ModernaTX, Inc.

Protocol mRNA-1010-P101

A Phase 1/2, Randomized, Stratified, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1010 Seasonal Influenza Vaccine in Healthy Adults 18 Years and Older

Statistical Analysis Plan

SAP Version 3.0
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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
BUN	blood urea nitrogen
BP	blood pressure
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DBP	data blinding plan
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
EoS	end of study
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMTr	ratio of geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
IA	interim analysis
ILI	influenza-like illness
IP	investigational product
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
NH	Northern Hemisphere

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
SAS	Statistical Analysis System
SD	standard deviation
SoE	schedule of events
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODrug Global	World Health Organization drug dictionary

1 Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1010-P101, is based on the most recent approved clinical study protocol (CSP), Amendment 4, dated 03-Feb-2022, and the most recent approved electronic case report form (eCRF), dated 01-Mar-2022.

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

Study mRNA-1010-P101 is a Phase 1/2, randomized, stratified, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of messenger ribonucleic acid (mRNA)-1010 seasonal influenza vaccine in healthy adults 18 years and older. Study design and analyses for Phase 1/2, and Phase 2 Northern Hemisphere, and Phase 2 Extension parts of the study will be described separately in the SAP, unless otherwise specified.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (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. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, study vaccination, injection of investigational product (IP)/ investigational vaccine, and injection are used interchangeably. The Phase 2 Northern Hemisphere part of the study will be referred to as Phase 2 NH, and previous flu vaccination status will be referred to as vaccination status throughout the SAP.

2 Study Objectives

2.1 Phase 1/2

2.1.1 Primary Objectives

The primary objectives are the following:

- To evaluate the safety and reactogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose.
- To evaluate the humoral immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose against vaccine-matched influenza A and B strains at Day 29.

2.1.2 Secondary Objectives

The secondary objective is the following:

- To evaluate the humoral immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose against vaccine-matched influenza A and B strains at all evaluable humoral immunogenicity time points.

2.1.3 Exploratory Objectives

The exploratory objectives (may be performed) are the following:

- To evaluate the humoral immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose against vaccine-mismatched or drifted influenza A and B strains.
- To evaluate the cellular immunogenicity of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose in a subset of participants.
- To further characterize antibody responses, for example, fragment crystallizable (Fc)-mediated function, avidity, or epitope specificity, of 3 dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine administered as a single dose.
- To assess the occurrence of influenza-like illness (ILI) in study participants and characterize their immune response to infection and viral isolates.

2.2 Phase 2 Northern Hemisphere and Phase 2 Extension

2.2.1 Primary Objectives

The primary objectives are the following:

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

2.2.2 Secondary Objectives

The secondary objective is the following:

- To evaluate the humoral immunogenicity of each vaccine group against vaccine-matched influenza A and B strains at Day 29.

2.2.3 Exploratory Objectives

The exploratory objectives (may be performed) are the following:

- To evaluate the relative vaccine efficacy of mRNA-1010 vaccine to an active comparator in preventing reverse transcriptase polymerase chain reaction (RT-PCR) confirmed ILI caused by any strain of influenza using different case definitions.
- To evaluate the humoral immunogenicity of mRNA-1010 vaccine to that of an active comparator against vaccine-matched or vaccine-mismatched influenza A and B strains, including the use of alternative methods.
- To evaluate the humoral immunogenicity at Days 91 and 181/end of study (EoS) in a subset of participants.
- To further characterize the immune response to mRNA-1010 vaccine and active comparator.

3 Study Endpoints

3.1 Phase 1/2

3.1.1 Primary Endpoints

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

- Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period after vaccination.
- Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period after vaccination.
- Frequency of any serious adverse events (SAEs), AE of special interest (AESI), and medically attended adverse events (MAAEs) from Day 1 to Day 181/end of study (EoS).
- Safety laboratory abnormalities through 7 days after vaccination.

The primary immunogenicity objectives will be evaluated by:

- Geometric mean titer (GMT) and geometric mean fold rise (GMFR) at Day 29 compared with Day 1 (baseline) and percentage of participants with seroconversion, defined as a Day 29 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.

3.1.2 Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- GMT and GMFR of anti-HA antibodies as measured by HAI or microneutralization (MN) assays at all evaluable humoral immunogenicity time points compared with Day 1 (baseline).

3.1.3 Exploratory Endpoints

The exploratory endpoints are the following:

- GMT and GMFR of anti-HA antibodies as measured by HAI or MN assays against vaccine-mismatched or drifted strains compared with Day 1 (baseline).
- Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods as well as targeted repertoire analysis of B cells and T cells after vaccination.
- Frequency, specificities, or other endpoints to be determined for further characterization of antibody responses.
- Frequency of laboratory-confirmed clinical influenza and assessment of immune responses in participants with clinical influenza.

3.2 Phase 2 Northern Hemisphere and Phase 2 Extension

3.2.1 Primary Endpoints

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

- Frequency and grade of each solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination.
- Frequency and severity of any unsolicited AEs during the 28-day follow-up period after vaccination.

- Frequency of any SAEs, AESIs, and MAAEs from Day 1 through Day 181/EoS.

The primary immunogenicity objectives will be evaluated by:

- GMT of anti-HA antibodies at Day 29 as measured by HAI assay.
- Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay. Seroconversion is defined as:
    1. If LLOQ is 1:10, a Day 29 titer ≥ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is ≥ 1:10 in anti- HA antibodies measured by HAI assay.
    2. If LLOQ is greater than 1:10 (e.g. 1:14), a Day 29 titer ≥ 4 times of LLOQ if baseline is < LLOQ or a 4-fold or greater rise if baseline is ≥ LLOQ in anti- HA antibodies measured by HAI assay.

3.2.2 Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- The frequency of participants with anti-HA antibodies seroconversion as measured by HAI assay, and the frequency of participants with an anti-HA antibodies titer ≥ 1:40 as measured by HAI assay at Day 29.
- GMFR of anti-HA antibodies comparing Day 29 to Day 1 (baseline) as measured by HAI assay.

3.2.3 Exploratory Endpoints

The exploratory endpoints are the following:

- RT-PCR-confirmed protocol- or United States Centers for Disease Control and Prevention (CDC)-defined ILI that begin at least 14 days after vaccination through Day 181/EoS caused by any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine.
- GMT and GMFR of anti-HA antibodies as measured 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 assay against vaccine-mismatched strains at Day 29 compared with Day 1 (baseline).

- GMT, GMFR of anti-HA antibodies, and frequency of participants with anti-HA antibodies titers ≥ 1:40 as measured by assays such as MN assays or alternative methods at Days 91 and 181/EoS.
- Frequency, specificities, or other endpoints to be determined for further characterization of immune responses.

4 Study Design

4.1 Overall Study Design

This is a first-in-human (FIH), Phase 1/2, randomized, observer-blind, dose-ranging study in healthy adult participants ≥ 18 years of age. The study comprises 3 parts: Phase 1/2, Phase 2 NH, and Phase 2 Extension. The study will screen and enroll healthy (Phase 1/2) and medically stable (Phase 2 NH and Phase 2 Extension) adults ≥ 18 years of age. All participants will participate in a screening period (up to 28 days before Day 1), treatment period (single dose of vaccine on Day 1), and follow-up period (up to 6 months after vaccination). The vaccination groups and dose level that will be evaluated in each part of the study is are presented in Table 1.

Table 1 Vaccination Groups and Dose Levels

	Vaccination Group	Investigational Product	mRNA or HA (µg)	Total Dose (µg)	Number of Participants		
					Initial Stage	Expansion Stage	Total
Phase 1/2	1	mRNA-1010	12.5	50	9	36	45
	2	mRNA-1010	25	100	9	36	45
	3	mRNA-1010	50	200	9	36	45
	4	Placebo	–	–	9	36	45
	Total				**36**	**144**	**180**
	Vaccination Group	**Investigational Product**	**mRNA or HA (µg)**	**Total Dose (µg)**	**Number of Participants**		
Phase 2 NH	1	mRNA-1010	6.25	25	150		
	2	mRNA-1010	12.5	50	150		
	3	mRNA-1010	25	100	150		
	4	Active comparator	15	60	50		
	Total				**500**		

	Vaccination Group	Investigational Product	Total Dose (µg)[1]	Number of Participants
Phase 2 Extension	1	mRNA-1010	6.25	50
	2	mRNA-1010	12.5	50
	3	mRNA-1010	25	50
	4	Active comparator	60	50
	Total			**200**

Abbreviations: HA = hemagglutinin; mRNA = messenger RNA; NA = not applicable; NH = Northern Hemisphere.
[1] For Phase 2 Extension, mass percent in mRNA-1010 is 25% for each of the 4 HAs.

4.1.1 Phase 1/2

The Phase 1/2 part of the study will be a randomized, observer-blind, dose-ranging, placebo-controlled study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1010 vaccine in healthy adult participants ≥ 18 years of age.

The mRNA-1010 vaccine to be tested includes mRNAs that encode for the surface glycoprotein HA of the following influenza virus strains recommended by the World Health Organization (WHO) for 2021 Southern Hemisphere cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019(H1N1)pdm09
- A/Hong Kong/45/2019(H3N2)
- B/Washington/02/2019 (B/Victoria lineage)
- B/Phuket/3073/2013 (B/Yamagata lineage)

Three dose levels (50, 100, and 200 µg) of mRNA-1010 vaccine (vaccination groups 1 through 3) will be evaluated. Vaccination group 4 will receive placebo. Overall, approximately 180 participants will be randomized in a 1:1:1:1 ratio to receive mRNA-1010 50 µg, mRNA-1010 100 µg, mRNA-1010 200 µg, or placebo, with approximately 45 participants randomized to each vaccination group. The vaccination groups and corresponding dose levels are presented in Table 1. Each vaccination group will have 2 stages: initial stage and expansion stage. The study schema is illustrated in Figure 1.

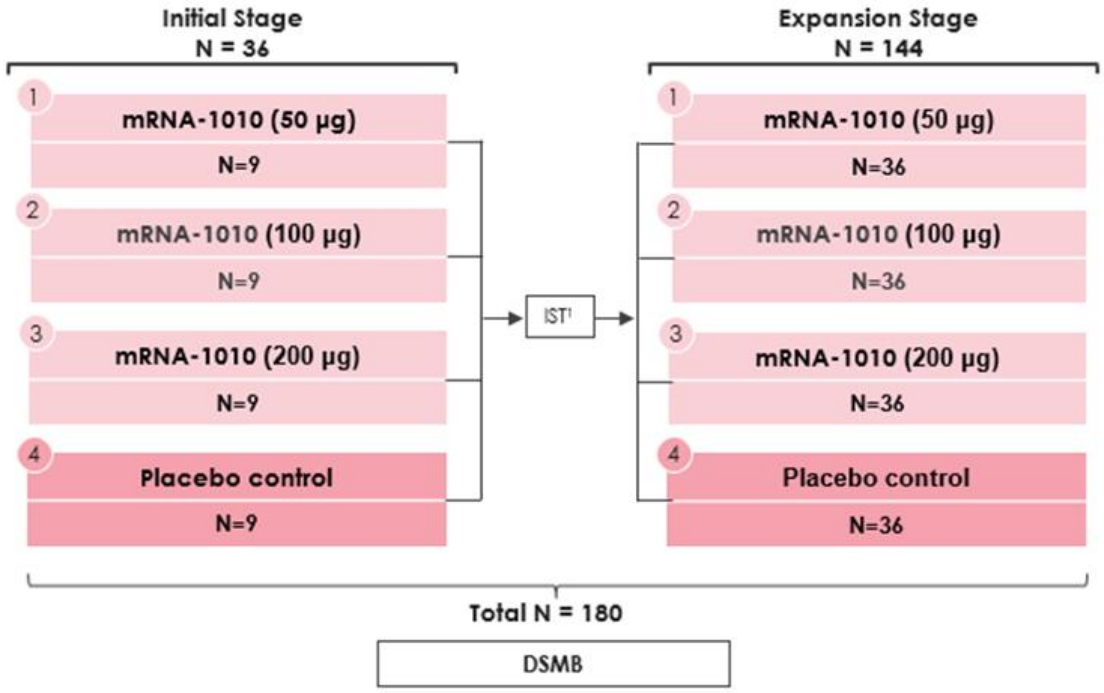
4.1.1.1 Stage 1, Initial Stage

A total of 36 participants (9 participants in each vaccination group) will be randomly assigned in the initial stage of the study. The internal safety team (IST) will perform a blinded review of all safety data up to 7 days after vaccination from the 36 participants in the initial stage.

4.1.1.2 Stage 2, Expansion Stage

After the IST confirms that no pause rules have been met in the 36 participants in the initial stage, enrollment will begin in the expansion stage. A total of 144 participants (36 participants in each vaccination group) will be randomly assigned in the expansion stage of the study. Randomization in the expansion stage will be stratified by age (18 to 49 years versus ≥ 50 years) and will be balanced across the 2 age groups within each vaccination group.

Figure 1 Phase 1/2 Study Schema



Abbreviations: DSMB = Data and Safety Monitoring Board; IST = internal safety team; N = number of participants.
[1] Expansion from initial stage to expansion stage is triggered by the IST.

4.1.2 Phase 2 Northern Hemisphere

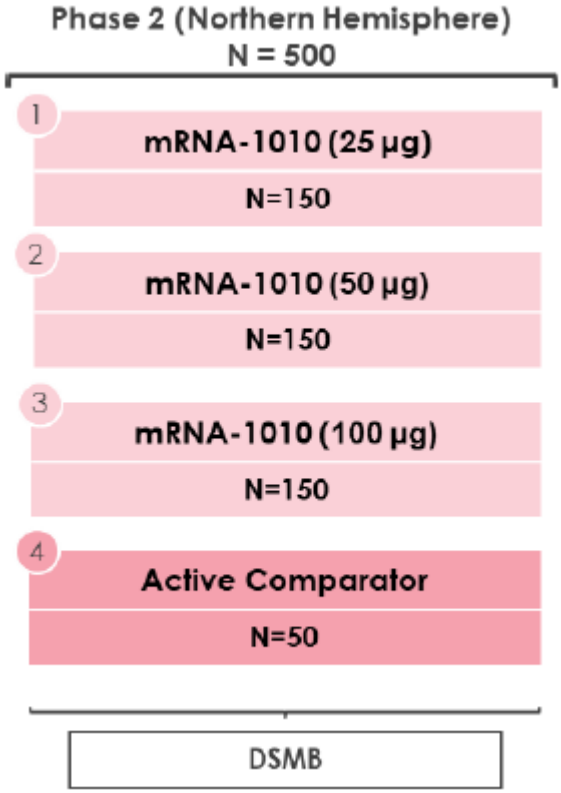
The Phase 2 NH part of the study will be a randomized, observer-blind, dose-ranging, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 vaccine in medically stable adults 18 years and older.

The mRNA-1010 vaccine to be tested, includes mRNAs that encode for the surface glycoprotein HAs of the following influenza virus strains recommended by the WHO for 2021-2022 NH cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019(H1N1)pdm09
- A/Cambodia/e0826360/2020 (H3N2)
- B/Washington/02/2019 (B/Victoria lineage)
- B/Phuket/3073/2013 (B/Yamagata lineage) I

Three dose levels (25, 50, and 100 µg) of mRNA-1010 vaccine (vaccination groups 1 through 3) will be evaluated. Vaccination group 4 will receive an active comparator (licensed quadrivalent seasonal influenza vaccine). Phase 2 NH part of the study will enroll and randomize approximately 500 participants in a 3:3:3:1 ratio to 1 of 4 vaccination groups to receive a single dose of mRNA-1010 at different dose levels (25, 50, 100 µg total mRNA) or a single dose of an active comparator. Randomization will be stratified by age categories (18 to < 50 years, 50 to < 65 years, or ≥ 65 years) and vaccination status in the previous flu season (received or not received). The study schema is illustrated in Figure 2.

Figure 2 Phase 2 Northern Hemisphere Study Schema



Abbreviations: DSMB = Data and Safety Monitoring Board; N = number of participants.

4.1.3 Phase 2 Extension

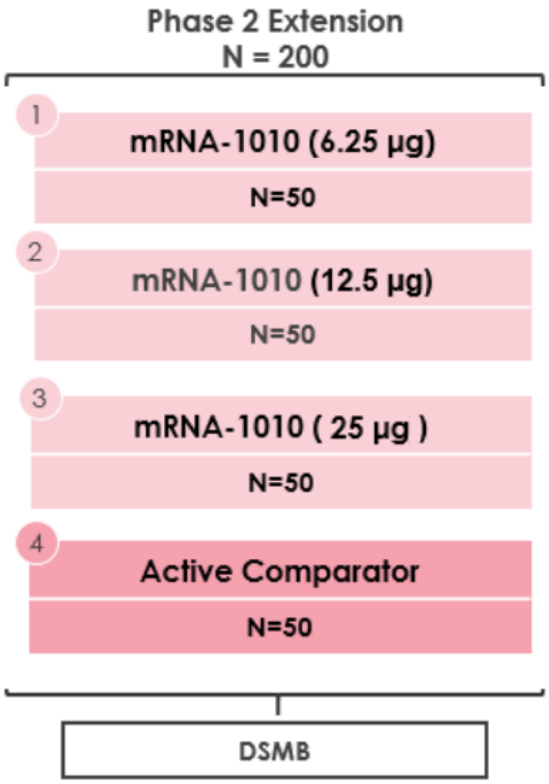
The Phase 2 Extension part of the study follows a similar design as Phase 2 NH, and the same influenza virus strains recommended by the WHO for 2021-2022 NH cell- or recombinant-based vaccines will be tested:

- A/Wisconsin/588/2019(H1N1)pdm09
- A/Cambodia/e0826360/2020 (H3N2)
- B/Washington/02/2019 (B/Victoria lineage)
- B/Phuket/3073/2013 (B/Yamagata lineage) I

Three dose levels (6.25, 12.5, and 25 µg) of mRNA-1010 vaccine (vaccination groups 1 through 3) will be evaluated. Vaccination group 4 will receive an active comparator (licensed quadrivalent seasonal influenza vaccine). Phase 2 Extension part of the study will enroll and randomize approximately 200 participants in a 1:1:1:1 ratio to 1 of 4 vaccination

groups to receive a single dose of mRNA-1010 at different dose levels (6.25, 12.5, or 25 µg total mRNA) or a single dose of an active comparator. Randomization will be stratified by age categories (18 to < 50 years or ≥ 50 years). The study schema is illustrated in Figure 3.

Figure 3 Phase 2 Extension Study Schema



Abbreviations: DSMB = Data and Safety Monitoring Board; N = number of participants

4.2 Statistical Hypotheses

No formal hypotheses will be tested for Phase 1/2, Phase 2 NH, and Phase 2 Extension.

4.3 Sample Size and Power

The sample size for this trial is not driven by statistical assumptions for formal hypothesis testing. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1010.

4.3.1 Phase 1/2

Approximately 180 participants will be randomized to 4 vaccination groups in a 1:1:1:1 ratio as specified in Table 1. With 45 participants receiving an investigational vaccine, there is a probability of approximately 90% to observe at least 1 participant with an AE, if the true incidence rate of the AE is 5%; if the true incidence rate is 10%, then the probability to observe it will be approximately 99%.

4.3.2 Phase 2 Northern Hemisphere

Approximately 500 participants will be randomly assigned in a 3:3:3:1 ratio to the mRNA-1010 25, 50, 100 µg groups, or the active comparator group as specified in Table 1. A total of 450 participants will receive the mRNA-1010 vaccine (150 participants at each dose level). A sample size of 150 participants at each dose level has at least a 95% (or 99%) probability to observe at least 1 participant with an AE at a true 2% (or 3%) AE rate.

4.3.3 Phase 2 Extension

Approximately 200 participants will be randomly assigned in a 1:1:1:1 ratio to the mRNA-1010 6.25, 12.5, 25 µg groups, or the active comparator Group. A total of 150 participants will receive the mRNA-1010 vaccine (50 participants at each dose level). With 50 participants receiving an investigational vaccine, there is a probability of approximately 92% to observe at least 1 participant with an AE, if the true incidence rate of the AE is 5%; if the true incidence rate is 10%, then the probability to observe it will be approximately 99%.

4.4 Randomization

4.4.1 Phase 1/2

Approximately 180 participants will be randomized in a 1:1:1:1 ratio to receive either mRNA-1010 50 µg, mRNA-1010 100 µg, mRNA-1010 200 µg, or placebo, with approximately 45 participants randomized to each vaccination group. A total of 36 participants (9 participants in each vaccination group) will be randomly assigned in the initial stage of the study. A total of 144 participants (36 participants in each vaccination group) will be randomly assigned in the expansion stage of the study. Randomization in the expansion stage will be stratified by age (18 to 49 years versus ≥ 50 years) and will be balanced across the 2 age groups within each vaccination group.

4.4.2 Phase 2 Northern Hemisphere

Approximately 500 participants will be randomized in a 3:3:3:1 ratio to receive either mRNA-1010 25 µg, mRNA-1010 50 µg, mRNA-1010 100 µg, , or a single dose of a licensed quadrivalent seasonal influenza vaccine (active comparator). Randomization to individual vaccination groups will proceed with parallel randomization among the 3 dose levels of mRNA-1010 (25, 50, and 100 µg total mRNA; vaccination groups 1 to 3) and the active comparator (vaccination group 4). Randomization will be stratified by age categories (18 to < 50 years, 50 to < 65 years, or ≥ 65 years) and vaccination status in the previous flu season (received or not received).

4.4.3 Phase 2 Extension

Approximately 200 participants will be randomly assigned in a 1:1:1:1 ratio to receive either mRNA-1010 6.25 µg, mRNA-1010 12.5 µg, mRNA-1010 25 µg, or licensed quadrivalent seasonal influenza vaccine (active comparator), with approximately 50 participants randomly assigned to each mRNA-1010 vaccination group and 50 participants to the Active Comparator Group. Randomization will be stratified by age (18 to < 50 years or ≥ 50 years), with at least 30% of participants in each dose group being ≥ 50 years of age.

4.5 Blinding and Unblinding

This study is an observer-blind study. The investigator, study staff, study participants, site monitors, and sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with certain exceptions please refer to Section 9.1 of the protocol for details.

A Day 29 IA is planned in this study for each of the Phase 1/2, Phase 2 NH, and Phase 2 Extension parts, separately. All relevant data to each IA will be cleaned (i.e., data that are as clean as possible).

The IA will be performed by a separate team of unblinded programmers and statisticians. Except for a limited number of Sponsor and contract research organization (CRO) personnel who will be unblinded to perform the IA, the study site staffs, investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis. Please refer to Section 6.6 and the data blinding plan (DBP) for more details on the IA.

The unblinded IA results will be shared with the Data and Safety Monitoring Board (DSMB).

5 Analysis Populations

For Phase 1/2, Phase 2 NH, and Phase 2 Extension, the following analysis sets are defined: Randomization Set, Full Analysis Set (FAS), Per-protocol (PP) Set, Safety Set, and Solicited Safety Set.

5.1 Randomization Set

The Randomization Set consists of all participants who are randomly assigned. Participants will be analyzed according to the vaccination group to which they were randomized.

5.2 Full Analysis Set (FAS)

The FAS consists of all randomly assigned participants who receive the IP. Participants will be analyzed according to the vaccination group to which they were randomized.

5.3 Per-protocol (PP) Set

The PP Set consists of all participants in the FAS who comply with the injection schedule, comply with the timing of immunogenicity blood sampling (see definition of criterion below), do not have influenza infection at baseline through Day 29 (as documented by RT-PCR testing), 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 vaccination group to which they were randomized.

Subjects that comply with the timing of immunogenicity blood sampling are required to have a baseline assessment, have at least one post-injection assessment, and have a Day 29 assessment that is within 22 days to 36 days after injection (+7 or -7 days of Day 29).

Subjects with dosing error will be considered as having a protocol deviation. However, the determination of whether to include/exclude subjects 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 subjects with dosing error are described in Table 2. For Phase 2 NH and Phase 2 Extension, subjects that are randomized to the

active comparator arm but received less than 40 µg (< 40 µg) of the active comparator or any amount of mRNA-1010 will be excluded from the PP Set.

Table 2 PP Set Exclusion Criteria for Dosing Errors

		Randomized Dose			
	Actual Dose Received	50 µg	100 µg	200 µg	Placebo (0 µg)
Phase 1/2	50 µg		Y	Y	Y
	100 µg	Y		Y	Y
	200 µg	Y	Y		Y
	> 0 - 25 µg	Y	Y	Y	Y
	> 25 - 50 µg		Y	Y	Y
	> 50- 75 µg		Y	Y	Y
	> 75 - 100 µg	Y		Y	Y
	> 100 - 125 µg	Y		Y	Y
	> 125 -150 µg	Y	Y	Y	Y
	> 150 – 175 µg	Y	Y	Y	Y
	> 175 -200 µg	Y	Y		Y
	> 200 -225 µg	Y	Y		Y
	> 225 µg	Y	Y	Y	Y
	Placebo (0 µg)	Y	Y	Y	
		Randomized Dose			
	Actual Dose Received	25 µg	50 µg	100 µg	Active Comparator[1]
Phase 2 NH	25 µg		Y	Y	Y
	50 µg	Y		Y	Y
	100 µg	Y	Y		Y
	> 0 - 25 µg		Y	Y	Y
	> 25 - 37.5 µg		Y	Y	Y
	> 37.5 - 50 µg	Y		Y	Y
	> 50- 75 µg	Y		Y	Y
	> 75 - 100 µg	Y	Y		Y
	> 100 - 125 µg	Y	Y		Y
	> 125 µg	Y	Y	Y	Y
	Active Comparator[1]	Y	Y	Y	
		Randomized Dose			
Phase 2 Extension	**Actual Dose Received**	6.25 µg	12.5 µg	25 µg	Active Comparator[1]
	6.25 µg		Y	Y	Y
	12.5 µg	Y		Y	Y

	25 µg	Y	Y		Y
	> 0 – 6.25 µg		Y	Y	Y
	> 6.25 – 9.375 µg		Y	Y	Y
	> 9.375 – 12.5 µg	Y		Y	Y
	> 12.5 – 18.75 µg	Y		Y	Y
	> 18.75 - 25 µg	Y	Y		Y
	> 25 – 37.5 µg	Y	Y		Y
	> 37.5 µg	Y	Y	Y	Y
	Active Comparator[1]	Y	Y	Y	

Note: Y = Excluded from PP Set.
[1] Subjects who are randomized to receive active comparator should receive at least 40 µg (≥ 40 µg) of the active comparator and 0 µg of mRNA-1010 to be included in the PP Set. Subjects in the active comparator arm that received < 40 µg or any amount of mRNA-1010 will be excluded from the PP Set.

5.4 Safety Set

The Safety Set consists of all randomly assigned participants who receive the IP. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the vaccination they actually received according to the following rules:

For Phase 1/2:

- mRNA-1010 50 µg group: If the received dose of mRNA-1010 is > 0 µg and ≤ 75 µg
- mRNA-1010 100 µg group: If the received dose of mRNA-1010 is > 75 µg and ≤ 150 µg
- mRNA-1010 200 µg group: If the received dose of mRNA-1010 is > 150 µg
- Placebo group: If the received dose of mRNA-1010 is 0 µg

For Phase 2 NH:

- mRNA-1010 25 µg group: If the received dose of mRNA-1010 is > 0 µg and ≤ 37.5 µg
- mRNA-1010 50 µg group: If the received dose of mRNA-1010 is > 37.5 µg and ≤ 75 µg
- mRNA-1010 100 µg group: If the received dose of mRNA-1010 is > 75 µg

- Active comparator group: If the received dose of active comparator is ≥ 40 µg and mRNA-1010 is 0 µg .

For Phase 2 Extension

- mRNA-1010 6.25 µg group: If the received dose of mRNA-1010 is > 0 µg and ≤ 9.375 µg
- mRNA-1010 12.5 µg group: If the received dose of mRNA-1010 is > 9.375 µg and ≤ 18.75 µg
- mRNA-1010 25 µg group: If the received dose of mRNA-1010 is > 18.75 µg

- Active comparator group: If the received dose of active comparator is ≥ 40 µg and mRNA-1010 is 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, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study injection they actually received.

6 Statistical Analysis

6.1 General Considerations

For Phase 1/2, Phase 2 NH, and Phase 2 Extension, the Schedules of Events (SoE) are provided in Appendix E.

General considerations for analyses will be applied to Phase 1/2, Phase 2 NH, and Phase 2 Extension, unless otherwise specified. All analyses will be conducted using SAS Version 9.4 or higher. Statistical outputs (tables, figures, listings, and datasets) will refer study participants as subjects and will use injection of IP and injection interchangeably.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

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. 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.

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

Categorical variables will be summarized using counts and percentages.

Baseline value is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before injection, unless otherwise specified. For immunogenicity tests and nasopharyngeal (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 available) of injection (Day 1).

Study day relative to injection will be calculated as below:

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

For calculation regarding antibody levels/titers, antibody values reported as below lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

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

- 7 days following vaccination: this period includes the day of vaccination and 6 subsequent days. This analysis period will be used for solicited local and systemic AR that occur during this time.
- Up to 28 days following 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 as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

- Overall period: this analysis period starts on Day 1 and continues through the earliest of the following: study completion, discontinuation from the study, or death.

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

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

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

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments (Phase 1/2 only), if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., < 0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the ULOQ (e.g., > 3000), the numeric values will be imputed by ULOQ in the summary.
- Other incomplete/missing data will not be imputed, unless otherwise specified.

6.1.1 Phase 1/2

Age groups:

The following age groups will be used for summary purposes:

- Overall
- Age: ≥ 18 to < 50 years
- Age ≥ 50 years

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1010 50 μg
- mRNA-1010 100 μg
- mRNA-1010 200 μg
- Placebo

For Phase 1/2, all analyses and data summaries/displays will be provided by vaccination group (and then by age group) using appropriate analysis population, unless otherwise specified. Summaries may also contain a display for all mRNA-1010 vaccination groups (Total mRNA-1010 group) or all vaccination groups, including placebo (Overall group).

6.1.2 Phase 2 Northern Hemisphere

Age groups:

The following age groups will be used for summary purposes:

- Overall
- Age: ≥ 18 to < 50 years
- Age ≥ 50 to < 65 years
- Age ≥ 65 years

Vaccination status:

The following previous flu vaccination status may be used for summary purposes:

- Received season flu vaccine in the previous season
- Not received season flu vaccine in the previous season

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1010 25 µg
- mRNA-1010 50 µg
- mRNA-1010 100 µg
- Active comparator

For Phase 2 NH, all analyses and data summaries/displays will be provided by vaccination group (and then by age group) using appropriate analysis population, unless otherwise specified. Summaries may also contain a display for all mRNA-1010 vaccination groups (Total mRNA-1010 group) or all vaccination groups, including active comparator (Overall group). Additional summaries/displays based on vaccination status will be provided for immunogenicity analyses only.

6.1.3 Phase 2 Extension

Age groups:

The following age groups will be used for summary purposes:

- Overall
- Age: ≥ 18 to < 50 years
- Age ≥ 50 years

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- mRNA-1010 6.25 µg
- mRNA-1010 12.5 µg
- mRNA-1010 25 µg
- Active comparator

For Phase 2 Extension, all analyses and data summaries/displays will be provided by vaccination group (and then by age group) using appropriate analysis population, unless otherwise specified. Summaries may also contain a display for all mRNA-1010 vaccination groups (Total mRNA-1010 group) or all vaccination groups, including active comparator (Overall group).

6.2 Background Characteristics

The following description of background characteristics analyses will be applied to Phase 1/2, Phase 2 NH, and Phase 2 Extension, unless otherwise specified.

6.2.1 Participant Disposition

The number and percentage of participants in the following categories will be summarized by vaccination group and then by age group) as defined in Section 6.1 based on Randomization Set:

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

The percentage will be based on participants in that vaccination group within the Randomization Set (as randomized).

A summary of reasons for participants who are in the Randomization Set but excluded from PP Set will also be provided.

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 for each 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 (and then by age group) based on the Randomization Set:

- Randomized by site
- Received injection

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

The denominator for all percentages will be the number of participants in the vaccination groups within the Randomized Set.

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. A separate listing will be provided for screen failure participants with reasons for screen failure.

For all study parts, a participant who completed the final visit on Day 181 (Month 6), defined as 6 months after the study vaccination on Day 1, is considered to have completed the study.

6.2.2 Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of participants will be provided for categorical variables such as sex, race, and ethnicity. The summaries will be presented by vaccination group (and then by age group) as defined in Section 6.1 based on the FAS, PP Set, and Safety Set. If the Safety Set differs from the Randomization Set (e.g., participants randomized but not received any study vaccination or participants received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomization Set.

For screened failure participants, age (years), as well as sex, race, and ethnicity will be presented in a listing.

In addition, participants who are in the Randomization Set but with any inclusion and exclusion criteria deviation will also 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).

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. SOCs will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency of Total mRNA-1010 group/Overall group and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4 Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization drug dictionary (WHODrug Global). The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 5.

The number and percentage of participants using concomitant medications and non-study vaccination 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 groups (as defined in Section 6.1) as follows:

- Any concomitant medications and non-study vaccination within 7 days post-injection
- Any concomitant medications and non-study vaccination within 28 days post-injection
- Seasonal influenza vaccine within 28 days post-injection
- Antipyretic or analgesic medication within 28 days post-injection

A summary table of concomitant medications and non-study vaccination that continued or newly received on the date of injection through 28 days post-injection will be provided by PT in descending frequency in the Total mRNA-1010 group.

Medications taken to prevent or treat pain or fever will be collected in the electronic diary (eDiary), and summaries will be provided based on the Solicited Safety Set by vaccination group (and then by age group) as defined in Section 6.1, including within 7 days after injection, beyond 7 days after injection, and any time after injection.

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

Concomitant procedures will be presented in a listing.

6.2.5 Study Exposure

Study IP administration data as well as subjects with dosing error will be presented in a listing.

Study duration will be summarized since randomization and since the injection.

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 that 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 the participants with each major protocol deviation type will be provided by vaccination group (and then by age group) as defined in Section 6.1 based on the Randomization Set.

Major protocol deviations will be presented in a listing.

6.2.7 COVID-19 Impact

A listing will be provided for the impact of coronavirus disease 2019 (COVID-19) on the execution of the study.

6.3 Safety Analysis

The following description of safety analyses will be applied to Phase 1/2, Phase 2 NH, and Phase 2 Extension, unless otherwise specified.
Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs (including any clinical safety laboratory abnormalities for Phase 1/2), treatment-related AEs, severe AEs, SAEs, AESIs, MAAEs, AEs leading to withdrawal from study vaccine and/or study participation, vital signs measurement, and physical examination findings. Solicited ARs and unsolicited AEs will be coded by SOC and PT according to MedDRA. AESIs are defined and described in detail in the protocol. The Toxicity Grading Scale for Healthy Adult and Adolescent

Volunteers Enrolled in Preventative Vaccine Clinical Trials (Department of Health and Human Services [DHHS] 2007) is used in this study for solicited ARs as presented in the protocol.

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 (and then by age group) unless otherwise specified.

6.3.1 Adverse Events

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

AEs will also be evaluated by the investigator for the coexistence of MAAE and/or AESI. MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner. 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. All AEs will be coded by SOC and PT using MedDRA.

Unsolicited AEs within 28 days after vaccination will be summarized by vaccination group. SAE, AESI, MAAE, and AE leading to discontinuation from the study up to 28 days after vaccination and overall period will be summarized by vaccination group. See Section 6.1 for definitions of analysis groups and analysis period.

All summary tables (except for the overall summary of AEs) for unsolicited TEAEs will be presented by SOC and/or PT with counts of participants included. SOCs will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency of Total mRNA-1010 group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity in the summaries by severity, if participants reported multiple events under the same SOC and/or PT.

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

6.3.1.1 Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of participants who experience the following will be presented:

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

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

In addition, separate listings containing individual participant AE data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from participation in the study, SAEs, AESI, and medically attended TEAEs will be provided separately.

6.3.1.2 TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All unsolicited serious TEAEs
- All unsolicited serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited severe TEAEs
- All unsolicited severe TEAEs that are treatment-related
- All unsolicited treatment-emergent AESI

- All unsolicited medically attended TEAEs
- All unsolicited medically attended TEAEs that are treatment-related

6.3.1.2 TEAEs by Preferred Term

Summary tables of all unsolicited TEAEs within 28 days after vaccination will be provided. PTs will be sorted in a descending order according to the frequency in Total mRNA-1010 group.

6.3.1.3 TEAEs by System Organ Class, Preferred Term, and Severity/Toxicity

The following summary tables of TEAEs within 28 days after vaccination will be provided by SOC, PT, and maximum severity (mild, moderate, severe) or toxicity (Grade 1 through Grade 5) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.3.2 Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the IP caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the participant in the eDiary. Any new safety information reported during safety telephone calls or at site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. Any AR reported in this manner must be entered on the Reactogenicity eCRF and will be included in the evaluation of solicited ARs in addition to the eDiary data.

The occurrence and intensity of selected signs and symptoms are actively solicited from participants during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs). If a solicited local or systemic AR continues beyond 7 days post injection, the participant will be prompted daily to capture solicited local or systemic AR in the eDiary until no longer reported, not to exceed 28 days after vaccination.

The following local ARs will be solicited: 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: fever (an oral temperature greater than or equal to 38.0°C/100.4°F), headache, fatigue, myalgia (muscle aches all over the body), arthralgia (joint aches in several joints), nausea/vomiting, and chills.

The solicited ARs will be graded based on the grading scales presented in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). The investigator will assess Grade 4 (with exception of fever) solicited ARs recorded in eDiary or Reactogenicity CRF.

Analyses of solicited ARs will be provided by vaccination group (and then by age 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. All solicited ARs will be considered causally related to injection.

The number and percentage of participants who reported each individual solicited local AR (has a severity grade of Grade 1 or greater) and solicited systemic AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after injection or persisting beyond 7 days after injection will be tabulated by vaccination group and toxicity grade. The number and percentage of participants who reported each individual solicited AR will also be summarized by vaccination group, toxicity grade, and day of reporting based on the eDiary and Reactogenicity CRF. Analyses will be displayed for each age group.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of participants who reported or any solicited AR, any solicited local AR, or any solicited systemic AR.

The onset of individual solicited AR is defined as the time point after injection at which the respective solicited AR first occurred. The number and percentage of participants with onset of individual solicited AR within 7 days will be summarized by vaccination group and onset day relative to injection day (Day 1). Analyses will be displayed for each age group.

The number of days reporting each solicited AR will be summarized descriptively and categorically for the following time windows (1-2 days, 3-4 days, 5-6 days, and ≥7 days) by vaccination group (and then by age group). The number of days will be calculated as

the day(s) the solicited AR is reported within 7 days of injection including the day of injection, no matter if it is intermittent or continued. If the solicited AR continues beyond 7 days, the days a solicited AR is reported after 7 days will be included (e.g., an event that lasted 5 days in the first 7 days post injection and 3 days beyond 7 days post injection, the duration will be reported as 8 (5 + 3) days). In addition, the duration for each solicited AR that started within 7 days of injection will be summarized descriptively. The duration of the solicited AR will be calculated as the last day – the first day + 1.

Solicited ARs collected in the eDiary and those collected in the reactogenicity eCRF will be provided in a listing, and the maximum toxicity grade from eDiary and reactogenicity eCRF will be presented. All solicited ARs that continue beyond 7 days post injection will be presented in separate data listings.

6.3.3 Clinical Laboratory Evaluations

Safety laboratory testing will include hematology and serum chemistry (Phase 1/2 only).

All laboratory test results will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the toxicity grading criteria (Grade 3 or higher) in Appendix F in any safety laboratory (hematology and serum chemistry) will be listed separately.

For continuous hematology and serum chemistry parameters, the observed values and changes from baseline will be summarized at each visit by vaccination group as defined in Section 6.1. Hematology and chemistry toxicity grades will be summarized using a shift table from baseline to Day 8 by vaccination group.

A pregnancy test will be performed on all female participants of childbearing potential at the Screening Visit and before vaccine administration on Day 1 via point-of-care urine, and as needed at unscheduled visits (urine or blood pregnancy test based on the investigator's discretion). A follicle stimulating hormone (FSH) test may be performed at the Screening Visit (Day 0), as necessary and at the discretion of the investigator, to confirm postmenopausal status.

6.3.4 Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures (BP), heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values that are outside the reference ranges will be flagged in the data listing. The abnormalities

meeting the toxicity grading criteria (Grade 3 or higher) in Appendix G in any vital sign measurement will be listed separately.

Observed values and changes from pre-injection to post-injection at Day 1 for all vital sign measurements will be summarized by vaccination group as defined in Section 6.1. Shift from baseline in the toxicity grades to post-injection result at Day 1 will also be summarized by vaccination group.

6.4 Immunogenicity Analysis

The following description of immunogenicity analyses will be applied to Phase 1/2, Phase 2 NH, and Phase 2 Extension. Phase 2 NH and Phase 2 Extension will share the same analyses, unless otherwise specified.

The analyses of immunogenicity will be based on the PP Set and will be performed by vaccination group as defined in Section 6.1. 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% for each age group, supportive analyses of immunogenicity may be conducted using the FAS. The supportive analysis is required if the condition is met.

The GMT and geometric mean (GM) level will be calculated using the following formula:

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

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 time points 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.

6.4.1 Immunogenicity Assessments

For Phase 1/2, there will be two types of humoral immunogenicity assessments:

- Anti-HA antibodies against vaccine-matched strains as measured by HAI or MN assays for primary and secondary analysis.
- Anti-HA antibodies against vaccine-mismatched or drifted strains as measured by HAI or MN assays for exploratory analysis.

For Phase 2 NH and Phase 2 Extension, there will be two types of humoral immunogenicity assessments:

- Anti-HA antibodies against vaccine-matched strains as measured by HAI assay for primary and secondary analysis.
- Anti-HA antibodies against vaccine-matched or vaccine-mismatched strains as measured by HAI, MN assays (or alternative methods) for exploratory analysis.

6.4.2 Phase 1/2

6.4.2.1 Primary Analysis of Immunogenicity Endpoints

For each vaccination group, the following evaluations will be performed at Day 29.

- GMT of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at Day 29. The following descriptive statistics will also be provided at Day 29: the number of participants (n), median, min, and max.
- GMFR of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at Day 29 over pre-injection baseline at Day 1. The following descriptive statistics will also be provided at Day 29: the number of participants (n), median, min, and max.
- Proportion of participants with seroconversion (defined as a Day 29 titer $\geq$ 1:40 if baseline is < 1:10 or a 4-fold or greater rise if baseline is $\geq$ 1:10 in anti-HA antibodies measured by HAI assay) will be tabulated with 2-sided 95% Clopper Pearson CIs.

6.4.2.2 Secondary Analysis of Immunogenicity Endpoints

For each vaccination group, the following evaluations will be performed at all evaluable humoral immunogenicity time points (unless otherwise specified).

- GMT of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each time point. GM level and corresponding 95% CI will be plotted at each time point. The following descriptive statistics will also be provided at each time point: the number of participants (n), median, min, and max.
- GMFR of vaccine-matched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection baseline at Day 1. GMFR and corresponding 95% CI will be plotted at each time point. The following descriptive statistics will also be provided at each time point: the number of participants (n), median, min, and max.
- Proportion of participants with seroconversion at each visit following Day 29. Summaries will be tabulated with 2-sided 95% Clopper Pearson CIs.

6.4.2.3 Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- GMT of vaccine-mismatched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each time point using methods described in Section 6.4.
- GMFR of vaccine-mismatched strain-specific anti-HA antibodies with corresponding 95% CI will be provided at each post-baseline time point over pre-injection baseline at Day 1 using methods described in Section 6.4.
- Descriptive summaries of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods as well as targeted repertoire analysis of B cells and T cells after vaccination.
- Descriptive summaries of immunologic endpoints to further characterize antibody responses.
- The number of participants with confirmed influenza infection by RT-PCR test.
- Listing of immune response of participants infected by influenza

6.4.3 Phase 2 Northern Hemisphere and Phase 2 Extension

6.4.3.1 Primary Analysis of Immunogenicity Endpoints

Immune responses, as measured by GMT and seroconversion rate in the mRNA-1010 groups based on Day 29 anti-HA antibodies titers as measured by HAI assay, will be compared with that of participants receiving active comparator for all 4 strains.

For Phase 2 NH and Phase 2 Extension, the following evaluations will be performed at Day 29:

- An analysis of covariance (ANCOVA) model will be carried out with anti-HA antibodies titers at Day 29 as a dependent variable and vaccination group as an independent variable. This model will be adjusted for the baseline antibody titer. For Phase 2 NH, age group and vaccination status will be included as covariates. For Phase 2 Extension, age group will be included as a covariate. The GMT of vaccine-matched influenza A and B strains at Day 29 will be estimated by the geometric least square mean (GLSM) from the model (model-based GMT). The ratio of GMT (GMTr) will be estimated by the ratio of GLSM from the model. The corresponding 2 sided 95% CI will be provided to assess the difference in immune response between the mRNA 1010 compared with the active comparator at Day 29. The model will be conducted based on the log transformed values then back transformed to the original scale for presentation.
- The number and proportion of participants with seroconversion (defined in Section 3.2.1) at Day 29 will be provided with 2-sided 95% CI using Clopper Pearson method for each vaccination group. To compare the seroconversion rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in the seroconversion rates.

The analyses above may also be performed by vaccination status.

6.4.3.2 Secondary Analysis of Immunogenicity Endpoints

- GMFR of vaccine-matched influenza A and B strains (as measured by HAI) at Day 29 with corresponding 95% CI using Clopper Pearson method for each vaccination group will be provided
- The number and proportion of participants with an anti-HA antibodies titer $\geq$ 1:40 at Day 29 will be provided with 2-sided 95% CI using Clopper Pearson method for each vaccination group. The Miettinen-Nurminen's method will be used to

calculate the 95% CI of the difference in the rates of anti-HA antibodies titer ≥ 1:40 at Day 29 between the vaccination groups.

6.4.3.3 Exploratory Analysis of Immunogenicity Endpoints

The below exploratory analyses of immunogenicity may be performed:

- The number and percentage of participants with RT-PCR-confirmed ILI, protocol-defined ILI, or CDC-defined ILI that begin at least 14 days after vaccination through Day 181/EoS caused by any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine

- The statistics analyses for the primary immunogenicity endpoints may also be performed for the exploratory objectives (as indicated in Section 3.2.3) to evaluate the humoral immunogenicity of mRNA-1010 vaccine to that of an active comparator against vaccine-matched or vaccine-mismatched influenza A and B strains as measured by MN assay (or alternative methods) at the applicable time points.

- Descriptive statistics may be performed for the frequency, specificities, or other exploratory immune endpoints to be determined.

6.5 Analysis of Influenza Infection

For Phase 1/2, Phase 2 NH, and Phase 2 Extension, influenza infection during the study is an exploratory endpoint, and the analyses of influenza infection by RT-PCR test may be performed using the FAS. Additionally, ILIs will be further identified in Phase 2 NH and Phase 2 Extension:

1. 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 defined below:

    - Sore throat
    - Cough/rhinorrhea/nasal congestion (≥ 1 of the 3 symptoms count as 1 respiratory symptom)
    - Sputum production
    - Wheezing

- Difficulty breathing

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

3. An RT-PCR confirmed ILI is defined as a positive influenza result by RT-PCR done at any setting during the study period.

Summaries below will be applied to Phase 1/2, Phase 2 NH, and Phase 2 Extension, unless otherwise specified.

- RT-PCR test results at baseline will be summarized by test and vaccination group. Participants with positive influenza results at baseline will be presented in a listing.
- The number and percentage of participants with at least one positive influenza result at post-baseline will be provided by vaccination group. Participants with at least one positive influenza result at post-baseline will be presented in a listing.
- For Phase 2 NH and Phase 2 Extension, the number of participants with RT-PCR confirmed ILI, protocol-defined ILI, or CDC-defined ILI that begin at least 14 days after vaccination through Day 181/EoS will be summarized by vaccination group. Participants with RT-PCR confirmed ILI, protocol-defined ILI, or CDC-defined ILI will be presented in a listing.

6.6 Interim Analysis

A Day 29 IA is planned in this study for the Phase 1/2, Phase 2 NH, and Phase 2 Extension. The IA for Phase 1/2 will be performed after all participants have completed the Day 29 visit. This interim analysis will be focused on providing insight on the primary and secondary study objectives using the available data. The IA for Phase 2 NH and Phase 2 Extension will be on safety (reactogenicity and immunogenicity as applicable) and will be performed after participants have completed the Day 29 visit. An interim study report may be generated, in which case a formal database lock will be performed to support the interim study report.

All relevant data for the Phase 1/2, Phase 2 NH, and Phase 2 Extension IA will be cleaned (i.e., data that are as clean as possible).

A limited number of Sponsor and CRO personnel will be unblinded to perform the IAs. Please refer to the DBP for more details on the blinding of IA.

An independent, unblinded statistics team will carry out the IA. The unblinded statistics team will not be involved in either study design or the regular study conduct. The study site staffs, investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis.

The final analysis of all applicable endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final clinical study report (CSR), including individual listings.

6.7 Data Safety Monitoring Board

An independent DSMB, composed of independent members with relevant therapeutic and/or biostatistical expertise, will conduct unblinded reviews of safety data on an ad hoc basis if any pause rule is met or as requested by the safety oversight and/or the internal safety team. The DSMB will also review unblinded IA results provided by the independent unblinded statistician. Refer to the DSMB charter for more details.

7 Changes from Planned Analyses in Protocol

Not applicable.

8 References

Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007

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

9 List of Appendices

9.1 Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

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

9.2 Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

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

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e., nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 3 (Phase 1/2) and Table 4 (Phase 2 NH and Phase 2 Extension) 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 3 Phase 1/2 Visit Windows

Visit	Target Study Day	Visit Window in Study Day
Labs		
Day 8	8	[6, 9]
Immunogenicity		
Day 1	1 (Date of Injection)	1, Pre-vaccination
Day 8	8	[2, 18]

Day 29	29	[19, 105]
Day 181	181	≥ 106

Table 4 Phase 2 NH and Phase 2 Extension Visit Windows

Visit	Target Study Day	Visit Window in Study Day
Immunogenicity		
Day 1	1 (Date of Injection)	1, Pre-vaccination
Day 29	29	[2, 60]
Day 91	91	[61, 136]
Day 181	181	≥ 137

9.3 Appendix C Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/end dates 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 after the date of injection or is missing AND the start month and year of the medication coincide with the start month and year of the injection. In this case, use the date of injection.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of injection or is missing AND the start year of the medication coincide with the start year of the injection. In this case, use the date of injection
   - If Day, Month, and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication end 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.

In summary, the prior, concomitant, or post categorization of a medication is described in Table 5 below.

Table 5 Prior, Concomitant, and Post Categorization of Medications and Non-Study Vaccinations

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

A = Post; C = Concomitant; P = Prior
[1] includes medications with completely missing end date
[2] includes medications with completely missing start date

9.4 Appendix A Imputation Rules for Missing AE Dates

Imputation rules for missing or partial AE start dates and end 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 after the date of the injection or is missing AND the start month and year of the AE coincide with the start month and year of the injection. In this case, use the date and time of the injection, even if time is collected.
- If Day and Month are both missing, use the first day of the year, unless:
  - The AE end date is after the date of the injection or is missing AND the start year of the AE coincides with the start year of the injection. In this case, use the date of the 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 injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed.

9.5 Appendix E Schedule of Events

9.5.1 Phase 1/2 - Schedule of Events

Visit Number	SCRN[1]	1	2	3	4	5, 6, and 7	8	Unscheduled
Type of Visit	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M1**	**M2**	**M3-M5**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D8**	**D29**	**D57**	**D91, D121, D151**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**–2 or +1**	**±2**	**±5**	**±5**	**±14**	**NA**
ICF, demographics, concomitant medications, medical history	X	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-
Blood collection for safety laboratory samples[2]	X	-	X	-	-	-	-	-
Physical examination[3]	X	-	-	-	-	-	-	-
Vital signs[4]	X	X	-	-	-	-	-	-
Pregnancy testing[5]	X	X	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-
Study vaccination (including 60-minute postdosing observation period)	-	X[6]	-	-	-	-	-	-
Blood collection for humoral immunogenicity[7]	-	X	X	X	-	-	X	-
Blood collection for cellular immunogenicity[7]	-	X	X	X	-	-	-	-
NP swab for virus detection[8]	-	X	-	-	-	-	-	X
eDiary activation for recording solicited ARs (7 days)[9]	-	X	-	-	-	-	-	-
Review of eDiary	-	-	X	-	-	-	-	-
Follow-up safety calls[10]	-	-	-	-	-	X	-	-
Recording of unsolicited AEs	-	X	X	X	-	-	-	-

Visit Number	SCRN[1]	1	2	3	4	5, 6, and 7	8	Unscheduled
Type of Visit	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M1**	**M2**	**M3-M5**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D8**	**D29**	**D57**	**D91, D121, D151**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**–2 or +1**	**±2**	**±5**	**±5**	**±14**	**NA**
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[11]	-	X	X	X	X	X	X	X
Recording of SAEs, AESIs, and concomitant medications relevant to or for the treatment of the SAE and/or AESI[11]	-	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[11]	X	X	X	X	X	X	X	X
Phase 1/2 completion	-	-	-	-	-	-	X	-

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; C = clinic visit (ie, study site visit); COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report form; eDiary = electronic diary; EoS = end of study; FSH = follicle-stimulating hormone; ICF = informed consent form; ILI = influenza-like illness; IM = intramuscular; IP = investigational product; M = month; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (phone or contact by electronic means); SCRN = screening; WBC = white blood cell.

[1] The Screening Visit and Day 1 Visit cannot be completed on the same day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.

[2] Safety laboratory tests: WBC count, hemoglobin, platelets, ALT, AST, total bilirubin, alkaline phosphatase, and creatinine.

[3] Physical examination: A full physical examination, including height and weight, will be performed at screening. Symptom-directed physical examinations may be performed at other time points at the discretion of the Investigator. Any clinically significant finding identified during a study visit should be reported as an MAAE.

[4] Vital sign measurement: systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Participants will be seated for at least 5 minutes before all measurements are taken. Vital signs will be collected at the Screening Visit and on the day of vaccination, once before and at least 1 hour after the vaccination. Vital signs will be collected at other study site visits only in conjunction with a symptom-directed physical examination. The preferred route of temperature assessment is oral. Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented in the AE section of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable or until the Investigator determines that follow-up is no longer medically necessary.

[5] A point-of-care urine pregnancy test will be performed at the Screening Visit and before the vaccine dose 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 FSH level may be measured at the Screening Visit as necessary and at the discretion of the Investigator to confirm postmenopausal status.

[6] A 50-µg dose of mRNA-1010 will be administered for Vaccination Group 1, a 100-µg dose of mRNA-1010 will be administered for Vaccination Group 2, a 200-µg dose of mRNA-1010 will be administered for Vaccination Group 3, and placebo will be administered for Vaccination Group 4. All participants will receive a single 0.5-mL IM injection of the IP.

[7] Samples for humoral and cellular immunogenicity (and safety laboratory samples) must be collected prior to receipt of vaccination on Day 1. Cellular immunogenicity samples will be collected from approximately 40 participants per vaccination group and assessed in a subset.

[8] An NP swab specimen will be collected on Day 1 prior to vaccination to assess for asymptomatic infection with respiratory pathogens, including influenza virus and SARS-CoV-2. An NP swab will also be collected at any time during the study through study completion if any signs or symptoms or an MAAE suggesting COVID-19 or ILI occur, to confirm the diagnosis by RT-PCR. For signs or symptoms during the study, a participant will be instructed to contact the study site to have an NP swab collected for testing for respiratory pathogens at an unscheduled visit. The NP swabs may be collected as part of a home visit in lieu of a study site visit.

[9] The eDiary entries will be recorded by the participant at approximately 1 hour after vaccination while at the study site under the supervision of the study site staff. Participants will continue to record data in the eDiary for solicited AEs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of injection, and for 6 days following injection. Any solicited AR that continues beyond Day 7 will be reported until it is no longer reported but only until 28 days after vaccination. Adverse reactions recorded in diaries beyond Day 7 should be reviewed either during the next scheduled telephone call or at the next study site visit.

[10] Trained study personnel will call all participants to collect information relating to any AEs, MAAEs, AEs leading to withdrawal from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.

[11] All concomitant medications and nonstudy vaccinations will be recorded through 28 days after vaccination; all concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 181/EoS.

9.5.2 Phase 2 NH - Schedule of Events

Visit Number	**SCRN[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**Unscheduled**
Type of Visit/Contact	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M0**	**M1**	**M3**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D8**	**D15**	**D29**	**D91**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**±3**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
ICF, demographics, concomitant medications, medical history[2]	X	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-
Physical examination[3]	X	-	-	-	-	-	-	-
Vital signs[4]	X	X	-	-	-	-	-	-
Pregnancy testing[5]	X	X	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-
Study vaccination (including 60-minute postdosing observation period)	-	X[6]	-	-	-	-	-	-
Blood collection for humoral immunogenicity (and exploratory assessments)[7]	-	X	-	-	X	X	X	-
Optional blood collection for pharmacogenomics	-	X	-	-	-	-	-	-
NP swab for virus detection[8]	-	-	-	-	-	-	-	X
eDiary activation for recording solicited ARs (7 days)[9]	-	X	-	-	-	-	-	-
Review of eDiary for solicited ARs	-	-	X	-	-	-	-	-
eDiary activation for active and passive surveillance[10]	-	X	-	-	-	-	-	-
eDiary active surveillance collection of symptoms of ILI[11]	-	3 to 4 times weekly				Twice weekly		-

Visit Number	SCRN[1]	1	2	3	4	5	6	Unscheduled
Type of Visit/Contact	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M0**	**M1**	**M3**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D8**	**D15**	**D29**	**D91**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**±3**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
eDiary passive surveillance collection of symptoms of ILI[11]	-	X						-
Review of eDiary[12]	-	Review participant-recorded ILI starting on Day 1 through Day 181/EoS						
Follow-up safety call	-	-	X	X	-	-	-	-
Recording of unsolicited AEs	-	X	X	X	X	-	-	-
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[13]	-	X	X	X	X	X	X	X
Recording of SAEs, AESIs, and concomitant medications relevant to or for the treatment of the SAE and/or AESI[13]	-	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[14]	X	X	X	X	X	X	X	X
Study completion	-	-	-	-	-	-	X[15]	-

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit (ie, study site visit); COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report; form; eDiary = electronic diary; EoS = end of study; FSH = follicle-stimulating hormone; ICF = informed consent form; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal swab; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (phone or contact by electronic means); SCRN = screening.

[1] The Screening Visit and Day 1 Visit may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.

[2] Verbal confirmation of medical history is acceptable.

[3] Physical examination: A full physical examination, including height and weight, will be performed at screening; symptom-directed physical examinations will be performed at all other clinic visits (ie, study site visits). Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.

[4] Vital sign measurement: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. Participants will be seated for at least 5 minutes before all measurements are taken. Vital signs will be collected on the day of vaccination, once before vaccination and approximately 1 hour after vaccination. Vital signs may be collected at other study site visits in conjunction with a symptom-directed physical examination. If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented in the AE section of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable or until the Investigator determines that follow-up is no longer medically necessary.

[5] A point-of-care urine pregnancy test will be performed at the Screening Visit (and before the vaccine dose on Day 1 if Day 1 is not on the same day as the Screening Visit). At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The FSH level may be measured at the Screening Visit as necessary and at the discretion of the Investigator, to confirm postmenopausal status.

[6] See Table 1 for dose levels and vaccination groups. All participants will be randomized to receive a single 0.5-mL IM injection.

[7] Samples for humoral immunogenicity (and exploratory assessments) must be collected prior to receipt of vaccination on Day 1. A subset of samples collected will be assessed for humoral immunogenicity (and exploratory assessments).

[8] An NP swab specimen for pathogens, including influenza virus and SARS-CoV-2 will be collected any time from Day 1 through Day 181/EoS if participants have protocol-defined ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection at the Investigator's discretion. If participants experience these symptoms/signs, they will be instructed to contact the study site to have an NP swab collected for testing. The NP swabs may be collected as part of a home visit in lieu of a study site visit.

[9] The eDiary entries will be recorded by all participants at approximately 1 hour after vaccination while at the study site under the supervision of the study site staff. Participants will continue to record data in the eDiary for solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of vaccination, and the 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until it is no longer reported but only until 28 days after vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed either during the next scheduled call or study site visit, or during an unscheduled visit.

[10] The eDiary will be activated for collection of ILI symptoms.

[11] Passive Surveillance: Participants will be instructed to report symptoms of ILI any time from Day 1 through Day 181/EoS; Active Surveillance: Participants will be instructed to report whether ILI symptoms have been experienced, 3 to 4 times weekly from Day 1 through Day 29 and twice weekly from Day 30 through Day 181/EoS, via eDiary or telephone calls. If symptoms occur, participants will be directed to return to the study site as soon as possible, but no later than 72 hours after the onset of symptoms for medical evaluation and an NP swab.

[12] Review of eDiary for recording of symptoms of ILI.

[13] Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.

[14] All concomitant medications and nonstudy vaccinations will be recorded through 28 days after vaccination; all concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 181/EoS.

[13] Participants who develop ILI will be followed through 30 days from the onset of ILI even if Day 30 is beyond Day 181/EoS.

9.5.3 Phase 2 Extension - Schedule of Events

Visit Number	SCRN[1]	1	2	3	4	5	6	7	Unscheduled
Type of Visit/Contact	**C**	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M0**	**M0**	**M1**	**M3**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D4**	**D8**	**D15**	**D29**	**D91**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**-2**	**±3**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
ICF, demographics, concomitant medications, medical history[2]	X	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-
Physical examination[3]	X	-	-	-	-	-	-	-	-
Vital signs[4]	X	X	-	-	-	-	-	-	-
Pregnancy testing[5]	X	X	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-
Study vaccination (including 60-minute postdosing observation period)	-	X[6]	-	-	-	-	-	-	-
Blood collection for humoral immunogenicity (and exploratory assessments)[7]	-	X	-	-	-	X	X	X	-
Optional blood collection for pharmacogenomics	-	X	-	-	-	-	-	-	-
Optional blood collection for potential biomarker analysis[8]			X						
NP swab for virus detection[9]	-	-	-	-	-	-	-	-	X
eDiary activation for recording solicited ARs (7 days)[10]	-	X	-	-	-	-	-	-	-
Review of eDiary for solicited ARs	-	-	-	X	-	-	-	-	-
Follow-up safety call	-	-	-	X	X	-	-	-	-
Recording of unsolicited AEs	-	X	-	X	X	X	-	-	-

Visit Number	**SCRN[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Unscheduled**
Type of Visit/Contact	**C**	**C**	**C**	**SC**	**SC**	**C**	**C**	**C**	**C**
Month Time Point	**NA**	**M0**	**M0**	**M0**	**M0**	**M1**	**M3**	**M6**	**M0-M6**
Study Visit Day	**-**	**D1 (Baseline)**	**D4**	**D8**	**D15**	**D29**	**D91**	**D181/EoS**	**NA**
Window Allowance (Days)	**-28**	**-**	**-2**	**±3**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[11]	-	X	-	X	X	X	X	X	X
Recording of SAEs, AESIs, and concomitant medications relevant to or for the treatment of the SAE and/or AESI[11]	-	X	-	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[12]	X	X	-	X	X	X	X	X	X
Study completion	-	-	-	-	-	-	-	X[13]	-

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit (ie, study site visit); COVID-19 = coronavirus disease 2019; D = day; eCRF = electronic case report; form; eDiary = electronic diary; EoS = end of study; FSH = follicle-stimulating hormone; ICF = informed consent form; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal swab; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (phone or contact by electronic means); SCRN = screening.

[1] The Screening Visit and Day 1 Visit may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.

[2] Verbal confirmation of medical history is acceptable.

[3] Physical examination: A full physical examination, including height and weight, will be performed at screening; symptom-directed physical examinations will be performed at all other clinic visits (ie, study site visits). Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.

[4] Vital sign measurement: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. Participants will be seated for at least 5 minutes before all measurements are taken. Vital signs will be collected on the day of vaccination, once before vaccination and approximately 1 hour after vaccination. Vital signs may be collected at other study site visits in conjunction with a symptom-directed physical examination. If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater, the abnormal value and grade will be documented in the AE section of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable or until the Investigator determines that follow-up is no longer medically necessary.

[5] A point-of-care urine pregnancy test will be performed at the Screening Visit (and before the vaccine dose on Day 1 if Day 1 is not on the same day as the Screening Visit). At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The FSH level may be measured at the Screening Visit as necessary and at the discretion of the Investigator, to confirm postmenopausal status.
[6] See Table 1 for dose levels and vaccination groups. All participants will be randomized to receive a single 0.5-mL IM injection.
[7] Samples for humoral immunogenicity (and exploratory assessments) must be collected prior to receipt of vaccination on Day 1. A subset of samples collected will be assessed for humoral immunogenicity (and exploratory assessments).
[8] Biomarker plasma and biomarker serum samples will be stored for potential future biomarker assessment
[9] An NP swab specimen for pathogens, including influenza virus and SARS-CoV-2 will be collected any time from Day 1 through Day 181/EoS if participants have protocol-defined ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection at the Investigator's discretion. If participants experience these symptoms/signs, they will be instructed to contact the study site to have an NP swab collected for testing. The NP swabs may be collected as part of a home visit in lieu of a study site visit.
[10] The eDiary entries will be recorded by all participants at approximately 1 hour after vaccination while at the study site under the supervision of the study site staff. Participants will continue to record data in the eDiary for solicited ARs each day after they leave the study site, preferably in the evening and at the same time each day, on the day of vaccination, and the 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until it is no longer reported but only until 28 days after vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed either during the next scheduled call or study site visit, or during an unscheduled visit.
[11] The eDiary will be activated for collection of ILI symptoms.
[12] Passive Surveillance: Participants will be instructed to report symptoms of ILI any time from Day 1 through Day 181/EoS; Active Surveillance: Participants will be instructed to report whether ILI symptoms have been experienced, 3 to 4 times weekly from Day 1 through Day 29 and twice weekly from Day 30 through Day 181/EoS, via eDiary or telephone calls. If symptoms occur, participants will be directed to return to the study site as soon as possible, but no later than 72 hours after the onset of symptoms for medical evaluation and an NP swab.
[13] Review of eDiary for recording of symptoms of ILI.
[11] Trained study personnel will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.
[12] All nonstudy vaccinations will be recorded through Day 181/EoS. All concomitant medications will be recorded through 28 days after vaccination; all concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 181/EoS.
[13] Participants who develop ILI will be followed through 30 days from the onset of ILI even if Day 30 is beyond Day 181/EoS.

9.6 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.

9.7 Appendix G 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.