ModernaTX, Inc.

Protocol mRNA-1011-P101

A Phase 1/2, randomized, open- label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines in healthy adults 50 to 75 years of age

Statistical Analysis Plan

SAP Final 1.0

Version Date: 27-Apr-2023

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
BMI	body mass index
CI	confidence interval
CMQ	customized Medical Dictionary for Regulatory Activities query
COVID-19	coronavirus disease 2019
CSR	clinical study report
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EoS	end of study
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HA	hemagglutinin
HAI	hemagglutination inhibition
HCP	healthcare practitioner
IA	interim analysis
ILI	influenza-like illness
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid

Abbreviation	Definition
NP	nasopharyngeal
PP	Per-Protocol
PT	preferred term
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardized Medical Dictionary for Regulatory Activities query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP) describes the planned analyses for study mRNA-1011-P101 and is based on the most recent approved clinical study protocol, dated 03 Jan 2023, and the most recent approved electronic case report form (eCRF), dated 15 Feb, 2023.

In addition to the information presented in the SAP section of the protocol (Section 9), which provides the principal features of analyses for this study, this SAP provides statistical analysis details and data derivations. It also documents modifications or additions to the analysis plan 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 SAP will be finalized and approved preferably prior to first patient first visit but no later than before receipt of the first live data.

The study is a Phase 1/2, randomized, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines in healthy adults 50 to 75 years of age.

Parexel Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis using SAS Version 9.4 or higher to generate all statistical outputs (tables, figures, listings, and datasets).

2. Study Objectives

2.1. Primary Objectives

To evaluate the safety and reactogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3).

2.2. Secondary Objectives

To evaluate the humoral immunogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1 in comparison with mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3) against vaccine-matched influenza A and B strains at Day 29.

2.3. Exploratory Objectives

The following exploratory objectives may be performed:

- To evaluate the humoral immunogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls against vaccine-matched influenza A and B strains at all evaluable humoral immunogenicity timepoints.
- To evaluate the humoral immunogenicity against vaccine-matched influenza A and B strains by alternative methods at all evaluable timepoints.
- To evaluate the humoral immunogenicity against vaccine-mismatched influenza A and B strains at all evaluable timepoints.
- To evaluate cellular immunogenicity in a subset of participants at all evaluable timepoints.
- To assess the occurrence of clinical influenza in study participants and characterize their immune response to infection and viral isolates.

3. Study Endpoints

3.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

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

3.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- Geometric mean titer (GMT) and geometric mean fold rise (GMFR), comparing Day 29 with Day 1 (baseline), and percentage of participants with seroconversion,

defined as postbaseline titer ≥1:40 if baseline is <1:10 or a 4-fold or greater rise if baseline is ≥1:10 in anti-hemagglutinin (HA) antibodies measured by hemagglutination inhibition (HAI) assay.

3.3. Exploratory Endpoints

The exploratory objectives may be evaluated for the following endpoints depending on availability of data:

- GMT, geometric mean titer ratio (GMTR) (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 against mRNA-1010), and GMFR (compared with Day 1) of anti-HA as measured by HAI assay.
- GMT and GMFR (compared with Day 1) of anti- HA antibodies as measured by microneutralization (MN) assays or other alternative methods against vaccine matched strains.
- GMT and GMFR (compared with Day 1) of anti- HA antibodies as measured by HAI or MN assays against vaccine-mismatched strains.
- Frequency, magnitude, and phenotype of virus- specific B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B-cells after vaccination.
- Frequency of RT-PCR-confirmed influenza-like illness (ILI) and assessment of immune responses in participants with RT-PCR-confirmed ILI.

4. Study Design

4.1. Overall Study Design

This prospective, open-label Phase 1/2 study will enroll approximately 700 healthy adults ≥50 to ≤75 years of age.

On Day 1, each participant will be randomized to receive a single injection administered intramuscularly in the deltoid muscle and followed for 6 months.

The candidate vaccines to be evaluated include:

- mRNA-1011.1 vaccine consisting of 5 mRNAs encoding the HA surface glycoproteins of 4 influenza strains (A/H1N1, A/H3N2, B/Victoria lineage, and

B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 additional A/H3N2 influenza strain (A/Newcastle/1/2021).

- mRNA-1011.2 vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, A/H3N2, and B/Victoria lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Newcastle/1/2021) to replace B/Yamagata.
- mRNA-1012.1 vaccine consisting of 5 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, A/H3N2, and B/Victoria lineage) recommended by the WHO for the 2022/2023 NH season, and 2 additional A/H3N2 influenza strains (A/Newcastle/1/2021 and A/Hong Kong/45/2019) to replace B/Yamagata.
- mRNA-1010: mRNA-1010 (Darwin) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 4 influenza strains (A/H1N1, A/H3N2, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season.
- mRNA-1010.2: mRNA-1010 (Newcastle) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Newcastle/1/2021).
- mRNA-1010.3: mRNA-1010 (Hong Kong) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Hong Kong/45/2019).

Participants will be stratified by prior season influenza vaccination status; those who received a licensed or investigational influenza vaccine within 180 days prior to enrollment will be excluded. A complete listing of inclusion and exclusion criteria is provided in Protocol Section 5.1 and Section 5.2, respectively.

Different dose levels will be assessed in parallel across 7 treatment arms with the number of participants and groups as detailed in Table 1. Data on all 3 investigational mRNA-1011/1012 influenza candidates compared to mRNA-1010 controls will be collected simultaneously.

Study visits will consist of a Screening Visit (up to 28 days before the Day 1 visit), Randomization Visit at Day 1 (Baseline), and subsequent study visits on Day 8, Day 29 (Month 1), and Day 181/(EoS; Month 6), with up to 7 months of study participation. Unscheduled visits for potential ILI symptoms will include testing with a multiplex respiratory infection panel (BioFire or similar).

In addition, there will be 5 safety telephone call visits at Days 15, 57, 91, 121, and 151 as specified in Table 1 (Schedule of Events) in the protocol. All participants will be asked to complete an electronic diary (eDiary) for solicited ARs from Day 1 to Day 7.

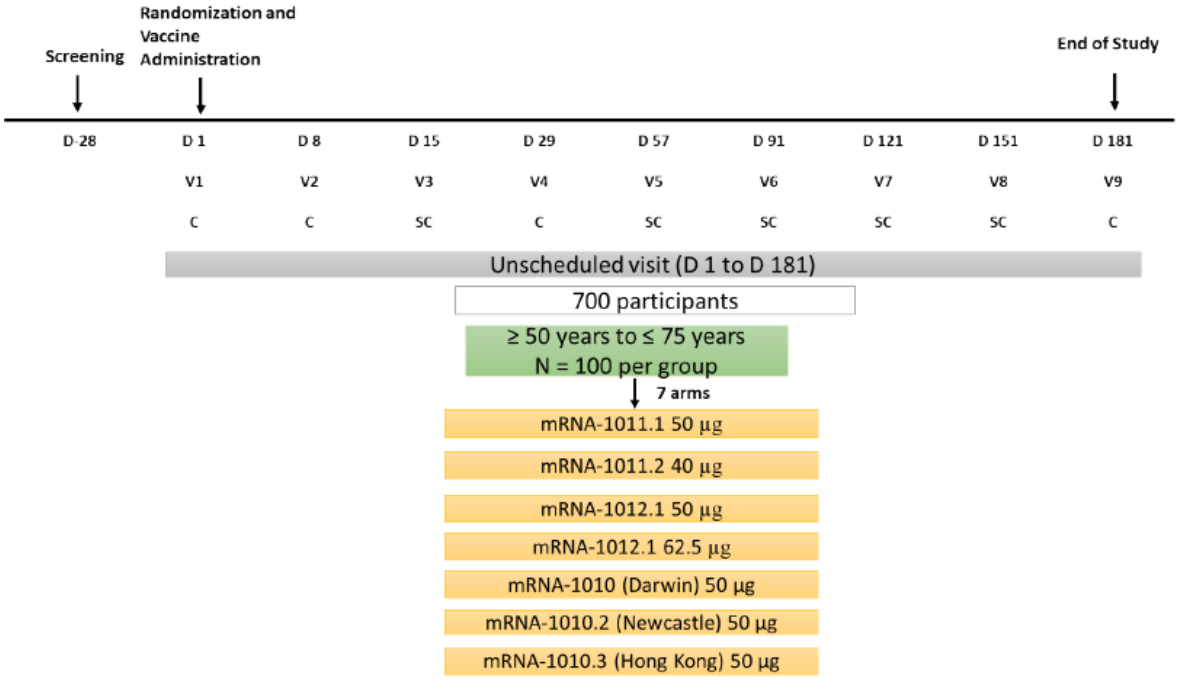
Table 1: Study Arms and Dose Levels

Vaccination Group	Group Name	Composition	Total Dose	N (total)
1	mRNA-1011.1	A/H1N1, B/Yamagata, B/Victoria, A/H3N2 (Darwin), A/H3N2 (Newcastle) at 1:1:1:1:1	50 µg	100
2	mRNA-1011.2	A/H1N1, B/Victoria, A/H3N2 (Darwin), A/H3N2 (Newcastle) at 1:1:1:1	40 µg	100
3	mRNA-1012.1	A/H1N1, B/Victoria, A/H3N2 (Darwin), A/H3N2 (Newcastle), A/H3N2 (Hong Kong) at 1:1:1:1:1	50 µg	100
4	mRNA-1012.1	A/H1N1, B/Victoria, A/H3N2 (Darwin), A/H3N2 (Newcastle), A/H3N2 (Hong Kong) at 1:1:1:1:1	62.5 µg	100
5	mRNA-1010 (Darwin) (Control)	A/H1N1, B/Yamagata, B/Victoria, A/H3N2 (Darwin) at 1:1:1:1	50 µg	100
6	mRNA-1010.2 (Newcastle) (Control)	A/H1N1, B/Yamagata, B/Victoria, A/H3N2 (Newcastle) at 1:1:1:1	50 µg	100
7	mRNA-1010.3 (Hong Kong) (Control)	A/H1N1, B/Yamagata, B/Victoria, A/H3N2 (Hong Kong) at 1:1:1:1	50 µg	100

Abbreviations: mRNA = messenger ribonucleic acid.

The study schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviation: C = Clinic; D = Day; mRNA = Messenger ribonucleic acid; N = Number of participants; SC = Safety Call; V = Visit

4.2. Statistical Hypotheses

No formal hypotheses will be tested. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety, reactogenicity and immunogenicity of different dose levels of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1.

4.3. Sample Size and Power

Approximately 700 participants will be randomized in this study, with approximately 100 participants into each of Vaccination Groups 1-7 (≥50 to ≤75 years of age). Details regarding the number of participants in each vaccination group are presented in Table 1. The probability of AEs based on sample size is presented in Table 2. With 100 participants in each group receiving the study intervention, there is an approximately 87% probability to observe at least 1 participant with an AE if the true incidence of the AE is 2%; if the true incidence rate is 3%, then the probability to observe an AE is approximately 95%.

Table 2: Probability of AEs Based on Sample Size

n	True AE Rate	Probability of 0 AE	Probability of at Least 1 AE Observed
100	1.0%	36.6%	63.4%
100	2.0%	13.3%	86.7%
100	3.0%	4.8%	95.2%
100	4.0%	1.7%	98.3%

4.4. Randomization

Randomization will be performed using an interactive response technology (IRT) system.

The Sponsor's Biostatistics Department or designee will generate the randomized allocation schedule(s) for vaccination group assignment. Overall, approximately 700 healthy adults will be randomized in parallel into 7 treatment arms to receive either mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines or mRNA-1010 control (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) vaccines, with approximately 100 healthy adult participants randomly assigned to each of vaccination groups 1 to 7. Different dose levels will be assessed in parallel (Table 1). Randomization will be stratified by influenza vaccination status in the previous influenza season (received or not received).

4.5. Blinding and Unblinding

This is an open-label study.

5. Analysis Sets

5.1. Randomization Set

The Randomization Set consists of all participants who are randomly assigned.

5.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who receive the study vaccination. Participants will be analyzed according to the vaccination group to which they were randomized.

5.3. Per-Protocol Set

The Per-Protocol (PP) Set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least the Day 29 post-injection assessment (-7 / +14 days of Day 29), have no RT-PCR-confirmed influenza infection prior to Day 29 visit (Day 29 immunogenicity

assessment+7 days) and have no major protocol deviations that impact the immune response. The PP Set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.

Participants with a dosing error will be considered as having a protocol deviation. However, the determination of whether to include/exclude participants from the PP Set due to dosing error will be based on the dosage difference (in µg) between the actual dose received and the randomized dose. The PP Set exclusion criteria for participants with dosing error are described in Table 3.

Table 3: PP Set Exclusion Criteria for Dosing Errors

Group Name	Exclusion Conditions
mRNA-1011.1 50 µg	Any mRNA-1011.2 received, any mRNA-1012.1 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.2 (Newcastle) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, mRNA-1011.1 received ≤ 37.5 µg, or mRNA-1011.1 received > 75 µg
mRNA-1011.2 40 µg	Any mRNA-1011.1 received, any mRNA-1012.1 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.2 (Newcastle) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, mRNA-1011.2 received ≤ 30 µg, or mRNA-1011.2 received > 60 µg
mRNA-1012.1 50 µg	Any mRNA-1011.1 received, any mRNA-1011.2 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.2 (Newcastle) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, mRNA-1012.1 received ≤ 37.5 µg, or mRNA-1012.1 received > 56.25 µg
mRNA-1012.1 62.5 µg	Any mRNA-1011.1 received, any mRNA-1011.2 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.2 (Newcastle) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, mRNA-1012.1 received ≤ 56.25 µg, or mRNA-1012.1 received > 93.75 µg
mRNA-1010 (Darwin) (Control) 50 µg	Any mRNA-1011.1 received, any mRNA-1011.2 received, any mRNA-1012.1 received, any mRNA-1010.2 (Newcastle) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, any mRNA-1010 (Darwin) (Control) received ≤ 37.5 µg, or any mRNA-1010 (Darwin) (Control) received > 75 µg
mRNA-1010.2 (Newcastle) (Control) 50 µg	Any mRNA-1011.1 received, any mRNA-1011.2 received, any mRNA-1012.1 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.3 (Hong Kong) (Control) received, mRNA-1010.2 (Newcastle) (Control) received ≤ 37.5 µg, or mRNA-1010.2 (Newcastle) (Control) received > 75 µg

mRNA-1010.3 (Hong Kong) (Control) 50 µg	Any mRNA-1011.1 received, any mRNA-1011.2 received, any mRNA-1012.1 received, any mRNA-1010 (Darwin) (Control) received, any mRNA-1010.2 (Newcastle) (Control) received, mRNA-1010.3 (Hong Kong) (Control) received ≤ 37.5 µg, or mRNA-1010.3 (Hong Kong) (Control) received > 75 µg

Note: For any missing injection, the dose is considered to be 0.0 µg and included in the lower category ('≤ x.x µg') .

5.4. Safety Set

The Safety Set consists of all randomly assigned participants who receive the study vaccination. The Safety Set will be used for analyses of safety, except for the solicited ARs. Participants will be included in the vaccination group corresponding to what they actually received according to the rules given in Table 4.

Table 4: Vaccination Group Corresponding to Dose Received

Group Name	Inclusion Conditions
mRNA-1011.1 50 µg	No mRNA-1011.2 received, no mRNA-1012.1 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.2 (Newcastle) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and mRNA-1011.1 dose > 0 µg
mRNA-1011.2 40 µg	No mRNA-1011.1 received, no mRNA-1012.1 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.2 (Newcastle) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and mRNA-1011.2 dose > 0 µg
mRNA-1012.1 50 µg	No mRNA-1011.1 received, no mRNA-1011.2 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.2 (Newcastle) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and 0 µg < mRNA-1012.1 dose ⩽ 56.25 µg
mRNA-1012.1 62.5 µg	No mRNA-1011.1 received, no mRNA-1011.2 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.2 (Newcastle) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and mRNA-1012.1 dose > 56.25 µg
mRNA-1010 (Darwin) (Control) 50 µg	No mRNA-1011.1 received, no mRNA-1011.2 received, no mRNA-1012.1 received, no mRNA-1010.2 (Newcastle) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and mRNA-1010 (Darwin) (Control) dose > 0 µg
mRNA-1010.2 (Newcastle) (Control) 50 µg	No mRNA-1011.1 received, no mRNA-1011.2 received, no mRNA-1012.1 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.3 (Hong Kong) (Control) received, and mRNA-1010.2 (Newcastle) (Control) dose > 0 µg
mRNA-1010.3 (Hong Kong) (Control) 50 µg	No mRNA-1011.1 received, no mRNA-1011.2 received, no mRNA-1012.1 received, no mRNA-1010 (Darwin) (Control) received, no mRNA-1010.2 (Newcastle) (Control) received, and mRNA-1010.3 (Hong Kong) (Control) dose > 0 µg

5.5. Solicited Safety Set

The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for analyses of solicited ARs, and participants will be included in the vaccination group corresponding to what they actually received.

6. Statistical Analysis

6.1. General Considerations

All analyses will be conducted using SAS Version 9.4 or higher.

All analyses will be performed by treatment arm, unless otherwise specified.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. The mean and median will be presented to one decimal place more than the minimum and maximum and the SD will be presented to two decimal places more than the minimum and maximum.

Categorical variables will be summarized using frequencies and percentages. Percentages will be presented to one decimal place. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of participants in the vaccination group within the analysis set of interest, unless otherwise specified.

Confidence interval (CI) will be presented to one more decimal place than the point estimate.

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

Visit window rules for protocol-defined visits are provided in Appendix A.

Unscheduled visits will be included in the analyses as follows:

- Mapped to the scheduled visit windows per specified visit windowing rules.
- Included in the derivation of baseline/last on-treatment measurements.

- Included in the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- Presented in individual participant data listings as appropriate.

Analysis periods to be used for safety analyses:

- Overall period: starts from the day of vaccination (Day 1) and continues through the earliest date of (study completion, discontinuation from the study, or death).
- 7 days following vaccination: starts from the day of vaccination and 6 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period will be used for solicited local and systemic ARs that occur during this time.
- Up to 28 days following vaccination: starts from the day of vaccination (Day 1) and 27 subsequent days, or up to the study discontinuation or death, whichever comes earlier. This analysis period will be used as the primary analysis period for safety analyses including unsolicited AEs, except for solicited ARs, unless specified otherwise.

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

a) Study day prior to the injection will be calculated as: date of assessment/event – date of the injection, and

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

Incomplete/missing data will be handled as follows**:**

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

- A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

Vaccination groups to be used for summary purposes:

- mRNA-1010 50 µg
- mRNA-1010.2 50 µg
- mRNA-1010.3 50 µg
- mRNA-1011.1 50 µg
- mRNA-1011.2 40 µg
- mRNA-1012.1 50 µg
- mRNA-1012.1 62.5 µg
- All (the combined group will be applicable to the disposition and baseline demographics only)

6.2. Background Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following categories will be summarized by vaccination group based on the Randomization Set:

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

Percentages will be based on the number of participants in the vaccination group within the Randomization Set. For the Solicited Safety Set, the percentages will be based on the number of participants in the vaccination group within the Safety Set (as treated). The number of participants in the Safety Set (as treated) will be provided.

The reason(s) for participants' exclusion from the PP Set will also be summarized.

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

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

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

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

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

This study treatment only consists of a single dose, thus discontinuation from study treatment is not applicable to this study. A participant is considered to have completed the study if he or she has completed the last scheduled procedure as shown in Table 1 (Schedule of Events) in the protocol.

A participant disposition listing will be provided, including informed consent, participants who received the study vaccination, participants who completed the study, participants who discontinued from the study, and reasons for discontinuation. A separate listing will be provided for screen failure participants with reasons for screen failure.

6.2.2. Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Summaries will be presented by vaccination group and overall based on the Safety Set and FAS.

In addition, randomized participants with any inclusion or exclusion criteria deviations will be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or above.

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in alphabetical order. Within each SOC, PT will be displayed in descending order of mRNA-1012.1 62.5 µg frequency and then alphabetically.

In addition, medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccinations will be coded using the World Health Organization drug dictionary (WHODD) version September 2022 or later. The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Table 5.

Table 5: Prior, Concomitant, and Post Categorization of a Medication

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

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

The number and percentage of participants using concomitant medications and non-study vaccinations during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after the injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination group as follows:

- Any concomitant medications and non-study vaccinations within 7 days post-injection

- Any concomitant medications and non-study vaccinations within 28 days post-injection
- Seasonal influenza or Coronavirus Disease 2019 (COVID-19) vaccine within 28 days post-injection
- Antipyretic or analgesic medication within 28 days post-injection

A summary table of concomitant medications and non-study vaccinations that continued, were newly received, or were received after the injection through 28 days will be provided by PT in descending frequency based on the mRNA-1012.1 62.5 μg group.

Medications to treat or prevent fever or pain will be collected in the eDiary, and summaries will be provided based on the Solicited Safety Set by vaccination group.

Prior, concomitant, and post medications and non-study vaccinations will be presented in a listing. Medications to treat or prevent fever or pain will also be presented in a listing.

Concomitant procedures will be presented in a listing.

6.2.5. Study Exposure

Study duration will be calculated from the date of randomization and the study vaccination as follows: date of completion or discontinuation from study − date of randomization or study vaccination + 1. This summary will be based on the Safety Set.

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

6.2.6. Major Protocol Deviations

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

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

Major protocol deviations will also be presented in a listing.

6.3. Efficacy Analysis

Not applicable. Because the study is not powered for efficacy assessments, symptoms of infection with respiratory pathogens via RT-PCR will be tracked as an exploratory objective in this study.

6.4. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by SOC and PT according to the MedDRA version 25.1 or above for AR Terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for solicited ARs and vital signs.

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 summarized by vaccination group.

6.4.1. 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 administration of study intervention. An eDiary will prompt daily participant reporting of solicited ARs. Participants will record such occurrences in the eDiary on the day of administration of study intervention and on each of the 6 days after dosing.

Severity grading of reactogenicity events will be automatically assigned upon participant entry into the eDiary based on the grading scales presented in Appendix D Solicited Adverse Reactions and Grades, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b). All solicited ARs (local and systemic) will be considered causally related to dosing.

Solicited ARs will be collected from Day 1 through 7 days after the study intervention (i.e., the day of study vaccination and 6 subsequent days).

If a participant reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study site staff in the electronic data capture (EDC).

If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant should notify the site to provide an end date and close out the event in the EDC.

If the participant reported an event that started after the solicited period (i.e., after Day 7), it should be recorded as an AE in the EDC. Causality for these events will be determined per assessment by the Investigator.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must be recorded by the study site staff in the EDC:

- Solicited AR that results in a visit to a healthcare practitioner (HCP) (MAAE).
- Solicited AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (AE leading to discontinuation).
- Solicited AR lasting beyond 7 days post injection.
- Solicited AR that otherwise meets the definition of an SAE.

The following local and systemic ARs will be solicited by the eDiary:

Solicited Local ARs

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

Solicited Systemic ARs

- Headache
- Fatigue
- Myalgia (muscles aches all over body)
- Arthralgia (joint aches in several joints)
- Nausea/vomiting
- Chills

- Fever (oral)

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

Analyses of solicited local and systemic ARs will be provided by vaccination group based on the Solicited Safety Set. Summaries of local solicited ARs will also be presented by vaccination group.

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

The number and percentage of participants who report each individual solicited local and systemic AR during the 7-day follow-up period after injection will be provided by severity grade.

The onset of each solicited AR will be calculated from the time of injection to the first occurrence of each solicited AR (i.e., solicited AR start date – injection date + 1). The number and percentage of participants with solicited ARs that occur within 7 days will be summarized by study day relative to the injection (Day 1 through Day 7) and vaccination group.

The duration of each solicited AR will be calculated as: solicited AR end date – solicited AR start date +1, regardless of whether it is intermittent, ongoing, or if it continues beyond 7 days. The duration of solicited ARs that occur within 7 days will be summarized by vaccination group.

All solicited ARs that continue beyond 7 days post-injection will be summarized by vaccination group. All delayed ARs with onset day after 7 days post injection will also be summarized by vaccination group. All ARs will be presented in a listing.

6.4.2. Unsolicited Treatment-Emergent Adverse Events

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol; or is specified as a solicited AR in the protocol, but starts outside the protocol-defined period for reporting solicited ARs (i.e., for the 7 days after study

intervention). Unsolicited AEs will be collected from Day 1 through 28 days after the study intervention (i.e., the day of study vaccination and 27 subsequent days).

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

Investigators will review AEs for the occurrence of any MAAEs which are defined as AEs that lead to an unscheduled visit to an HCP. This would include visits to a study clinic for unplanned assessments (e.g., rash assessment, abnormal laboratory follow-up) and visits to HCPs external to the study clinic (e.g., emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured in EDC.

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the Sponsor are required. AESIs for this study are pre-defined in the protocol (Table 8), including thrombocytopenia, neurologic diseases, anaphylaxis, and myocarditis/pericarditis.

MAAEs, SAEs, and AESIs will be collected from participants as specified in Table 1 in the protocol from Day 1 until the end of their participation in the study. Refer to Section 11.3 in the protocol for a list of AESIs pertinent to this study.

AEs will be coded by PT and SOC using the MedDRA. All AE summary tables will be presented by SOC and PT unless otherwise specified. SOC will be displayed in alphabetical order. PTs will be displayed in descending order of frequency in the mRNA-1012.1 62.5 µg group and then alphabetically within SOC.

When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Percentages will be based upon the number of participants in the Safety Set within each vaccination group. The strongest relationship level will be presented in the relationship summaries.

Unsolicited TEAEs occurring up to 28 days after study vaccination and occurring throughout the study (up to Day 181/EoS) will be summarized.

In addition, the number of participants with occurrences of selected TEAEs of clinical interest identified by standardized MedDRA queries (SMQs) or customized MedDRA queries (CMQs) will be summarized. SMQs will be summarized by PT, if applicable. Percentages will be based upon the number of participants in the Safety Set within each vaccination group. Detailed descriptions of SMQs and CMQs are presented in Appendix G.

6.4.2.1. Overview of Unsolicited TEAEs

An overall summary of TEAEs up to 28 days after study vaccination will include the number and percentage of participants, along with the number of events, by vaccination group who experience the following:

- Any TEAEs
- Any serious TEAEs
- Any non-serious TEAEs
- Any non-serious TEAEs severe/Grade 3 or higher
- Any AESIs
- Any treatment-emergent MAAEs
- Any TEAEs leading to discontinuation from participation in the study
- Any severe/Grade 3 or higher TEAEs
- Any TEAEs that are fatal

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

The above summary will be repeated on all reported events up to EoS.

In addition, separate listings for TEAEs leading to discontinuation from participation in the study, SAEs, treatment-related SAEs, and treatment-emergent MAAEs will be provided. Listings of deaths including cause of death and TEAEs in participants who died will also be provided.

6.4.2.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs up to 28 days after study intervention 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:

- All TEAEs
- All TEAEs that are treatment-related
- All AESIs
- All AESIs that are treatment-related
- All treatment-emergent SAEs
- All treatment-emergent SAEs that are treatment-related
- All TEAEs leading to discontinuation from participation in the study
- All severe/Grade 3 or higher TEAEs
- All severe/Grade 3 or higher TEAEs that are treatment-related
- All treatment-emergent MAAEs
- All treatment-emergent MAAEs that are treatment-related

Summary tables of all TEAEs, SAEs, treatment-related SAEs, MAAEs, and TEAEs leading to discontinuation in the study will also be provided by SOC and PT considering all events reported throughout the study.

6.4.2.3. TEAEs by Preferred Term

Tables of all TEAEs will be provided by PT sorted in a descending order of mRNA-1012.1 62.5 µg frequency.

6.4.2.4. TEAEs by Severity

Separate summary tables for all TEAEs and all treatment-related TEAEs will be provided by SOC, PT, and the maximum severity using frequency counts and percentages. Only the maximum severity level will be used in the summaries by severity .

6.4.3. Vital Sign Measurements

Vital signs will be measured by study site staff at Screening and at the Day 1 visit prior to study intervention and at least 60 minutes after study intervention administration, prior to

discharge of the participant. Vital signs may be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

Vital sign measurements, including systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature (oral being the preferred route) will be presented in a data listing, including the toxicity grade.

Abnormalities meeting the toxicity grading criteria (Grade 3 or higher) in Appendix E will be listed. If a participant has a vital sign result with Grade 3 or higher abnormality after the injection visit, then all results of that specific vital sign for that participant will be presented in the listing.

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

6.4.4. Clinical Laboratory Evaluations

Hematology and chemistry safety laboratory assessments including white blood cell count, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, creatinine, alkaline phosphatase, and total bilirubin will be assessed at Screening and Day 8.

For continuous hematology and serum chemistry parameters, the observed values and changes from baseline will be summarized at each timepoint by vaccination group. The number and percentage of participants who have hematology and serum chemistry results below or above the normal laboratory ranges will be tabulated by timepoint.

Hematology and chemistry toxicity grades will also be summarized using a shift table from baseline to Day 8 by vaccination group. Refer to Appendix F for laboratory abnormalities meeting the toxicity grading criteria.

Individual results of safety laboratory assessments will be presented in data listings. The toxicity grade will be presented and values which are below or above the normal laboratory ranges will be flagged.

A point-of-care urine pregnancy test will be performed for all female participants of childbearing potential at the Screening Visit and before study intervention administration on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating hormone

(FSH) level may be measured at the Screening visit, at the discretion of the Investigator, when necessary, to confirm postmenopausal status.

Pregnancy test results will be provided in a listing.

6.4.5. Physical Examinations

A full physical examination will be performed at the Screening visit (according to standard medical practice, including assessment of height and weight). Symptom-directed physical examinations will be performed at all other scheduled timepoints. Interim physical examinations may be performed at the discretion of the Investigator. Any clinically significant finding identified by an HCP during study visits should be reported as a MAAE.

Physical examination results will be presented in a data listing.

6.5. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Set. If the number of participants in the FAS and PP Set differs (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

6.5.1. Immunogenicity Assessments

Blood samples for humoral and cellular immunogenicity assessments will be collected at the timepoints specified in Table 1 in the protocol. The following analytes may be measured:

- Serum antibody level as measured by HAI assay.
- Serum antibody level as measured by MN assay or similar method, if necessary.
- Virus-specific B-cell responses measured by flow cytometry or other methods, and targeted repertoire analysis of B cells after vaccination.

Analytes may be measured using other exploratory serological assays and cellular immunogenicity assays.

6.5.2. Immunogenicity Analysis

The following immunogenicity endpoint will be evaluated:

- GMT and GMFR, comparing Day 29 with Day 1 (baseline), and percentage of participants with seroconversion, defined as a postbaseline titer ≥ 1:40 if baseline is

<1:10 and a 4-fold or greater rise if baseline is ≥ 1:10 in anti-HA antibodies measured by HAI assay.

For the immunogenicity endpoints, the geometric mean (GM) of specific antibody titers with corresponding 95% CI at each timepoint and the GMFR of specific antibody titers with the corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by vaccination group. For each vaccination group, all influenza strains will be tested.

Descriptive summary statistics, including median, minimum, and maximum, will also be provided. The GM will be calculated using the following formula (Nauta 2011):

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

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

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

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

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity titers or levels for participant i at timepoints j and k, $j \neq k$.

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

For summarizations of GMT and GMFR, antibody titers reported as below LLOQ will be replaced by 0.5×LLOQ. Values that are greater than the ULOQ will be converted to the ULOQ.

The model-based GM titer will be estimated based on an analysis of covariance (ANCOVA) model. In the ANCOVA model, the log-transformed antibody titer at the post-baseline timepoint (Day 29) will be treated as the dependent variable with the vaccination group as the explanatory variable and influenza vaccination status in the previous influenza season (received or not received) and the log-transformed baseline antibody titer as the covariates.

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

For each between-group comparison in Table 6, the GMTR (i.e. ratio of GMTs) between the two vaccination groups at Day 29 will be estimated from the ANCOVA model, with 95% CI provided accordingly.

Seroconversion rate from baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. For HA, the rate of seroconversion is defined as the proportion of participants with either a pre-vaccination HAI titer < 1:10 and a post-vaccination HAI titer ≥ 1:40 or a pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer.

For each between-group comparison specified in Table 6, the difference of seroconversion rates between the two vaccination groups at Day 29 for each applicable pair will be provided along with 95% CIs estimated using Miettinen-Nurminen method.

Table 6: Between-Group Immunogenicity Comparisons

	Treatment Arm			
Control Arm	mRNA-1011.1 50 µg	mRNA-1011.2 40 µg	mRNA-1012.1 50 µg	mRNA-1012.1 62.5 µg
mRNA-1010 (Darwin) 50 µg	X	X	X	X
mRNA-1010.2 (Newcastle) 50 µg	X	X	X	X
mRNA-1010.3 (Hong Kong) 50 µg	X	X	X	X
mRNA-1011.2 40 µg	X	NA	X	X

6.6. Exploratory Analyses

The below exploratory analyses of immunogenicity may be performed:

- GMT, GMTR (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 against mRNA-1010), and GMFR (compared with Day 1) of anti-HA as measured by HAI assay.
- GMT and GMFR (compared with Day 1) of anti- HA antibodies as measured by MN assays or other alternative methods against vaccine matched strains.
- GMT and GMFR (compared with Day 1) of anti- HA antibodies as measured by HAI or MN assays against vaccine-mismatched strains.

- Frequency, magnitude, and phenotype of virus-specific B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of B cells after vaccination.
- Frequency of RT-PCR-confirmed ILI and assessment of immune responses in participants with RT-PCR–confirmed ILI.

In the ANCOVA model, the log-transformed antibody titers at each available post-baseline timepoint (Day 29 and Day 181/EoS) are treated as the dependent variable, with the treatment group as the explanatory variable and influenza vaccination status in the previous influenza season (received or not received) and the log-transformed baseline antibody titer as the covariates.

An NP swab specimen for viral respiratory pathogens will be collected prior to the study intervention administration on Day 1. Throughout the study, the participant will be instructed to contact the study site if he/she has symptoms suggestive of ILI. An unscheduled visit for symptom assessment and NP swab for viral respiratory pathogens will be conducted if a participant has protocol-defined ILI $\leqslant$7 days of symptom onset.

The frequency of RT-PCR-confirmed ILI, including RT-PCR-confirmed protocol-defined influenza infection and RT-PCR–confirmed CDC-defined influenza infection, is an exploratory efficacy endpoint. A participant may have multiple RT-PCR results for influenza post-baseline and is counted as positive if the participant had at least one positive post-baseline result for influenza. The following outputs will be provided for RT-PCR-confirmed ILI based on the FAS:

- The number and percentage of participants with negative, positive, and inconclusive/invalid RT-PCR test results for influenza at baseline and post-baseline will be summarized by vaccination group.
- Participants with baseline and post-baseline positive RT-PCR results for influenza will be presented in a listing.

6.7. Subgroup Analyses

The primary endpoints will be further analyzed to examine the consistency of the treatment effect across the subgroups. Following subgroups are defined:

- Influenza vaccination status in the previous influenza season: received or not received.

6.8. Planned Analyses

An interim analysis and a final analysis are planned in the study.

As this Phase 1/2 study has the primary objective as the safety and reactogenicity evaluations and has no formal statistical hypothesis, no alpha adjustment will be needed for the multiplicity control either between the interim analysis and final analysis, or across the immunogenicity endpoints within the interim analysis or final analysis.

6.8.1. Interim Analyses

In this study, an interim analysis of safety, reactogenicity and immunogenicity will be performed after all participants have completed Day 29 and will include, at a minimum, cleaned data from available safety and immunogenicity datasets. The interim analysis will include all immunogenicity data up to Day 29, the solicited reactogenicity data in the first 7 days after vaccination, any unsolicited AEs within 28 days after vaccination, and other safety data up to Day 28.

6.8.2. Final Analyses

The final analysis of all endpoints will be performed after all participants have completed Day 181/EoS. The final clinical study report (CSR) will include full analyses of all safety, reactogenicity and immunogenicity data available through Day 181/EoS.

7. Changes from Planned Analysis in Protocol

There are no changes in planned analysis.

8. References

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

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

Nauta J. Statistics in Clinical Vaccine Trials. Heidelberg: Springer, 2011.

9. Appendices

9.1.1. Appendix A Analysis Visit Windows

Analysis visit windows will be utilized for immunogenicity assessments only.

Data will be mapped using the following approach:

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

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 7 below.

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

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

Table 7: Analysis Visit Windows for Immunogenicity Assessments

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

9.1.2. Appendix B Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partially missing prior/concomitant medications and non-study vaccinations start/stop dates are defined below:

1. Missing or partially missing medication start date:
   - If only Day is missing, use the first day of the month, unless the start month and year of the medication coincide with the month and year of the study injection.
     - If not marked as a prior medication on the Prior/Concomitant CRF page (“Was the medication taken prior to study administration?” = “No”), then use the date of the study injection.

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

- If Day and Month are both missing, use the first day of the year, unless the start year of the medication coincides with the year of the study injection.
  - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then use the date of the study injection.
  - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), then use the earlier of the first day of the year or the date of the study injection -1.
  - If the mark on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?") is missing and the medication end date is on/after the date of the study injection or is missing, then use the date of the study injection.
- If Day, Month and Year are all missing, the date will not be imputed, but will use the following rules for purposes of determining the status as prior and/or concomitant.
  - If not marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "No"), then the medication will be treated as having begun after study injection.
  - If marked as a prior medication on the Prior/Concomitant CRF page ("Was the medication taken prior to study administration?" = "Yes"), or if the mark is missing, then the medication will be treated as a prior medication (and as a concomitant medication unless the stop date indicates the medication was stopped prior to study injection).

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 on ongoing medication.
- For non-study vaccination, the end date will be imputed to the same date as the start date.

9.1.3. Appendix C Imputation Rules for Missing AE Dates

Imputation rules for missing or partial AE start dates and stop dates 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 the study injection or is missing/partial AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date of the study injection.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The AE end date is on/after the date of the study injection or is missing/partial AND the start year of the AE coincides with the start year of the study injection. In this case, use the date of the study injection.
   - If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of the study injection, the AE will be considered pre-treatment AE; otherwise, the AE will be considered treatment emergent-.
2. Missing or partially missing AE end dates will not be imputed.

9.1.4. Appendix D Solicited Adverse Reactions and Grades

Reaction	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Local				
Injection site pain	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/ induration (hardness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Systemic				
Headache	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/ vomiting	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock

Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

Note: Events listed above but starting > 7 days post study intervention will be recorded in EDC. Causality for each event reported in EDC will be determined per assessment by the investigator.

9.1.5. Appendix E Severity Grading of Vital Sign Abnormalities

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

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

9.1.6. Appendix F Severity Grading of Laboratory Abnormalities

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

Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

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

Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

9.1.7. Appendix G Definition of TEAE of Special Interest by SMQ/CMQ

Outputs will be generated for analysis based on MedDRA SMQs, to be determined by Safety team prior to the final CSR.