
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.

3.2.3. Exploratory Endpoints

The exploratory objectives may be evaluated by the following endpoints:

- GMT at Day 181 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
- GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline).

- GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

3.3. Study Design

3.3.1. Overall Study Design

Part B is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the safety and reactogenicity of mRNA-1010 seasonal influenza vaccine in adults 18 to <65 years old.

The mRNA-1010 to be tested contains 4 mRNAs in an equivalent mRNA mass ratio that encode membrane-bound HA of the 4 different influenza strains recommended by WHO for 2023-2024 NH cell- or recombinant-based vaccines. The licensed SD seasonal influenza vaccine, Fluarix Quadrivalent contains 4 HAs of the 4 different influenza strains recommended by the WHO for 2023-2024 NH egg-based vaccines.

Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA 1010 or a single dose of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent, Table 7).

Table 7 Treatment Groups and Dose Levels (Part B)

Treatment Group	Study Intervention Received	mRNA/Antigen HA (each) (µg)	Total Dose (µg)	Number of Participants
3	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	1500
4	Active Comparator (Fluarix Quadrivalent)	15 (of protein)	60 (of protein)	1500

Abbreviations: HA=hemagglutinin; mRNA=messenger ribonucleic acid

Clinic/in-person visits will consist of a Screening Visit (up to 28 days before the Day 1 visit and may be performed over multiple visits if within the 28-day screening window), a dosing visit on Day 1 (Baseline; may be on the same day as the Screening Visit), a visit on Day 29 (Month 1), and a subsequent visit on Day 181 (Month 6)/EoS (in a subset of ~1000 participants) with up to 7 months of study participation for each participant. There will also be contacts by electronic means or telephone calls on Day 8, Day 91 (Month 3), and Day 181 (non-subset participants) (Month 6).

3.3.2. Statistical Hypotheses

The primary objective in Part B is to evaluate the noninferiority of the immunogenicity response to mRNA-1010 versus the licensed SD Fluarix Quadrivalent, as measured by GMT and seroconversion rate at Day 29 using HAI assay, for all 4 vaccine-matched influenza virus A and B strains:

- For each of the 4 vaccine-matched strains, the noninferiority hypothesis in terms of the GMT is:

  Null Hypothesis: $H_0{}^1$: GMR $\leq$0.667 (inferior) vs.
  Alternative Hypothesis: $H_0{}^1$: GMR >0.667 (noninferior)

  Using a noninferiority margin of 1.5, where the GMR is the ratio of the GM HAI titer in the mRNA 1010 group compared with the GM HAI titer in the Fluarix Quadrivalent group.

- For each of the 4 vaccine-matched strains, the noninferiority hypothesis in seroconversion rate is:

  Null Hypothesis: $H_0{}^2$: SCR differences $\leq -10\%$ (inferior) vs.
  Alternative Hypothesis: $H_0{}^2$: SCR differences $> -10\%$ (noninferior)

  Using a noninferiority margin of 10%, where the SCR difference is the difference in the SCR between the mRNA 1010 group compared with the Fluarix Quadrivalent group.

The noninferiority hypotheses in the GMT and SCR will be evaluated for all 4 strains and Part B is considered a study success if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Therefore, each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level:

- For each strain, the noninferiority in GMT will be demonstrated by the lower bound of the 95% CI of the GMR ruling out 0.667, ie. the lower bound of the 95% CI >0.667
- For each strain, the noninferiority in SCR will be demonstrated by the lower bound of the 95% CI of the SCR difference ruling out −10%, ie. the lower bound of the 95% CI > −10%

Upon successful demonstration of noninferiority for Part B, ie. the noninferiority success criteria have been met for all 8 coprimary immunogenicity endpoints, the following superiority hypotheses will be tested:

- For each of the 4 vaccine-matched strains, the superiority hypothesis in terms of the GMT is:

  Null Hypothesis: $H_0{}^3$: GMR = 1 vs.
  Alternative Hypothesis: $H_0{}^3$: GMR >1 (superior)

- For each of the 4 vaccine-matched strains, the superiority hypothesis in seroconversion rate is:

  Null Hypothesis: $H_0{}^4$: SCR differences = 0 vs.

  Alternative Hypothesis: $H_0{}^4$: SCR differences >0 (superior)

The multiplicity adjustment procedures for the superiority tests of the 8 immunogenicity endpoints are specified in Section 3.5.4 (also see Figure 1).

3.3.3. Sample Size and Power

Assuming approximately 15% of 3000 randomized participants will be excluded from the PP Immunogenicity Set, with approximately 2550 participants in the PP Immunogenicity Set (1:1 ratio; approximately 1275 participants in each treatment group):

- The study has at least 99% power to meet the noninferiority success criteria in GMT for all 4 strains at a 1-sided alpha of 0.025 level with a noninferiority margin of 1.5. An underlying GMR (mRNA-1010 vs. the licensed Fluarix SD Quadrivalent vaccine) of 0.90 is assumed for each of the 4 strains and the standard deviation of the natural log-transformed levels is assumed to be 1.5.
- The study has at least 98% power to meet the noninferiority success criteria in SCR for all 4 strains, at a 1-sided alpha of 0.025 level with a noninferiority margin of 10%. The SCRs of 58% for influenza A strains and SCRs of 48% for influenza B strains, respectively, are assumed in the mRNA 1010 group, whereas the SCRs in the licensed SD Fluarix Quadrivalent group are assumed to be 59% and 49% for the influenza A and B strains, respectively.

The overall power for achieving the primary noninferiority objective in Part B would be approximately 98%. Furthermore, the sample size provides 1) an approximately 79.5% power for a superiority test of GMT for an individual strain with an underlying GMR of 1.2 (mRNA-1010 vs. Fluarix SD Quadrivalent); 2) an approximately 63% power for a superiority test of SCR for an A strain (assuming an SCR of 64% for mRNA-1010 vs. 59% for Fluarix SD Quadrivalent), and an approximately 61% power for a superiority test of SCR for a B strain (assuming an SCR of 54% for mRNA-1010 vs 49% for Fluarix SD Quadrivalent) at 2-sided alpha of 0.025 (with alpha split for multiplicity adjustment).

3.3.4. Randomization

Randomization will be performed using an IRT. Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent, Table 7). Randomization will be stratified by previous flu season (since September 2022) vaccination status (Received; Received from mRNA-1010-P302, Not received).

3.3.5. Blinding and Unblinding

See Section 2.3.5 for details.

3.4. Analysis Sets

See Section 2.4 for details.

3.5. Statistical Analysis

3.5.1. General Considerations

SoA is presented in Section 7.1.2. Additional details are presented in Section 2.5.1.

For the Day 29 primary analysis, the analysis will include all participants' safety data collected up to Day 29 post-vaccination.

Subgroups:

Table 8 Definition for Subgroups (Part B)

Subgroup Variable*	Categories
Age Group	≥18 to <50 years old ≥50 to <65 years old
Previous Flu Season Vaccination Status	Received Received from mRNA-1010-P302 Not Received
Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
Sex	Male Female
BMI (only for immunogenicity analyses)	<30 kg/m^2 ≥30 kg/m^2

*Subgroup derivations will be based on the information from eCRF.

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

3.5.2. Background Characteristics

3.5.2.1. Participant Disposition

See Section 2.5.2.1 for details.

3.5.2.2. Demographics and Baseline Characteristics

Descriptive statistics for age, weight, height, and BMI are described in Section 2.5.2.1.

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

- Age group (18 to <50 years old, ≥50 to <65 years old)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown, Not reported)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Previous Flu Season Vaccination Status (Received, Received from mRNA-1010-P302, Not Received)

The summaries will be provided separately for all analysis sets (except for Solicited Safety Set) defined in Section 3.4.

3.5.2.3. Medical History

See Section 2.5.2.3 for details.

3.5.2.4. Prior and Concomitant Medications and Vaccinations

See Section 2.5.2.4 for details.

3.5.2.5. Protocol Deviations

See Section 2.5.2.5 for details.

3.5.2.6. Study Exposures

See Section 2.5.2.6 for details.

3.5.3. Immunogenicity Analysis

Immunogenicity analyses for Part B will be conducted using the PP Immunogenicity Set.

3.5.3.1. Analysis of Primary Endpoints

- GMT as measured by HAI against 4 vaccine-matched influenza virus A and B strains at Day 29 (noninferiority testing)
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI (noninferiority testing)

See Section 2.5.3.1 for details.

3.5.3.2. Supplementary Analysis

The primary analyses will be repeated using the Immunogenicity Set as a supplementary analysis.

3.5.3.3. Subgroup Analysis

To assess the consistency of immunogenicity response of mRNA-1010 across subgroups, subgroup analysis of the co-primary endpoints may be conducted by subgroups defined by age group, previous flu vaccine status, race, sex, and BMI category (see Table 8), based on the PP Immunogenicity Set. For each subgroup category, the co-primary immunogenicity endpoints will be analyzed using the same statistical methods as for primary analysis. Additional details are documented in Section 2.5.3.1.

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

3.5.3.4. Analysis of Secondary Endpoints

- GMT as measured by HAI against vaccine-matched influenza virus A strains at Day 29 (superiority testing)

Upon successful demonstration of noninferiority for Part B, superiority of mRNA-1010 relative to a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza A strains (A/H1N1 and A/H3N2) at Day 29 will be tested at a two-sided $\alpha = 0.025$ level. The same ANCOVA model for primary immunogenicity analysis will be applied. The superiority of GMT in participants who received mRNA-1010 compared to GMT in participants who received Fluarix Quadrivalent will be demonstrated by the lower bound of the 97.5% CI of the GMR ruling out 1 (lower bound > 1).

- Proportion of participants reaching seroconversion at Day 29 as measured by HAI against vaccine-matched influenza virus A strains (superiority testing)

If superiority has been demonstrated based on GMT for vaccine-matched influenza A strains, the SCR of the vaccine-matched influenza A strains at Day 29 between the vaccination groups will be compared. The Miettinen-Nurminen's method will be used to calculate the 97.5% CI for the difference in SCRs. The superiority of SCR will be considered demonstrated if the lower bound of the 97.5% CI of SCR difference is > 0.

- GMT as measured by HAI against vaccine-matched influenza virus B strains at Day 29 (superiority testing)

Upon successful demonstration of superiority (either one or both hypotheses) for vaccine-matched influenza A strains, superiority of mRNA-1010 relative to a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza B strains (B/Victoria and B/Yamagata) at Day 29 will be tested:

  - If both GMT and SCR hypotheses for vaccine-matched influenza A strains are successful, testing for vaccine-matched influenza B strains will be performed at a two-sided $\alpha = 0.025$ level.
  - If only one of GMT and SCR hypotheses for vaccine-matched influenza A strains is successful, testing for vaccine-matched influenza B strains will be performed at a two-sided $\alpha=0.0125$ level.

The same ANCOVA model for primary analysis will be applied. The superiority of GMT in participants who received mRNA-1010 compared to GMT in participants who received a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) for vaccine-matched influenza B strains will be demonstrated by the lower bound of the 97.5% or 98.8% CI of the GMR ruling out 1 (lower bound > 1).

- Proportion of participants reaching seroconversion at Day 29 as measured by HAI against vaccine-matched influenza virus B strains (superiority testing)

If superiority has been demonstrated based on GMT for vaccine-matched influenza B strains, the SCR of the vaccine-matched influenza B strains at Day 29 between the vaccination groups will be compared at the same α level. The Miettinen-Nurminen's method will be used to calculate the 97.5% or 98.8% CI for the difference in SCRs. The superiority of SCR will be considered demonstrated if the lower bound of the 97.5% or 98.8% CI of SCR difference is > 0.

- The proportion of participants with HAI titer ≥1:40 at Day 29

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

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

Descriptive statistics (n, median, min, max) will be provided for the GMFR of HAI titers with corresponding 95% CI at Day 29 over Day 1 (Baseline). The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMFR with corresponding 95% CI will be plotted at Day 29.

3.5.3.5. Analysis of Exploratory Endpoints

- GMT at Day 181 as measured by HAI.

Descriptive statistics (n, median, min, max) will be provided for the GMT of HAI titers with corresponding 95% CI at Day 181. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

- Proportion of participants reaching seroconversion at Day 181 as measured by HAI

The number and percentage of participants with seroconversion at Day 181 will be provided with 2-sided 95% CI using the Clopper-Pearson method.

- GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline)
- GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine mismatched strains on Day 29 compared with Day 1 (Baseline).

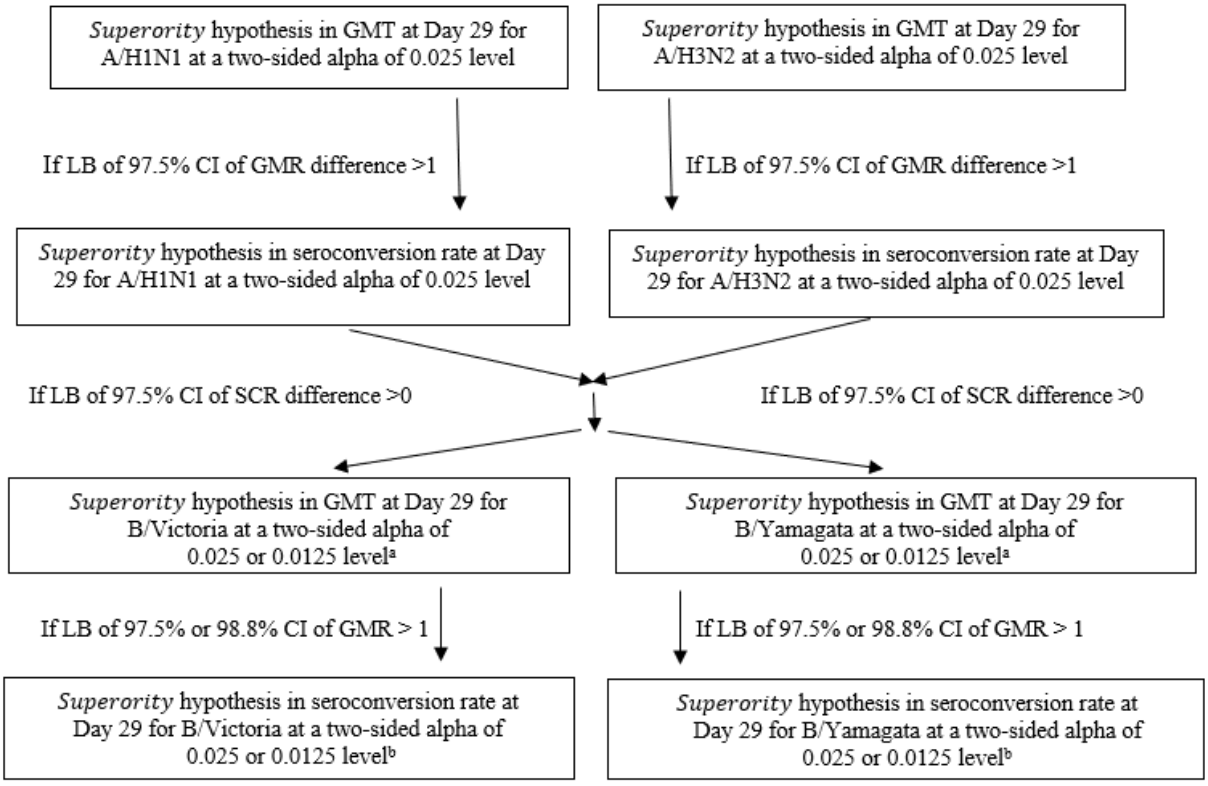
Descriptive statistics (n, median, min, max) will be provided for these endpoints with corresponding 95% CI at each time point. The 95% CIs will be calculated based on the t distribution of the log-transformed values then back transformed to the original scale for presentation. In addition, the GMT and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

3.5.4. Multiplicity

Part B will be considered successful only if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level.

Upon successful demonstration of the noninferiority, the superiority hypotheses specified in Section 4.3.2 will be tested following the prespecified order of the superiority tests.

Figure 1: Pre-specified Order for Superiority Hypothesis Testing



a. If both hypotheses at the previous step are successful, the hypothesis at the current step will be tested at two-sided alpha of 0.025; if only one hypothesis at the previous step is successful, the current hypothesis will be tested at two-sided alpha of 0.0125.
b. The hypothesis will be tested at the same alpha level from the previous step (if success achieved at previous steps).

3.5.5. Safety Analysis

See Section 2.5.5 for details.

3.5.5.1. Analysis of Solicited Adverse Reactions

See Section 2.5.5.1 for details. Refer to subgroups defined in Table 8 when subgroup analysis applies.

Besides the situations indicated in the Section 2.5.5.1 for the solicited ARs to be recorded by the clinical staff in EDC (i.e. Reactogenicity CRF), accordingly to the CRF Completion Guidelines, solicited ARs will also be reported in EDC if meeting any of the following situations:

- If a participant had a >= grade 1 solicited AR but missed an eDiary entry during the 7 days post-vaccination period so could not report it in eDiary
- Any new information verbally reported by the participant during the 7-day post-vaccination period or at the Day 8 safety call.

The statistical outputs for solicited ARs will be based on both eDiary and Reactogenicity CRF, and the highest grade will be included if the grade from eDiary and Reactogenicity is different. Before unblinding the selected roles/personals for the primary analysis, if the grade from eDiary is confirmed as an input error by the participant, a Note to File (NTF) will be created to document the input error and be used as a source for the corrected information for the outputs.

3.5.5.2. Unsolicited Adverse Events

See Section 2.5.5.2 for details.

3.5.5.2.1. Overview of Unsolicited AEs

See Section 2.5.5.2.1 for details.

3.5.5.2.2. Unsolicited AEs by SOC and PT

See Section 2.5.5.2.2 for details.

3.5.5.2.3. Unsolicited AEs by PT

See Section 2.5.5.2.3 for details.

3.5.5.2.4. Unsolicited AEs by Severity

See Section 2.5.5.2.4 for details.

3.5.5.2.5. Independent Cardiac Event Adjudication Committee

See Section 2.5.5.2.5 for details.

3.5.5.2.6. Subgroup Analysis of Unsolicited AEs

Analysis of unsolicited TEAEs will be conducted for subgroups defined in Table 8. Overall summary of the unsolicited TEAEs up to 28 days will be provided for each subgroup. Summary tables for TEAE, treatment-related TEAEs, and SAEs by SOC and PT may also be provided for each subgroup up to 28 days after the vaccine.

3.5.5.3. Death

See Section 2.5.5.3 for details.

3.5.5.4. Other Safety Data

3.5.5.4.1. Pregnancy

See Section 2.5.5.4.1 for details.

3.5.5.4.2. Vital Signs

See Section 2.5.5.4.2 for details.

3.5.6. Exploratory Analysis

3.5.6.1. COVID-19 Impact

See Section 2.5.6.3 for details.

3.5.7. Planned Analyses

3.5.7.1. Primary Analysis

The primary analysis of Part B will be performed after all participants have completed the Day 29 Visit. All data relevant to the primary study analysis through the Day 29 Visit will be cleaned for the primary analysis (i.e., data that are as clean as possible) and a report may be generated.

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

3.5.7.2. Final Analysis

Final analysis of Part B will be performed once all participants complete the Day 181 (Month 6)/EoS Visit.

4. Part C

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objective is to evaluate:

- The humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults ≥ 65 years old.
- The reactogenicity and safety of mRNA-1010.

4.1.2. Secondary Objectives

The secondary objective is to evaluate:

- The immunological response of mRNA-1010 (for superiority) relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched influenza virus A and B strains at Day 29.
- To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza virus A and B strains at Day 29.

4.1.3. Exploratory Objectives (May be Performed)

The following exploratory objectives may be performed:

- To evaluate humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.
- To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched or vaccine-mismatched A and B strains.

4.2. Study Endpoints

4.2.1. Primary Endpoints

The primary objectives will be evaluated by the following endpoints:

- Immunogenicity endpoints:
    - GMT at Day 29 as measured by HAI.
    - Proportion of participants reaching seroconversion at Day 29 as measured by HAI.

GMT and rate of seroconversion will be evaluated for each individual A and B strain (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). Therefore, there will be eight co-primary immunogenicity endpoints in the study.

- Reactogenicity and safety endpoints:
    - Frequency and grade of solicited local and systemic reactogenicity ARs during a 7-day follow-up period postinjection.
    - Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection.
    - Frequency of any SAEs, MAAEs, and AESIs from Day 1 to Day 181/EoS.

4.2.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- GMT at Day 29 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
- The proportion of participants with HAI titer ≥1:40 at Day 29.
- GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.

4.2.3. Exploratory Endpoints

The exploratory objectives may be evaluated by the following endpoints:

- GMT at Day 181 as measured by HAI.
- Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
- GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline).
- GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine mismatched strains on Day 29 compared with Day 1 (Baseline).

4.3. Study Design

4.3.1. Overall Study Design

Part C is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults ≥ 65 years old.

mRNA-1010 to be tested contains 4 mRNAs in an equivalent mRNA mass ratio that encode membrane-bound HA of the 4 different influenza strains recommended by WHO for 2023-2024 NH cell- or recombinant-based vaccines. Fluzone HD Quadrivalent contains 4 HAs of the 4 different influenza strains recommended by the WHO for 2023-2024 NH egg-based vaccines.

Medically stable adults, ≥ 65 years old, will be screened and enrolled. Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA 1010 or a single dose of a licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent, Table 9).

Table 9 Treatment Groups and Dose Levels (Part C)

		mRNA/Antigen		

Treatment Group	Study Intervention Received	HA (each) (µg)	Total Dose (µg)	Number of Participants
5	mRNA-1010	12.5(of mRNA)	50 (of mRNA)	1500
6	Active Comparator (Fluzone HD Quadrivalent)	15 (of protein)	240 (of protein)	1500

Abbreviations: HA=hemagglutinin; mRNA=messenger ribonucleic acid

Clinic/in-person visits will consist of a Screening Visit (up to 28 days before the Day 1 visit and may be performed over multiple visits if within the 28-day screening window), a dosing visit on Day 1 (Baseline; may be on the same day as the Screening Visit), a visit on Day 29 (Month 1), and a subsequent visit on Day 181 (Month 6)/EoS (in a subset of ~1000 participants) with up to 7 months of study participation for each participant. There will also be contacts by electronic means or telephone calls on Day 8, Day 91 (Month 3) and Day 181 (non-subset participants) (Month 6).

4.3.2. Statistical Hypotheses

The primary objective in Part C is to evaluate the noninferiority of the immunogenicity response to mRNA-1010 versus the licensed Fluzone HD Quadrivalent, as measured by GMT and seroconversion rate at Day 29 using HAI assay, for all 4 vaccine-matched influenza virus A and B strains:

- For each of the 4 vaccine-matched strains, the noninferiority hypothesis in terms of the GMT is:

  Null Hypothesis: $H_0{}^1$: GMR $\leq$0.667 (inferior) vs.
  Alternative Hypothesis: $H_0{}^1$: GMR >0.667 (noninferior)

  using a noninferiority margin of 1.5, where the GMR is the ratio of the GM HAI titer in the mRNA 1010 group compared with the GM HAI titer in the Fluzone HD Quadrivalent group.

- For each of the 4 vaccine-matched strains, the noninferiority hypothesis in seroconversion rate is:

  Null Hypothesis: $H_0{}^2$: SCR differences $\leq -10\%$ (inferior) vs.
  Alternative Hypothesis: $H_0{}^2$: SCR differences $> -10\%$ (noninferior)

using a noninferiority margin of 10%, where the SCR difference is the difference in the SCR between the mRNA 1010 group compared with the Fluzone HD Quadrivalent group.

The noninferiority hypotheses in the GMT and SCR will be evaluated for all 4 strains and Part C is considered a study success if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Therefore, each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level:

- For each strain, the noninferiority in GMT will be demonstrated by the lower bound of the 95% CI of the GMR ruling out 0.667, ie. The lower bound of the 95% CI >0.667
- For each strain, the noninferiority in SCR will be demonstrated by the lower bound of the 95% CI of the SCR difference ruling out −10%, ie. The lower bound of the 95% CI > −10%

Upon successful demonstration of noninferiority for Part C, ie. the noninferiority success criteria have been met for all 8 coprimary immunogenicity endpoints, the following superiority hypotheses will be tested:

- For each of the 4 vaccine-matched strains, the superiority hypothesis in terms of the GMT is:

  Null Hypothesis: $H_0{}^3$: GMR = 1 vs.
  Alternative Hypothesis: $H_0{}^3$: GMR >1 (superior)

- For each of the 4 vaccine-matched strains, the superiority hypothesis in seroconversion rate is:

  Null Hypothesis: $H_0{}^4$: SCR differences = 0 vs.

  Alternative Hypothesis: $H_0{}^4$: SCR differences >0 (superior)

4.3.3. Sample Size and Power

Assuming approximately 15% of 3000 randomized participants will be excluded from the PP Immunogenicity Set, with approximately 2550 participants in the PP Immunogenicity Set (1:1 ratio; approximately 1275 participants in each treatment group):

- The study has at least 99% power to meet the noninferiority success criteria in GMT for all 4 strains at a 1-sided alpha of 0.025 level with a noninferiority margin of 1.5. An underlying GMR (mRNA-1010 vs. the licensed Fluzone HD Quadrivalent vaccine) of 0.90 is assumed for each of the 4 strains and the standard deviation of the natural log-transformed levels is assumed to be 1.5.
- The study has at least 93% power to meet the noninferiority success criteria in SCR for all 4 strains, at a 1-sided alpha of 0.025 level with a noninferiority margin of 10%. The SCRs of 58% for influenza A strains and SCRs of 48% for influenza B strains, respectively, are assumed in the mRNA 1010 group, whereas the SCRs in the licensed Fluzone HD Quadrivalent group are assumed to be 60% and 50% for the influenza A and B strains, respectively.

The overall power for achieving the primary noninferiority objective in Part C would be approximately 93%. Furthermore, the sample size provides 1) an approximately 79.5% power for a superiority test of GMT for an individual strain with an underlying GMR (mRNA-1010 vs. Fluzone HD Quadrivalent) of 1.2; 2) an approximately 43% power for a superiority test of SCR for an A strain (assuming an SCR of 64% for mRNA-1010 vs. 60% for Fluzone HD Quadrivalent), and an approximately 41% power for a superiority test of SCR for a B strain (assuming an SCR of 54% for mRNA-1010 vs 50% for Fluzone HD Quadrivalent) at 2-sided alpha of 0.025 (with alpha split for multiplicity adjustment).

4.3.4. Randomization

Randomization will be performed using an IRT. Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent, Table 9). Randomization will be stratified by the previous flu season (since September 2022) vaccination status (Received, Received from mRNA-1010-P302.; Not received).

4.3.5. Blinding and Unblinding

See Section 2.3.5 for details.

4.4. Analysis Sets

See Section 2.4 for details.

For PP Immunogenicity Set, the following major dosing error ranges for planned Fluzone Quadrivalent will be used to determine participant exclusion from the analysis populations:

Table 10 Major Dosing Errors for Participants Randomized into Fluzone HD Quadrivalent (Part C)

Actual Vaccine Received	Major Dosing Errors
Fluzone HD Quadrivalent ≤ 180 µg	Yes
Fluzone HD Quadrivalent > 180 µg – 300 µg	No
Fluzone HD Quadrivalent > 300 ug	Yes
Any mRNA-1010 or Fluarix Quadrivalent	Yes

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

- mRNA-1010 50 µg group: If received any non-zero dose of mRNA-1010 and didn't receive any dose of Fluzone Quadrivalent or Fluarix Quadrivalent .
- Fluzone HD Quadrivalent 240 µg group: If received any non-zero dose of Fluzone Quadrivalent and didn't receive any dose of mRNA-1010 or Fluarix Quadrivalent.

4.5. Statistical Analysis

4.5.1. General Considerations

SoA is presented in Section 7.1.3. Additional details are presented in Section 2.5.1.

Subgroups:

Table 11 Definition for Subgroups (Part C)

Subgroup Variable*	Categories
Age Group	≥65 to <75 years old ≥75 years old

Previous Flu Season Vaccination Status	Received Received from mRNA-1010-P302 Not Received
Race	White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other (combining Not Reported and Unknown)
Sex	Male Female
BMI (only for immunogenicity analyses)	<30 kg/m^2 ≥30 kg/m^2

*Subgroup derivations will be based on the information from eCRF

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

4.5.2. Background Characteristics

4.5.2.1. Participant Disposition

See Section 2.5.2.1 for details.

4.5.2.2. Demographics and Baseline Characteristics

Descriptive statistics for age, weight, height, and BMI are described in Section 2.5.2.2. The number and percentage of participants will be provided for the following categorical variables:

- Age group (≥65 to <75 years old, ≥75 years old)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Previous Flu Season Vaccination Status (Received, Received from mRNA-1010-P302, Not Received)

The summaries will be provided separately for all analysis sets (except Solicited Safety Set) defined in Section 4.4.

4.5.2.3. Medical History

See Section 2.5.2.3 for details.

4.5.2.4. Prior and Concomitant Medications and Vaccinations

See Section 2.5.2.4 for details.

4.5.2.5. Protocol Deviations

See Section 2.5.2.5 for details.

4.5.2.6. Study Exposures

See Section 2.5.2.6 for details.

4.5.3. Immunogenicity Analysis

The immunogenicity analyses for Part C will be conducted separately using the PP Immunogenicity Set.

4.5.3.1. Primary Analysis

- GMT as measured by HAI against 4 vaccine-matched influenza virus A and B strains at Day 29 (noninferiority testing)
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI (noninferiority testing)

See Section 2.5.3.1 for details.

4.5.3.2. Supplementary Analysis

The primary analyses will be repeated using the Immunogenicity Set as a supplementary analysis.

4.5.3.3. Subgroup Analysis

To assess the consistency of immunogenicity response of mRNA-1010 across subgroups, subgroup analysis of the co-primary endpoints may be conducted by subgroups defined by age group, previous year's flu vaccine status, race, sex, and BMI category (see Table 11), based on

the PP Immunogenicity Set. For each subgroup category, the co-primary immunogenicity endpoints will be analyzed using the same statistical methods as for primary analysis. Additional details are documented in Section 4.3.2.

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

4.5.3.4. Analysis of Secondary Endpoints

- GMT as measured by HAI against vaccine-matched influenza virus A strains at Day 29 (superiority testing)

See Section 3.5.3.4 for details, the comparator will be Fluzone HD.

4.5.4. Multiplicity

Part C will be considered successful only if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level.

Upon successful demonstration of the noninferiority, the superiority hypotheses specified in Section 4.3.2 will be tested the prespecified order of the superiority tests (Figure 1), the comparator will be Fluzone HD.

4.5.5. Safety Analysis

See Section 2.5.5 for details.

4.5.5.1. Analysis of Solicited Adverse Reactions

See Section 2.5.5.1 for details. Refer to subgroups defined in Table 11 when subgroup analysis applies.

4.5.5.2. Unsolicited Adverse Events

See Section 2.5.5.2 for details.

4.5.5.2.1. Overview of Unsolicited AEs

See Section 2.5.5.2.1 for details.

4.5.5.2.2. Unsolicited AEs by SOC and PT

See Section 2.5.5.2.2 for details.

4.5.5.2.3. Unsolicited AEs by PT

See Section 2.5.5.2.3 for details.

4.5.5.2.4. Unsolicited AEs by Severity

See Section 2.5.5.2.4 for details.

4.5.5.2.5. Independent Cardiac Event Adjudication Committee

See Section 2.5.5.2.5 for details.

4.5.5.2.6. Subgroup Analysis of Unsolicited AEs

Analysis of unsolicited TEAEs will be conducted for subgroups defined in Table 11. Overall summary of the unsolicited TEAEs up to 28 days will be provided for each subgroup. Summary tables for TEAE, treatment-related TEAEs, and SAEs by SOC and PT may also be provided for each subgroup up to 28 days after the vaccine.

4.5.5.3. Death

See Section 2.5.5.3 for details.

4.5.5.4. Other Safety Data

4.5.5.4.1. Pregnancy

See Section 2.5.5.4.1 for details.

4.5.5.4.2. Vital Signs

See Section 2.5.5.4.2 for details.

4.5.6. Exploratory Analysis

4.5.6.1. COVID-19 Impact

See Section 2.5.6.3 for details.

4.5.7. Planned Analyses

4.5.7.1. Primary Analysis

The primary analysis of immunogenicity and safety for Part C will be performed after all participants have completed the Day 29 Visit. All data relevant to the primary study analysis through the Day 29 Visit will be cleaned for the primary analysis (i.e., data that are as clean as possible) and a report may be generated.

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

4.5.7.2. Final Analysis

Final analysis of all immunogenicity and safety data for Part C will be performed once all participants complete the Day 181 (Month 6)/EoS Visit.

5. Changes in the Planned Analysis

Not applicable.

6. References

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

https://www.fda.gov/media/73691/download.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007b [cited 2021 Aug 19]. Available from:

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

7. Appendices

7.1. Schedule of Activities (SoA)

7.1.1. Part A

Visit Number		**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit	C	C	SC	C	SC	C	C
Month Time Point				M1	M3	M6	Up to M6
Visit Day	Screening	D1 (Baseline)	D8	D29	D91	D181/ EoS	N/A
Window Allowance (Days)	-28	N/A	+3	-7 to +3	±5	±14	N/A
Informed consent form, demographics, concomitant medications, medical history[b]	X						
Inclusion/exclusion criteria	X	X					
Physical examination[b]	X						
Vital signs measurements	X	X					
Pregnancy testing	X	X					
Randomization		X					
Blood collection for future research sample (optional)		X					
Blood collection for transcriptomics (optional)		X		X			
Study intervention dosing (including 30-minute, post-dose observation period)[c]		X					

Visit Number		**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit	C	C	SC	C	SC	C	C
Month Time Point				M1	M3	M6	Up to M6
Visit Day	Screening	D1 (Baseline)	D8	D29	D91	D181/ EoS	N/A
Window Allowance (Days)	-28	N/A	+3	-7 to +3	±5	±14	N/A
Blood collection for humoral immunogenicity		X		X		X	
NP swab for virus detection[d]		X					X
eDiary activation for recording solicited ARs (7 days)[c]		X					
Review of solicited AR and medication eDiary		X	X				
Follow up safety call[f]			X		X		
Recording of unsolicited AEs		X	X	X			X[g]
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[h]		X	X	X	X	X	X[g]
Recording of concomitant medications[i]		X	X	X			
Recording of concomitant procedures/surgeries		X	X	X	X	X	X[g]
Recording of non-study vaccinations[j]		X	X	X	X	X	
Study completion						X	

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; C=clinic/in-person visit; D=day; eDiary=electronic diary; EoS=end of study; ILI=influenza-like illness; IM=intramuscular(ly); M=month; MAAE=medically attended adverse event; N/A=not applicable; NP=nasopharyngeal; SAE=serious adverse event; SC=safety call (or contact by electronic means); USV=unscheduled visit.

[a]. The Screening Visit and D1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.

[b]. Verbal medical history is acceptable. Clinically significant findings during the Screening Visit physical examination should also be recorded in the participant's medical history.

[c]. See Section 2.3.1, Table 1 for dose levels and treatment groups.

[d]. An NP swab specimen for viral respiratory pathogens will be collected prior to the study intervention dosing on D1. If a participant reports ILI symptoms within 7 days after symptom onset, an unscheduled visit for symptom assessment should occur. If the symptoms meet the criteria for protocol-defined ILI, an NP swab must be collected if it is within 7 days after ILI symptom onset.
[e]. The eDiary entries will be recorded at approximately 30 minutes after study intervention dosing 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, on the day of study intervention dosing and the subsequent 6 days following study intervention dosing.
[f]. An unscheduled follow up safety call may be triggered if an eDiary record results in identification of a relevant safety event. A safety phone call may trigger an unscheduled visit.
[g]. There may be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study.
[h]. Trained clinic staff will call (or contact by electronic means) all participants to collect information relating to any MAAEs, AEs leading to discontinuation from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any non-study vaccinations.
[i]. All concomitant medications will be recorded from D1 through D29; thereafter, only concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded through D181 (Month 6)/EoS.
[j]. All non-study vaccinations will be recorded through 181 days after the dose of study intervention.

7.1.2. Part B

Visit Number		**1**	**2**	**3**	**4**	**5**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**
Month Timepoint				**M1**	**M3**	**M6**
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**
Informed consent form, demographics, concomitant medications, medical history[b]	X					
Inclusion/exclusion criteria	X	X				
Physical examination[b]	X					
Vital signs measurements	X	X				
Pregnancy testing	X	X				
Randomization		X				
Blood collection for humoral immunogenicity		X		X		X[i]
Study intervention dosing (including 30-minute, post-dose observation period)		X				
eDiary activation for recording solicited ARs/medication recording (7 days)[d]		X				
Follow up safety call[e]			X		X	X[i]
Review of solicited ARs and medication eDiary		X	X			
Recording of unsolicited AEs		X	X	X		

Visit Number		**1**	**2**	**3**	**4**	**5**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**
Month Timepoint				**M1**	**M3**	**M6**
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[f]		X	X	X	X	X
Recording of concomitant medications[g]		X	X	X		
Recording of non-study vaccinations[h]		X	X	X	X	X
Recording of concomitant procedures/surgeries		X	X	X	X	X
Study completion						X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic/in-person visit; D = day; eDiary = electronic diary; EoS = end of study; IM = intramuscular(ly); M = month; MAAE = medically attended adverse event; SAE = serious adverse event; SC = safety call (or contact by electronic means).

[a]. 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.

[b]. Verbal medical history is acceptable. Clinically significant findings during the Screening Visit physical examination should also be recorded in the participant's medical history.

[c]. See Section 3.3.1, Table 7 for dose levels and treatment groups.

[d]. The eDiary entries will be recorded at approximately 30 minutes after study intervention dosing 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, on the day of study intervention dosing and the subsequent 6 days following study intervention dosing.

[e]. An unscheduled follow-up safety call may be triggered by the identification of a relevant safety event from an eDiary record, or other participant contact. A safety phone call may trigger an unscheduled visit.

[f]. Trained clinic staff will call (or contact by electronic means) all participants to collect information relating to any MAAEs, AEs leading to discontinuation from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.

[g]. All concomitant medications will be recorded from Day 1 through Day 29; thereafter, only concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded through Day 181 (Month 6)/EoS.
[h]. All non-study vaccinations will be recorded through 181 days after the dose of study intervention.
[i]. Samples for humoral immunogenicity on Day 181 (Month 6)/EoS will be collected for first 1000 participants and analyzed in a subset. Participants in the subset require a clinic visit on Day 181 (Month 6)/EoS for sample collection. All other participants will require a safety call.

7.1.3. Part C

Visit Number		**1**	**2**	**3**	**4**	**5**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**
Month Timepoint				**M1**	**M3**	**M6**
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**
Informed consent form, demographics, concomitant medications, medical history[b]	X					
Inclusion/exclusion criteria	X	X				
Physical examination[b]	X					
Vital signs measurements	X	X				
Randomization		X				
Blood collection for humoral immunogenicity		X		X		X[i]
Study intervention dosing (including 30-minute, post-dose observation period)		X				
eDiary activation for recording solicited ARs/medication recording (7 days)[d]		X				
Follow up safety call[e]			X		X	X[i]
Review of solicited ARs and medication eDiary		X	X			
Recording of unsolicited AEs		X	X	X		

Visit Number		**1**	**2**	**3**	**4**	**5**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**
Month Timepoint				**M1**	**M3**	**M6**
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[f]		X	X	X	X	X
Recording of concomitant medications[g]		X	X	X		
Recording of non-study vaccinations[h]		X	X	X	X	X
Recording of concomitant procedures/surgeries		X	X	X	X	X
Study completion						X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic/in-person visit; D = day; eDiary = electronic diary; EoS = end of study; IM = intramuscular(ly); M = month; MAAE = medically attended adverse event; SAE = serious adverse event; SC = safety call (or contact by electronic means).

[a]. 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.

[b]. Verbal medical history is acceptable. Clinically significant findings during the Screening Visit physical examination should also be recorded in the participant's medical history.

[c]. See Section 4.3.1, Table 9 for dose levels and treatment groups.

[d]. The eDiary entries will be recorded at approximately 30 minutes after study intervention dosing 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, on the day of study intervention dosing and the subsequent 6 days following study intervention dosing.

[e]. An unscheduled follow-up safety call may be triggered by the identification of a relevant safety event from an eDiary record, or other participant contact. A safety phone call may trigger an unscheduled visit.

[f]. Trained clinic staff will call (or contact by electronic means) all participants to collect information relating to any MAAEs, AEs leading to discontinuation from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.

[g]. All concomitant medications will be recorded from Day 1 through Day 29; thereafter, only concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded through Day 181 (Month 6)/EoS.
[h]. All non-study vaccinations will be recorded through 181 days after the dose of study intervention.
[i]. Samples for humoral immunogenicity on Day 181 (Month 6)/EoS will be collected for approximately the first 1000 participants and analyzed in a subset. Participants in the subset require a clinic visit on Day 181 (Month 6)/EoS for sample collection. All other participants will require a safety call.

7.2. Standards for Variable Display in TLFs

The following applies to Part A, Part B, and Part C:

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

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

7.3. Analysis Visit Windows for Immunogenicity Analysis

The following applies to Part A, Part B, and Part C:

Immunogenicity Analysis will be summarized using the following analysis visit window for post-injection assessments:
Step 1: If the immunogenicity assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the immunogenicity assessments are not collected at the scheduled visits, assessments collected at an unscheduled visit will be used using the analysis visit windows described in Table 12 below.

Table 12 Analysis Visit Window

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

7.4. Imputation Rules for Missing Dates

The following applies to Part A, Part B, and Part C:

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

1) Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless the medication end date is on/after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection.
   - If Day and Month are both missing, use the first day of the year, unless the medication end date is on/after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection.
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.
2) Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

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

1) Missing or partial AE start date:
   - If only Day is missing, use the first day of the month, unless the AE end date is on/after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if AE time was collected.

- If Day and Month are both missing, use the first day of the year, unless the AE end date is on/after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date and time of first injection, when time is available.

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

7.5. Prior and Concomitant Categorization of a Medication

The following applies to Part A, Part B, and Part C:

Table 13 Categorization of Medication

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

C= Concomitant; P=Prior

[1] Includes medications with completely missing end date.

[2] Includes medications with completely missing start date.

7.6. Solicited Adverse Reactions and Grades

The following applies to Part A, Part B, and Part C:

Table 14 Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	**Grade 0 (None)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-threatening)**
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/2.5 cm	25-50 mm/2.5-5 cm	51-100 mm/5.1-10 cm	>100 mm/>10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	<25 mm/2.5 cm	25-50 mm/2.5-5 cm	51-100 mm/5.1-10 cm	>100 mm/>10 cm	Necrosis

Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	<38.0°C <100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	>40.0°C >104.0°F

7.7. Toxicity Grading of Vital Sign Abnormalities

The following applies to Part A, Part B, and Part C:

Table 15 Toxicity Grading of Vital Sign Abnormalities

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia

Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

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

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

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

7.8. Estimands and Estimand Specifications

The following applies to Part A, Part B, and Part C, unless otherwise specified:

Table 16 Intercurrent Events

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

Abbreviation: IcEv: intercurrent event.

Table 17 Summary of Primary Immunogenicity Estimands with Rationale for Strategies to Address Intercurrent Events (Part A)

Objective: To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 based on GMT		
Estimand Label	**Primary Immune Estimand 1a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 1b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting immune response and no RT-PCR-confirmed influenza between Days 1 to 29.	Immune response to seasonal influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 18 years or inclusive who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Target Population	Adults aged at least 18 years inclusive who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay after the IP administration, and have no significant protocol deviations impacting the key or critical data. Participants with RT-PCR-confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity Set	Adults aged at least 18 years inclusive who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Endpoint	GMT of anti-HA levels on Day 29	As per Estimand 1a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Quadrivalent)	As per Estimand 1a.

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

Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged at least 18 years inclusive who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the significant protocol criteria (i.e., significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 1a.
Objective: to evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 based on seroconversion rate		
Estimand Label	**Primary Immune Estimand 2a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 2b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting key or critical data and no RT-PCR-confirmed influenza between Days 1 to 29.	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.

Target Population	Adults aged at least 18 years inclusive who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged at least 18 years inclusive who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.
Endpoint	Seroconversion rate difference of antibody measured by HAI assay on Day 29.	As per Estimand 2a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Quadrivalent)	As per Estimand 2a.
Population-Level Summary	Immune response to influenza defined as seroconversion rate difference of antibody using Miettinen-Nurminen's method.	As per Estimand 2a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination)	Principal stratum	Treatment policy

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

Table 18 Summary of Primary Immunogenicity Estimands with Rationale for Strategies to Address Intercurrent Events (Part B)

Objective: To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults 18 to <65 years old based on GMT.		
Estimand Label	**Primary Immune Estimand 1a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 1b** (on the Immunogenicity Set)

Estimand Description	Immune response to influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive and less than 65 years who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting immune response.	Immune response to seasonal influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 18 years or inclusive and less than 65 years who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Target Population	Adults aged at least 18 years inclusive and less than 65 years who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay after the IP administration, and have no significant protocol deviations impacting the key or critical data.	Adults aged at least 18 years inclusive and less than 65 years who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Endpoint	GMT of anti-HA levels on Day 29	As per Estimand 1a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Quadrivalent)	As per Estimand 1a.
Population-Level Summary	Immune response to seasonal influenza defined as GMT of anti-HA level as measured by HAI assay using an ANCOVA model on the log-transformed tiers on Day 29, with the vaccination group as the fixed variable, adjusted for stratified previous flu vaccination status used for randomization and log-transformed baseline tiers.	As per Estimand 1a.
Intercurrent Event Strategy		

IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination)	Principal stratum	Treatment policy
Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged at least 18 years inclusive and less than 65 years who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the significant protocol criteria (i.e., significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 1a.
Objective: to evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 based on seroconversion rate		

Estimand Label	**Primary Immune Estimand 2a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 2b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive and less than 65 years who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting key or critical data.	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 18 years inclusive and less than 65 years who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.
Target Population	Adults aged at least 18 years inclusive and less than 65 years who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged at least 18 years inclusive and less than 65 years who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.
Endpoint	Seroconversion rate difference of antibody measured by HAI assay on Day 29.	As per Estimand 2a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluarix Quadrivalent)	As per Estimand 2a.
Population-Level Summary	Immune response to influenza defined as seroconversion rate difference of antibody using Miettinen-Nurminen's method.	As per Estimand 2a.
Intercurrent Event Strategy		

IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination) **Rationale for Strategies**	Principal stratum This estimand seeks to understand immune response impact of influenza vaccine on adults aged at least 18 years inclusive and less than 65 years who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, wrong vaccination, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	Treatment policy A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the key major protocol criteria (i.e., significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 2a.

Table 19 Summary of Primary Immunogenicity Estimands with Rationale for Strategies to Address Intercurrent Events (Part C)

Objective: To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults ≥65 years old based on GMT.		
Estimand Label	**Primary Immune Estimand 1a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 1b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 65 years inclusive who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting immune response.	Immune response to seasonal influenza measured as GMT of vaccine-matched anti-HA level as measured by HAI assay on Day 29 in adults aged at least 65 years or inclusive who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Target Population	Adults aged at least 65 years inclusive who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay after the IP administration, and have no significant protocol deviations impacting the key or critical data.	Adults aged at least 65 years inclusive who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment as measured by HAI assay.
Endpoint	GMT of anti-HA levels on Day 29	As per Estimand 1a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluzone HD Quadrivalent)	As per Estimand 1a.

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

Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged at least 65 years inclusive who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the significant protocol criteria (i.e., significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 1a.
Objective: to evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluzone HD Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 based on seroconversion rate		
Estimand Label	**Primary Immune Estimand 2a** (on the PP Immunogenicity Set)	**Supplementary Immune Estimand 2b** (on the Immunogenicity Set)
Estimand Description	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 65 years inclusive who receive IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment without significant protocol deviations impacting key or critical data.	Immune response to influenza measured as seroconversion rate difference of vaccine-matched anti-HA levels as measured by HAI assay on Day 29 in adults aged at least 65 years inclusive who receive IP administration irrespective of any significant protocol deviations impacting immune response and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.

Target Population	Adults aged at least 65 years inclusive who receive the assigned IP administration, complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment after the IP administration, and have no major protocol deviations impacting the immune response.	Adults aged at least 65 years inclusive who receive any IP administration and complied with immunogenicity blood sampling to have a baseline and Day 29 antibody assessment.
Endpoint	Seroconversion rate difference of antibody measured by HAI assay on Day 29.	As per Estimand 2a.
Treatment Conditions	mRNA-1010 vs. active comparator (Fluzone HD Quadrivalent)	As per Estimand 2a.
Population-Level Summary	Immune response to influenza defined as seroconversion rate difference of antibody using Miettinen-Nurminen's method.	As per Estimand 2a.
Intercurrent Event Strategy		
IcEv1 (early discontinuation or unrelated death)	Principal stratum	Principal stratum
IcEv2 (alternative influenza vaccine)	Principal stratum	Treatment policy
IcEv3 (COVID-19 vaccine)	Principal stratum	Treatment policy
IcEv4 (prohibited medications)	Principal stratum	Treatment policy
IcEv5 (early infection)	Principal stratum	Treatment policy
IcEv6 (wrong vaccination)	Principal stratum	Treatment policy

Rationale for Strategies	This estimand seeks to understand immune response impact of influenza vaccine on adults aged at least 65 years inclusive who receive the IP administration and comply with key major protocol criteria. A principal stratum is used for early discontinuation, unrelated deaths, early infection and significant deviations (such as use of alternative vaccines, COVID-19 vaccines, wrong vaccination, and prohibited medications) so that analysis is a sub-population composed of participants free from intercurrent events.	A treatment policy strategy is used for following up immune response including all participants vaccinated irrespective of early infection or whether they subsequently were found not to strictly meet the key major protocol criteria (i.e., significant protocol deviations affecting immune response, use of the alternative influenza or COVID-19 vaccine, wrong vaccination or use of the prohibited medications). There is interest in understanding immune response in the light of poor compliance which may happen in clinical practice and may reflect reactions to the IP administration as well as poor compliance for unrelated reasons. The principal stratum is employed for the other intercurrent events which match Estimand 2a.

7.9. Definition of TEAE of Special Interest by SMQ

The following applies to Part A, Part B, and Part C:

Table 20 List of TEAE of Special Interest by SMQ

TEAE of Special Interest*	Type of MedDRA Query	Broad or Narrow Search **	SMQ Search Criteria
Anaphylactic Reaction	SMQ	Algorithm	A or (B and C) or (D and (B or C)), Specified PT and algorithm approach included in
Angioedema	SMQ	Narrow	Specified PT terms
Arthritis	SMQ	Narrow	Specified PT terms
Cardiac Arrhythmias	SMQ	Narrow	Specified PT terms
Cardiac Failure	SMQ	Narrow	Specified PT terms
Cardiomyopathy	SMQ	Narrow	Specified PT terms
Central Nervous System Vascular Disorders	SMQ	Narrow	Specified PT terms
Convulsions	SMQ	Narrow	Specified PT terms
Demyelination	SMQ	Narrow	Specified PT terms
Embolic and Thrombotic Events	SMQ	Narrow	Specified PT terms
Guillain-Barre Syndrome	SMQ	Narrow	Specified PT terms

Haematopoietic Cytopenias	SMQ	Narrow	Specified PT terms
Hearing and Vestibular Disorders	SMQ	Narrow	Specified PT terms
Hypersensitivity	SMQ	Narrow	Specified PT terms
Immune-mediated/Autoimmune Disorders	SMQ	Narrow	Specified PT terms
Ischaemic Heart Disease	SMQ	Narrow	Specified PT terms
Noninfectious Myocarditis/Pericarditis	SMQ	Narrow	Specified PT terms
Peripheral Neuropathy	SMQ	Narrow	Specified PT terms
Thrombophlebitis	SMQ	Narrow	Specified PT terms
Vasculitis	SMQ	Narrow	Specified PT terms
*Based on MedDRA 25.0 ** Narrow + Broad search may also be applied, as needed.			

Table 21 Algorithm Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

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

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
A	Narrow	Anaphylactic reaction
A	Narrow	Anaphylactic shock
A	Narrow	Anaphylactic transfusion reaction
A	Narrow	Anaphylactoid reaction
A	Narrow	Anaphylactoid shock
A	Narrow	Circulatory collapse
A	Narrow	Dialysis membrane reaction
A	Narrow	Kounis syndrome
A	Narrow	Procedural shock
A	Narrow	Shock
A	Narrow	Shock symptom
A	Narrow	Type I hypersensitivity
B	Broad	Asthma
B	Broad	Bronchial oedema

B	Broad	Bronchospasm
B	Broad	Cardio-respiratory distress
B	Broad	Chest discomfort
B	Broad	Choking
B	Broad	Choking sensation
B	Broad	Circumoral oedema
B	Broad	Cough
B	Broad	Cough variant asthma
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema
B	Broad	Laryngospasm
B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
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