CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older
Protocol Number:	mRNA-1010-P301
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number(s):	IND 27460 EudraCT: Not applicable
Amendment Number	2
Date of Protocol Amendment 2	19 Jul 2022
Date of Protocol Amendment 1	10 Feb 2022
Date of Original Protocol:	05 Nov 2021

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older
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Protocol accepted and approved by:

See eSignature and date signed on last page of the document

Date

PPD

ModernaTX, Inc.

200 Technology Square

Cambridge, MA 02139

Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years dated 19 Jul 2022 and older and the most recent version of the investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without institutional review board (IRB)/independent ethics committee (IEC) approval except to eliminate an immediate risk to participants.

I agree to administer study vaccine only to participants under my personal supervision or the supervision of a subinvestigator. I will not supply study vaccine to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB/IEC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	19 Jul 2022
Amendment 1	10 Feb 2022
Original Protocol	05 Nov 2021

Amendment 2, 19 Jul 2022: Current Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment:

The main rationale for this amendment is to enhance clarity, implement additional protocol administrative changes, and to address feedback received from regulatory agencies.

The summary of changes table provided below describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. The synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol. Minor grammar and formatting corrections were made throughout the document to enhance clarity and readability (which did not affect the conduct of the study).

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Synopsis	• Updated the estimated dates of first participant enrolled and last participant completed.	• To better reflect current projections.
1.2 Schedule of Events (Table 1)	• Removed footnote 24, the specification that participants who develop influenza-like illness (ILI) will be followed up for 30 days even if this is after the end of the study. • Footnote 8, referring to blood draws for genomic, transcriptomic, and immunogenicity analyses was made applicable only to Day 1 visit as it is only applicable to the day of vaccination.	• To remove incorrect information. • To correct an error.
1.2 Schedule of Events (Table 1); 4.1 General Design	• Clarified that approximately the first 1000 participants will have additional humoral immunogenicity blood samples taken, and that immunogenicity analysis will be performed on a subset of these participants.	• To clarify how the participants for the immune response biomarker subset will be selected.
Schedule of Events (Table 1); 4.1 General Design; 8.9.4	• Clarified that participants can report symptoms of ILI from Day 1 to Day 361	• To clarify the participants' and

Section # and Name	Description of Change	Brief Rationale
Use of Electronic Diaries	(Month 12)/EoS via the electronic diary (eDiary) or by contacting the site. • Specified that if symptoms are reported, the Investigator must contact the participant to assess symptoms and collect nasopharyngeal (NP) swabs within 72 hours of symptom onset, preferably prior to initiation of antiviral therapy.	Investigators' responsibilities.
2.2.3 Clinical Studies	• Updated results from study mRNA-1010-P101.	• To provide the most recent interim analysis results.
3 Objectives and Endpoints (Table 2)	• Added adverse events (AEs) leading to discontinuation to coprimary endpoint. • Removed influenza B strain from the secondary endpoint of superiority. • Added proportion of participants reaching seroconversion at Day 29 as measured by HAI assay to secondary endpoint. • Specified that analyses of the secondary endpoint will involve only the first episode of RT–PCR confirmed ILI. • Changed Day 361 (Month 12)/EoS to Day 181 (Month 6)/end of influenza season for the secondary endpoint. • Clarified that only a proportion of participants will be analyzed in the secondary endpoint. • Added further analyses at Day 181 and Day 361 in the exploratory endpoints for vaccine-matched and -mismatched strains. • Added the proportion of participants with seroconversion and with a titer ≥ 1:40 at Day 181 and Day 361 to exploratory endpoints. • Added number of cases of RT-PCR–confirmed protocol-defined ILI cases that begin at least 14 days postvaccination through Day 361/EoS to exploratory endpoints.	• Administrative changes for consistency throughout the protocol. These items were previously part of the statistical section.
3 Objectives and Endpoints	• Updated other exploratory objectives to specify that number and percentage of participants aged ≥ 65 years will be analyzed for protocol-defined ILI.	• Administrative change for consistency with the statistical section.

Section # and Name	Description of Change	Brief Rationale
	• Updated all other exploratory objectives to specify protocol-defined ILI will be considered.	• To clarify how ILI will be defined.
4.1 General Design; 6.2 Randomization and Blinding	• Added that it is anticipated that approximately 300 participants will be ≥ 75 years old.	• To clarify the expectations for enrollment of participants ≥ 75 years old.
4.1 General Design; Table 3; 4.3 Justification for Dose, Control Product, and Choice of Study Population; 5 Study Population; 6.1 Investigational Product and Active Comparator Administered; Table 4	• Amended the name of the comparator from Fluarix to Fluarix Tetra.	• To use the full name of the comparator product.
4.1 General Design (Table 3)	• Added "of mRNA" to the amount of mRNA-1010 and "of protein" to the amount of comparator.	• To be more precise and specify that the study vaccine contains HA mRNA, and the comparator contains HA protein.
4.3 Justification for Dose, Control Product, and Choice of Study Population	• Changed the status of the Phase 2 Extension of study mRNA-1010-P101 from "planned" to "ongoing".	• To reflect the progress of the study.
5.2 Exclusion Criteria	• Added to Exclusion Criterion #4 that participants with stable immune-mediated disease who do not require immunosuppressants are eligible to enroll into the study. • Added to Exclusion Criterion #9 that inhaled, nasal and topical steroids are allowed. • Added to Exclusion Criterion #15 that participants who have received long-acting biological therapies that affect immune responses within 90 days, or plan to receive them, will be excluded.	• To enhance clarity.

Section # and Name	Description of Change	Brief Rationale
6.2 Randomization and Blinding; 9.1 Blinding and Responsibility for Analyses	• "Efficacy analysis" was changed to "6-month analysis."	• To clarify that analyses other than efficacy may be performed at the 6-month time point.
6.5.1 Recording of Concomitant Medications, Concomitant Vaccinations, and Concomitant Procedures	• "Concomitant Procedures" was added to section title. • Specified that all concomitant procedures/surgeries must be recorded in the electronic case report form (eCRF). • Specified that biological therapies that affect immune responses should be recorded as concomitant medications.	• To better reflect the content of the section. • To correct an omission. • To enhance clarity.
6.5.2 Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant From Per-protocol Analyses	• Specified that the use of biological therapies may lead to exclusion from the per protocol analysis.	• To enhance clarity.
8.5 Randomization	• Changed "Exposure page" to "Injection page".	• To correct an error.
8.9 Safety Assessments	• Removed that pregnancy data received after the end of the study may not be collected in the clinical database.	• To remove unnecessary text (pregnancies are not collected in the clinical database).
8.9.2 Assessments for Respiratory Viral Infections	• Clarified reporting requirement of ILI and COVID-19 to: All cases that meet the protocol definition of RT-PCR–confirmed influenza infection and RT-PCR–confirmed symptomatic COVID-19 will be captured as MAAEs • Specified that asymptomatic SARS-CoV-2 infections will not be recorded as MAAEs.	• To clarify that RT-PCR–confirmed protocol-defined influenza infection should be reported as an MAAE. • To clarify that only RT-PCR confirmed symptomatic COVID-19 infection should be reported as an MAAE.
8.9.4 Use of Electronic Diaries	• Specified that participants should report medications taken to prevent or treat pain or fever on the day of injection and for the next 6 days, instead of "or for the next 6 days."	• To clarify requirements for concomitant medication reporting in the eDiary.
8.10 Clinical Assessments	• Removed "and will be assessed as MAAEs unless the definition of SAE is met."	• To correct an error.

Section # and Name	Description of Change	Brief Rationale
8.10 Clinical Assessments	• Added a link to Section 8.11.5 (Influenza-like Illness Case Definitions).	• To enhance clarity.
8.11.3 Solicited Adverse Reactions	• Changed "AE eCRF page" to "Reactogenicity eCRF page."	• To correct an error.
8.11.4 Medically Attended Adverse Events	• Added to the definition of MAAEs that these are events that require unplanned visits to HCPs for assessments and/or treatment not required per study protocol and that the Investigators will review all AEs for occurrences of MAAEs.	• To enhance clarity.
8.11.5 Influenza-like Illness Case Definitions	• Added that through Day 28 any illness assessed for protocol- defined ILI/suspected COVID-19 infection will be captured as an AE on the AE eCRF and that starting on Day 29, only RT-PCR–confirmed influenza infection and RT-PCR–confirmed symptomatic COVID-19 infection will be recoded as an MAAE.	• To clarify that after Day 28 only RT-PCR–confirmed influenza infection and RT-PCR–confirmed symptomatic COVID-19 infection should be reported as MAAEs.
8.11.5 Influenza-like Illness Case Definitions	• Specified that an RT-PCR–confirmed protocol-defined influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local certified laboratory within 7 days of onset of protocol-defined ILI symptoms at any time during the study period. • Added definition for RT-PCR–confirmed CDC defined ILI.	• To enhance clarity.
8.11.6 Adverse Event of Special Interest	• Added "SAE" to the name of the form for reporting SAEs/AESIs.	• To update internal process for AE reporting.
8.11.8 Recording and Follow-up of an AE and/or SAE	• Deleted "Any AEs occurring before receipt of IP will be analyzed separately from TEAEs."	• To update internal process for AE reporting.
8.11.12 Reporting Serious Adverse Events	• Replaced "outlined in the 21 US CFR Parts 312 and 320" with "required per applicable regulations." • Deleted contact information for SAE mailbox, hotline, and fax line and instead added that if eCRF is unavailable, SAEs should be recorded on the SAE/AESI paper form.	• To make the requirement more broadly applicable. • To update internal process for AE reporting.

Section # and Name	Description of Change	Brief Rationale
9.2 Statistical Hypotheses	• Updated statistical hypotheses based on regulatory agencies' comments.	• To incorporate regulatory agencies' comments on superiority of immunogenicity endpoints for mRNA-1010 vs. active comparator.
9.3 Sample Size Determination	• Updated sample size for the PP Immunogenicity Set. • Replaced "2-sided alpha of 0.05" with "2-sided 0.025 level."	• To accommodate for higher percentage of participants excluded from PP immunogenicity analysis and to streamline testing. • To follow the new multiplicity testing procedure.
9.4 Analysis Populations	• Updated the analysis sets for efficacy and immunogenicity analyses.	• To clarify efficacy analysis sets and to update the immunogenicity analyses sets based on sample size change.
9.5.1 Immunogenicity Analyses	• Changed the confidence interval for GMT ratio and seroconversion rate difference between mRNA-1010 vs. active comparator from 95% to 97.5%.	• To follow the new multiplicity testing sequence for pre-specified statistical hypotheses.
9.5.2 Efficacy Analyses	• Changed the primary analysis population for efficacy from Per-Protocol set to mITT set. • Changed the efficacy analysis method from using Cox proportional hazard model to estimate hazard ration to using Exact method estimating the incidence rate for the efficacy endpoint.	• To fit the objective of analyzing efficacy endpoints.
9.5.4 Exploratory Analyses	• Specified that ILI cases will need to be protocol defined and/or CDC defined for analysis by vaccination group. • Added that number and percentage of participants aged ≥ 65 years with first episode of protocol-defined ILI will be presented by baseline frailty status for each vaccination group.	• To specify that cases of ILI need to be either protocol defined or CDC defined. • To correct an omission.

Section # and Name	Description of Change	Brief Rationale
9.6.2 Multiplicity	• Multiple testing sequence was updated based on study hypotheses change.	• To incorporate regulatory agencies' comments on superiority testing of immunogenicity endpoints.
11.1.5 Recruitment Strategy	• Updated title to "Recruitment Strategy" and text added: "Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate. Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site."	• To align with EU-CTR.
11.1.9 Data Protection	• Confidentiality information updated to add: "The contract between the sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties. • Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access."	• To align with EU-CTR.

1. PROTOCOL SUMMARY

1.1 Protocol Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1010

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

Protocol Number: mRNA-1010-P301 Amendment 2

Study Period: Approximately 13 months per participant

Phase of Development: Phase 3

Estimated date first participant enrolled: June 2022

Estimated date last participant completed: August 2023

Total Number of Sites:

Site Locations: approximately 50 sites across approximately 5 countries in Latin America and Asia-Pacific

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains at Day 29	• Geometric mean titer (GMT) at Day 29 as measured by hemagglutination inhibition (HAI) assay • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay
• To evaluate the safety and reactogenicity of mRNA-1010	• Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period post vaccination

	• Frequency and severity of any unsolicited adverse events (AEs) during the 28-day follow-up period post vaccination • Frequency of any serious AEs (SAEs), AEs of special interest (AESIs), medically attended AEs (MAAEs), and AEs leading to discontinuation from Day 1 through Day 361 (Month 12)/end of study (EoS)	
Secondary		
• To further evaluate the immunological response of mRNA-1010 (for superiority) relative to an active comparator against vaccine-matched influenza A virus strains at Day 29	• GMT at Day 29 as measured by HAI assay • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay	
• To evaluate relative vaccine efficacy to prevent influenza caused by any strain of influenza virus	• First episode of reverse transcription polymerase chain reaction (RT-PCR)-confirmed protocol-defined influenza-like illness (ILI) that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine • First episode of RT-PCR confirmed Centers for Disease Control and Prevention (CDC)-defined ILI that begins at least 14 days postvaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine • First episode of RT-PCR-confirmed protocol-defined ILI cases that begin at least 14 days post-vaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the	

	seasonal vaccine, in participants aged 50 years and older or 65 years and older
• To evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29	• The proportion of participants with a titer ≥ 1:40 at Day 29 as measured by HAI assay • Geometric mean fold rise (GMFR) comparing Day 29 to Day 1 (Baseline) as measured by HAI assay

Other exploratory objectives are as follows:

- To explore the number and percentage of participants aged 65 years and older with first episode of protocol-defined ILI by baseline frailty status.
- To describe EuroQoL 5-dimension 5-levels (EQ-5D-5L) health questionnaire utility score at regular intervals as well as for participants with protocol-defined ILI.
- To describe Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness (WPAI:ILI) v2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with protocol-defined ILI.

Overall Study Design

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

The mRNA-1010 vaccine to be tested includes messenger ribonucleic acids (mRNAs) encoding for the surface HAs of the influenza strains recommended by the World Health Organization (WHO) for 2022 Southern Hemisphere (SH) cell or recombinant-based vaccines:

- A/Wisconsin/588/2019 (A/H1N1)-like virus;
- A/Darwin/6/2021 (A/H3N2)-like virus;
- B/Michigan/01/2021 (B/Victoria lineage)-like virus; and
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Study vaccine administration is planned prior to or during the typical SH influenza vaccination campaign period. Medically stable adults, aged 18 years and older, will be screened and enrolled.

The Sponsor's Phase 1/2 mRNA-1010-P101 study is currently ongoing to provide first-in-human safety and immunogenicity data on 3 dose levels of mRNA-1010 encoding strains (50, 100, or 200 µg total mRNA) recommended by the WHO for the 2021 SH. An amendment to mRNA-1010-P101 includes a Phase 2 Northern Hemisphere (NH) portion to the study to increase the size of the safety database for the 50 µg and 100 µg dose levels and to test an additional 25 µg dose level of mRNA-1010, as well as a licensed seasonal influenza vaccine

as an active comparator. mRNA-1010 encoding strains recommended for the 2021/22 NH influenza season will be used in the Phase 2 NH portion. A Phase 2 Extension portion is ongoing to study additional dose levels of 6.25 µg and 12.5 µg mRNA-1010 as well as 25 µg mRNA-1010 and an active comparator. The interim analysis of safety data through Day 29 of 180 healthy adults in the Phase 1/2 portion of mRNA-1010-P101 showed a preferable reactogenicity profile for the 50 µg dose of mRNA-1010. The Phase 2 NH interim analysis of safety data through Day 29 demonstrated no significant safety concerns of the dose levels tested (25, 50, and 100 µg).

Approximately 6000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 vaccination groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Tetra, see table below). Randomization will be stratified by age categories (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) and influenza vaccine status in the prior 12 months (received or not received) at Screening. At least 50% of enrollees will be ≥ 50 years old, including approximately 20% who will be ≥ 65 years old. The Sponsor anticipates approximately 300 participants will be ≥ 75 years old.

Vaccination Groups and Dose Levels

Vaccination Group	**Vaccination Received**	**mRNA/Antigen** HA (each) (µg)	**Total Dose (µg)**	**Number of Participants**
1	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	3000
2	Active Comparator (Fluarix Tetra)	15 (of protein)	60 (of protein)	3000

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

Clinic visits will consist of a Screening Visit (up to 28 days before the Day 1 visit), a Vaccination Visit on Day 1 (may be on the same day as the Screening Visit), a clinic visit on Day 29, and subsequent clinic visits in a subset of participants on Day 181 and Day 361 (Month 12)/EoS, with up to 13 months of study participation for each participant. There will also be 1 optional visit on Day 4. Contact by electronic means or telephone calls will proceed as specified in the Schedule of Events (SoE). Unscheduled clinic visits for potential ILI symptoms and viral respiratory panel testing will also be conducted.

All participants will provide blood samples at baseline and on Day 29 (28 days post vaccination) for assessment of geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroconversion, as measured by HAI assay. In addition, approximately the first 1000 randomized participants will also provide blood samples at Day 181 and Day 361, a subset of which will be used for immunogenicity analysis. These participants will require a clinic visit on Day 181 and Day 361 (Month 12)/EoS. There will be an optional visit on Day 4 at which blood will be drawn for future biomarker assessment.

Participants who manifest protocol-defined ILI, will be evaluated by real-time reverse transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal (NP) swab specimen(s) for influenza (and other respiratory pathogens).

Participants will be instructed to report via Symptom Reporting electronic diary (eDiary) or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms are reported, the investigator must contact the participant to assess symptoms and ensure an NP swab is collected within 72 hours of symptom onset. If possible, NP swabs should be collected prior to initiation of antiviral therapy. If there is no response to an eDiary prompt for 2 consecutive entries, the clinic staff will attempt to contact the study participant by telephone. All participants who report symptoms of ILI will receive eDiary prompts to complete PRO questionnaires for EuroQoL 5-dimension 5-levels (EQ-5D-5L) and Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness (WPAI:ILI).

For participants aged 65 years and older, the frailty status will be assessed by clinic staff at baseline using the Edmonton Frail Scale (EFS).

There may be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms should be completed for each unscheduled visit.

All personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding, except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors. Neither the participant nor the investigator nor clinical staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study. The investigator may unblind in the event of an emergency.

Safety Oversight:

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and contract research organization medical monitor, as well as safety reviews by an unblinded Data and Safety Monitoring Board (DSMB). The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB, composed of external, independent subject matter experts, including an unblinded statistician, will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

Study Duration: Approximately 13 months for each participant.

Study participants may be screened up to 28 days prior to randomization and vaccination and will be followed for 12 months after a single intramuscular (IM) administration of investigational product (IP).

Number of Participants: Approximately 6000 participants will be enrolled in a 1:1 ratio to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (approximately 3000 participants in each vaccination group).

Study Eligibility Criteria:

Inclusion Criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

1. Individual is at least 18 years of age at the time of consent (Screening Visit).
2. Investigator has assessed that the participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified by this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Non-childbearing potential is defined as post-menopausal or permanently sterilized. Follicle-stimulating hormone may be measured at the discretion of the investigator to confirm postmenopausal status (see additional information in Section 11.2).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at the Screening Visit and on the day of vaccination prior to vaccine dose being administered on Day 1.
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1). Adequate female contraception is defined as consistent and correct use of a local health authority-approved contraceptive method in accordance with the product label.
    - Has agreed to continue adequate contraception through 90 days following vaccine administration.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Participant has had close contact to someone with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) as defined by the US CDC or has had a positive SARS-CoV-2 test in the past 10 days prior to the Screening Visit.

2. Participant is acutely ill or febrile (temperature ≥ 38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window and will retain their initially assigned participant number.
3. Participant has a history of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 60 days prior to the Screening Visit and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
4. Reported history of congenital or acquired immunodeficiency, immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    a) Participants who have HIV and on antiretroviral therapy with cluster of differentiation 4 count ≥ 350 cells/mm^3 and HIV RNA ≤ 500 copies/mL within the past 12 months.
    b) Participants with immune-mediated diseases which are stable, (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or autoimmune ovarian failure which do not require systemic immunosuppressants per Exclusion Criterion 9.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
6. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA or influenza vaccines or any components of the mRNA or influenza vaccines, including egg protein.
7. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
8. Any medical, psychiatric, or occupational condition, including reported history of substance abuse, that, in the opinion of the investigator, may pose additional risk due to participation in the study or that could interfere with the interpretation of study results.
9. Participant has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 180 days prior to the Screening Visit (for corticosteroids, ≥ 10 mg/day of prednisone or equivalent) or is anticipating the need for systemic

immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed.

10. Participant has received any vaccine authorized or approved by local health agency ≤ 28 days prior to study injection (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after the study injection.
11. Participant is not aware whether they have received an influenza vaccine in the past 12 months.
12. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine within 180 days prior to Day 1.
13. Participant has tested positive for influenza by local health authority-approved testing methods within 180 days prior to the Screening Visit.
14. Participant has a history of myocarditis, pericarditis, or myopericarditis within 60 days prior to the Screening Visit. Participants who have not returned to baseline after their convalescent period will also be excluded.
15. Participant has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to the Screening Visit, or plan to receive them, during the study are also excluded.
16. Participant has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
17. Participant has participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
18. Participant is an immediate family member or household member of study personnel, clinic staff, or Sponsor personnel.

Study Vaccines:

Investigational Product, Dosage, and Mode of Administration:

mRNA-1010 IP contains lipid nanoparticle (LNP) dispersions encoding the seasonal influenza vaccine antigens, HA, from influenza strains A/Wisconsin/588/2019 (A/H1N1)pdm09-like virus; A/Darwin/6/2021 (A/H3N2)-like virus; B/Michigan/01/2021 (B/Victoria lineage)-like virus; and B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

All mRNAs are formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available) and provided as a sterile liquid for injection, white-to-off-white dispersion in appearance, at a concentration of 0.1 mg/mL in CCI Tris buffer containing CCI sucrose and CCI sodium acetate at pH 7.0-8.0.

mRNA-1010 IP will be administered as a single IM injection dose at mRNA total dose level of 50 µg.

Active Comparator, Dosage, and Mode of Administration:

Quadrivalent, inactivated influenza vaccine, Fluarix Tetra, administered as single 0.5 mL IM injection.

Procedures and Assessments:

Immunogenicity Assessments:

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE. The following analytes will be measured:

- Serum antibody level as measured by HAI assay.
- Serum nAb level as measured by MN assay or similar methods may also be performed.

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following the study injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following the study injection (ie, the day of injection and 27 subsequent days).

- AEs leading to discontinuation from study participation from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study.
- MAAEs from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study.
- SAEs and AESIs from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study.
- Details of all pregnancies in female participants will be collected after the start of study vaccine and until the end of their participation in the study. All pregnancies must be followed to determine the outcome.

Clinical Assessments:

Participants who develop symptoms consistent with protocol-defined ILI and/or COVID-19 will have NP swabs collected for testing. The initial test will be a real-time, RT-PCR-based assay, to determine if either influenza A and/or B strains, as well as other respiratory viruses such as SARS-CoV-2, are present in the clinical sample. For samples that test positive for influenza in the RT-PCR assay, further testing by PCR-based genetic sequencing of the HA segments and/or other influenza virus genes may be performed to identify the specific subtype of the influenza strain. The RT-PCR-positive samples may be cultured. Cultured viruses may be used to evaluate similarity (match) to the current year's vaccine strains using ferret antisera to determine antigenic similarity to vaccine strains.

ILI Case Definitions:

Protocol-defined ILI:

A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom, or the occurrence of any 2 or more respiratory symptoms:

Respiratory symptoms	Systemic symptoms
1. Sore throat 2. Cough/rhinorrhea/nasal congestion (≥ 1 of the 3 symptoms count as 1 respiratory symptom) 3. Sputum production 4. Wheezing 5. Difficulty breathing	1. Body temperature > 37.2°C [> 99°F] 2. Chills 3. Tiredness 4. Headache 5. Myalgia 6. Nausea/vomiting 7. Diarrhea

CDC-defined ILI:

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

RT-PCR-confirmed Protocol-defined Influenza Infection:

An RT-PCR-confirmed protocol-defined influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local certified laboratory within 7 days of onset of protocol-defined ILI symptoms, at any time during the study period.

RT-PCR-confirmed CDC-defined Influenza Infection:

An RT-PCR-confirmed CDC-defined influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local certified laboratory within 7 days of onset of CDC-defined ILI symptoms at any time during the study period.

Statistical Methods:

Statistical Hypotheses:

The null hypothesis H^1_0: immunogenicity response to mRNA-1010, as measured by GMT or by seroconversion rate at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for A strains (ie, H1N1, H3N2). Four coprimary immunogenicity endpoints will be tested for noninferiority of mRNA-1010 vs. active comparator for A strains at two-sided 0.025 level.

The null hypothesis H^2_0: immunogenicity response to mRNA-1010, as measured by GMT or by seroconversion rate at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for B strains (ie, B/Victoria, B/Yamagata). Four coprimary immunogenicity endpoints will be tested for non-inferiority of mRNA-1010 vs. active comparator for B strains at two-sided 0.025 level.

At Day 29, for each individual influenza virus strain,

- The noninferiority in GMT in participants who received mRNA-1010 compared to that of participants who received the active comparator will be demonstrated by the lower bound of the 97.5% confidence interval (CI) of the GMT ratio (geometric mean ratio [GMR]) ruling out 0.667 (lower bound > 0.667) using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of HAI titer in those receiving mRNA-1010 compared with the GMT of those receiving the active comparator.
- The noninferiority in seroconversion rate in the mRNA-1010 group compared to that of the active comparator group will be demonstrated by the lower bound of the 97.5% CI of the seroconversion rate difference (mRNA-1010 vs. active comparator) ruling out -10% (lower bound > -10%) using a noninferiority margin of 10%.

The success criteria of non-inferiority for A strains are met if H^1_0 is rejected at a two-sided 0.025 level on all four co-primary endpoints. Similarly, the success criteria of non-inferiority

for B strains are met if H^2_0 is rejected at a two-sided 0.025 level on all four co-primary endpoints.

Additional details about the hypothesis testing can be found in the statistical section of the protocol.

Sample Size Justification:

With approximately 3000 participants exposed to IP in the mRNA-1010 group, the study has an approximately 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate.

Assuming approximately 15% of randomized participants will be excluded from Per-Protocol (PP) Immunogenicity Set, with approximately 5100 participants in the PP Immunogenicity Set (1:1 ratio, approximately 2550 in each vaccine group), the study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by the GMT in participants receiving mRNA-1010 compared with that in the active comparator group, at a 2-sided alpha of 0.025, assuming an underlying GMR of 0.9 in all 4 strains and a non-inferiority margin of 1.5. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

The study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by seroconversion rate in the mRNA-1010 group compared with that in the active comparator group, at a 2-sided alpha of 0.025, assuming a seroconversion rate of 70% in influenza A strains and 60% in influenza B strains, respectively, in the mRNA-1010 group (a true rate difference is 0 compared to the active comparator group), and a non-inferiority margin of 10%.

Analysis Populations: The analysis sets are defined in the following table:

Population	Description
Randomization Set	All participants who are randomly assigned to treatment, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All participants randomly assigned to treatment who received any study vaccination. Participants will be analyzed according to the group to which they were randomized.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who provide any follow-up for ILI beginning at least 14 days following administration of study intervention. Participants will be analyzed according to the group to which they were randomized.
PP Set for Efficacy	A subset of participants in the mITT Set who do not have significant protocol deviations that could adversely impact efficacy, eg, disease or therapeutic intervention that might cause suboptimal response to the study intervention. Participants will be analyzed according to the group to which they were randomized.

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

Abbreviations: AR = adverse reaction; IP = investigational product; PP = Per-protocol; RT-PCR = reverse transcription polymerase chain reaction.

Immunogenicity Analyses:

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

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

An analysis of covariance model will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The geometric least square mean (GLSM), and its corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale, as an estimate of the GMT. GMR, estimated by the ratio of GLSM and the corresponding 2-sided 97.5% CI will be provided to assess the treatment difference. The corresponding 2-sided 97.5% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 compared to the active comparator group at Day 29. For each strain, the non-inferiority of GMT will be considered demonstrated

if the lower bound of the 97.5% CI of the GMR is > 0.667 based on the non-inferiority margin of 1.5.

The number and percentage of participants with seroconversion due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method at Day 29. To compare the seroconversion rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 97.5% CI for the difference in seroconversion rates. The seroconversion rate difference with the corresponding 97.5% CI at Day 29 will be provided. For each strain, the non-inferiority of seroconversion rate will be considered demonstrated if the lower bound of the 97.5% CI of the seroconversion rate difference is > -10% based on the non-inferiority margin of 10%.

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

Subgroup analysis for the coprimary immunogenicity endpoints will be conducted as appropriate.

Once the noninferiority criteria are met for A strains, superiority of mRNA-1010 relative to the active comparator for A strains may be further evaluated. More details about the testing sequence can be found in Section 9.6.2 and the statistical analysis plan (SAP).

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

For summarizations of GMTs, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

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

Efficacy analyses:

The analysis population of efficacy is the mITT Set.

To evaluate the incidence of the first episode of RT-PCR-confirmed protocol-defined ILI after vaccination with mRNA-1010 or the active comparator, the incidence rate will be calculated as the number of participants with a case (ie, first occurrence of ILI at least 14 days after the study injection through Day 181/end of influenza season) divided by the number of participants at risk adjusted by person-time (years). The person-time is calculated as the time from randomization to the date of the first episode for participants with a case, or the time from randomization to the date of discontinuation or death, or Day 181/end of influenza season, whichever occurs first, for participants without a case. Person-time, incidence rate, and 95% CI for incidence rate will be provided by vaccination group. Relative vaccine efficacy will be estimated by 1- ratio of incidence rate (mRNA-1010 vs. active comparator) adjusting for person-time, and the 95% CI will be computed using the exact method conditional upon the total number of cases adjusting for person-time.

Sensitivity analyses may be performed on the PP Set for Efficacy.

RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed CDC-defined ILI in participants aged 50 years and older or 65 years and older will be analyzed similarly.

Safety Analyses:

All safety analyses will be based on the Safety Set, except summaries for solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group. Participants will be included in the vaccination group corresponding to what they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, and AEs leading to discontinuation.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7-day follow-up period after the injection will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation will be summarized. Unsolicited AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and presented by MedDRA system organ class and preferred term.

Solicited ARs will be coded by system organ class and preferred term according to the MedDRA for AR terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used in this study with modification for rash, solicited ARs, and vital signs.

The number of events of unsolicited AEs, SAEs, AESIs, and MAAEs will be reported in summarization tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided.

Planned Analyses:

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

A 6-month analysis may be performed once all participants complete the Day 181 Visit or the influenza season ends, whichever occurs later. All of safety, immunogenicity, and efficacy data will be cleaned and locked for the analysis. Additional safety analyses at other time points may be performed.

The above 2 analyses will be performed by a separate team of unblinded programmers and statisticians. More details can be found in the study data blinding plan.

Final analysis of all safety, immunogenicity, and efficacy data will be performed once all participants complete the Day 361 (Month 12)/EoS Visit.

The SAP will describe the planned analyses in greater detail.

1.2 Schedule of Events

Table 1: Schedule of Events

Visit Number		1	2	3	4	5	6	7	8	9	USV
Type of Visit/Contact	C	C	C	SC	SC	C	SC	SC/C	SC	SC/C	C
Month Timepoint						M1	M3	M6	M9	M12	Up to M12
Study Visit	Screening[1]	D1 (Baseline)	D4	D8	D15	D29	D91	D181	D271	D361/EoS	USV
Window Allowance (Days)	-28	N/A	-2	±3	±3	-7 to +3	±5	±14	±14	±14	N/A
Informed consent form, 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 30-minute post-dosing observation period)[6]		X									
Collection of Edmonton Frail Scale[7]		X									
Blood collection for humoral immunogenicity		X[8]				X		X[9]		X[9]	
Genomic sample (optional)		X[8]									
Transcriptomic sample (optional)		X[8]				X					
Optional blood sample for potential biomarker analysis[10]			X								
NP swab for virus detection[11]											X
eDiary activation for recording solicited ARs (7 days)[12]		X									
Review of eDiary for solicited ARs				X							
Symptom Reporting eDiary activation[13]		X									
Symptom Reporting eDiary for collection of symptoms of ILI[14]		Once weekly									

Visit Number		1	2	3	4	5	6	7	8	9	USV
Type of Visit/Contact	C	C	C	SC	SC	C	SC	SC/C	SC	SC/C	C
Month Timepoint						M1	M3	M6	M9	M12	Up to M12
Study Visit	Screening[1]	D1 (Baseline)	D4	D8	D15	D29	D91	D181	D271	D361/EoS	USV
Window Allowance (Days)	-28	N/A	-2	±3	±3	-7 to +3	±5	±14	±14	±14	N/A
Review of Symptom Reporting eDiary[15]		Review participant-recorded ILI starting on Day 1 through Day 361 (Month 12)/EoS									
Follow-up safety call				X	X		X	X[16]	X	X[16]	
eDiary collection of EQ-5D-5L[17]		X	eDiary prompts[18]								
eDiary collection of WPAI:ILI[19]			eDiary prompts[20]								
Recording of unsolicited AEs		X		X	X	X					
Recording of SAEs, AESIs, and MAAEs, as well as AEs that led to discontinuation and relevant concomitant medications/procedures[21]		X		X	X	X	X	X	X	X	X
Recording of concomitant medications and non-study vaccinations[22]		X		X	X	X					
Recording of hospitalizations and outpatient treatment-related to or for the treatment of the MAAE or SAE[23]		X		X	X	X	X	X	X	X	X
Study completion										X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; EFS = Edmonton Frail Scale; EoS = end of study; EQ-5D-5L = EuroQoL 5-dimension 5-levels; FDA = Food and Drug Administration; HRQoL = health-related quality of life; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety call (or contact by electronic means); USV = unscheduled visit; WPAI:ILI = Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness.
Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (FDA 2020), investigators may convert clinic visits to telemedicine visits with the approval of the Sponsor.

1. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.
2. Verbal medical history is acceptable.
3. Physical examination: A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as an MAAE.

4. Vital signs measurements: Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
5. A pregnancy test either via blood or point-of-care urine test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle stimulating- hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status.
6. See Table 3 for dose levels and vaccination groups. All participants will be randomized to receive a single IM injection.
7. Assessment of EFS will only be performed for participants aged 65 years and older. EFS is a brief, valid and reliable tool for the assessment of frailty across 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.
8. Samples for humoral immunogenicity and transcriptomics must be collected prior to receipt of vaccination on Day 1.
9. Samples for humoral immunogenicity on Day 181 and Day 361 (Month 12)/EoS will be collected for approximately the first 1000 participants and analyzed in a subset. These participants will require a clinic visit on Day 181 and Day 361 (Month 12)/EoS.
10. Biomarker plasma and biomarker serum samples will be stored for potential future biomarker assessment
11. The NP swab specimen(s) for pathogens, including influenza virus and other respiratory pathogens (e.g., SARS-CoV-2) will be collected any time from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined- ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection as defined in the ILI Case Definitions in Section 8.11.5. If participants experience these signs or symptoms, they will be instructed to contact the clinic to have an NP swab collected for testing. Nasopharyngeal (NP) swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza and/or SARS CoV-2 testing results performed outside of the study should be captured in the eCRF.
12. The eDiary entries will be recorded at approximately 30 minutes after injection while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and the subsequent 6 days following injection. If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant should notify the site to provide an end date and close out the event on the Reactogenicity page of the eCRF. If the participant reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF. All solicited ARs (local and systemic) will be considered causally related to dosing.
13. The Symptom Reporting eDiary will be activated for collection of ILI symptoms starting at Day 1 and lasting until Day 361 (Month 12)/EoS.
14. Symptom Reporting eDiary: Participants will be instructed to report via Symptom Reporting eDiary or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms are reported, the investigator must contact the participant to assess symptoms and ensure an NP swab is collected within 72 hours of symptom onset. If possible, NP swabs should be collected prior to initiation of antiviral therapy. If there is no response to an eDiary prompt for 2 consecutive entries, the clinic staff will attempt to contact the study participant by telephone.
15. Review of eDiary for recording of symptoms of ILI.
16. Participants in the subset require a clinic visit on Day 181 and Day 361 (Month 12)/EoS for sample collection.
17. EQ-5D-5L is a well-validated, reliable, standardized instrument for measuring non-disease-specific HRQoL. EQ-5D-5L consists of a short descriptive system questionnaire and a visual analogue scale (EQ-VAS). The short descriptive questions are designed to assess 5 dimensions of health including

mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the health status on a scale between 0 and 100, with 0 indicating the worst imaginable health and 100 indicating the best imaginable health.

18. All participants will receive eDiary prompts to complete the EQ-5D-5L at Day 1 (baseline), Day 91, Day 181, Day 271, and Day 361 (Month 12)/EoS. For participants reporting symptoms of ILI, the EQ-5D-5L responses will be collected using the eDiary on the day of the symptoms reporting (+1 day) and 5 days (+1 day) later.
19. WPAI consists of 6 questions, which can quantitatively assess the amount of absenteeism, presenteeism, overall work impairment, and activity impairment attributable to a patient's health issues based on a 1-week recall period. The WPAI is available in different versions, such as WPAI: Specific Health Problem (WPAI:SHP), which can be adapted to a specific disease.
20. For participants reporting symptoms of ILI, the WPAI over the previous 7 days will be collected using the eDiary 5 days (+1 day) following the start of ILI symptoms reporting.
21. 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 non-study vaccinations. All concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 361 (Month 12)/EoS.
22. All concomitant medications and non-study vaccinations will be recorded through 28 days after IP injection (including receipt of any authorized or investigational COVID-19 vaccine).
23. All hospitalizations, outpatient/physician visits, emergency room/urgent care visits, and telemedicine visits associated with MAAEs or SAEs will be recorded from Day 1 through Day 361 (Month 12)/EoS.

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LIST OF ABBREVIATIONS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
EFS	Edmonton Frail Scale
EoS	end of study
EQ-5D	EuroQoL 5-dimension
EQ-5D-5L	EuroQoL 5-dimension 5-levels
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition

Abbreviation or Specialist Term	Definition
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
ILI	influenza-like illness
IM	intramuscular(ly)
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mITT1	modified intent-to-treat-1
MN	Microneutralization
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NH	Northern Hemisphere
NP	Nasopharyngeal
PP	per protocol
QA	quality assurance
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or Specialist Term	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SH	Southern Hemisphere
SoE	Schedule of Events
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
USP	United States Pharmacopeia
WHO	World Health Organization
WPAI:ILI	Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness

2. INTRODUCTION

2.1 Study Rationale

Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year, which is a severe challenge to public health (WHO 2018). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the Northern Hemisphere (NH) and Southern Hemisphere (SH), respectively (Riedel et al 2019). Since influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto 2018). Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice a year (once for the NH and once for the SH. Influenza A and B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages).

Currently licensed seasonal influenza virus vaccines rarely exceed 60% overall effectiveness and are poorly effective during the years when circulating viruses do not match the strains elected for the vaccine antigens (Centers for Disease Control and Prevention [CDC] 2020a). Influenza vaccines based on messenger ribonucleic acid (mRNA) technology could provide several benefits compared with current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, and improved protection in older adults (Rockman et al 2020).

2.2 Background and Overview

ModernaTX, Inc. (the Sponsor) has developed a rapid response proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigens(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently.

Two mRNA vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) including Pfizer, Inc.'s BNT162b2 (Polack et al 2020) and the Sponsor's mRNA-1273 (NCT04283461, NCT04405076, and NCT04470427) have received full authorizations by the US Food and Drug Administration (FDA).

2.2.1 mRNA-1010

The Sponsor is using its mRNA-based platform to develop a lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against disease caused by influenza virus types A and B. The proposed development candidate, mRNA-1010, is a quadrivalent vaccine containing mRNAs that encode for the hemagglutinin (HA) of the 4 strains recommended by the WHO for cell- or recombinant-based vaccines. Equal amounts of mRNAs encoding for each of the 4 different strains will be used for the HA components. The mRNA-1010 development candidate is

administered as a single intramuscular (IM) injection and aims to elicit protection from all seasonal influenza viruses covered by the vaccine.

The Sponsor is conducting this pivotal Phase 3 trial of its seasonal influenza mRNA vaccine (mRNA-1010) to establish immunogenicity and safety in support of licensure. The design of this study will include immunogenicity objectives for hemagglutination inhibition (HAI), a surrogate endpoint of prevention of influenza illness and its complications. The rationale for this approach is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (Department of Health and Human Services [DHHS] 2007a; Dunning et al 2016; European Medicines Agency 2016).

Summaries of nonclinical and clinical studies of mRNA-1010 can be found in Section 2.2.2 and Section 2.2.3, respectively.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2.2.2 Nonclinical Studies

Using individually formulated HA-encoding mRNAs (preclinical material), 2 mouse immunogenicity studies were performed. The HA sequences used for preclinical formulation were from wild-type HAs.

Both studies used a prime/boost regimen with a 3-week interval. Immunized mice were bled on Day 21 (3 weeks after the prime dose) and Day 36 (2 weeks after the boost dose), and immunoglobulin G (IgG) antibody titers were determined with an enzyme-linked immunosorbent assay using recombinant HA proteins.

The first study compared mice immunized with individual mRNAs or a combination of all 4 HA mRNAs at 2 different doses (2 or 0.4 µg of each mRNA), based on the following strains recommended for the 2020 to 2021 NH influenza season:

- A/Hawaii/70/2019(H1N1)pdm09
- A/Hong Kong/45/2019(H3N2)
- B/Washington/02/2019 (B/Victoria lineage)
- B/Phuket/3073/2013 (B/Yamagata lineage)

High IgG antibody titers were observed against all HAs following immunization, with both individual mRNA constructs and mRNA combinations after a single dose. A dose response and booster effect were observed for most mRNA constructs (individual and combinations).

The second mouse immunogenicity study aimed to confirm that the 2021 SH composition is similarly immunogenic with the 2020 to 2021 NH composition. The compositions differed only for the H1N1 strain; the SH composition included A/Wisconsin/588/2019(H1N1)pdm09 instead of the A/Hawaii/70/2019(H1N1)pdm09 strain.

No difference in immunogenicity (HA IgG antibody titers) based on the strain/mRNA construct used for immunization (A/Hawaii/70/2019 in the NH composition versus A/Wisconsin/588/2019

in the SH composition) was observed, suggesting that the mRNA platform will support annual strain updates.

Additional studies to assess protection of mice from challenge with mouse-adapted H1N1 and H3N2 viruses after a single immunization and a study to assess immunogenicity and protection from H1N1 challenge after 2 immunizations in ferrets have been completed. Using non-GMP co-formulated material, mice and ferrets were immunized with mRNA-1010 of the SH 2021 composition (mRNA-1010-SH21) followed by a viral challenge. Control animals were immunized with phosphate-buffered saline or a commercially available MF59-adjuvanted influenza vaccine (FLUAD®, 2020/21 NH composition).

Ferrets were administered via IM injection on a prime/boost schedule with a 3-week interval, antibody responses were measured at Day 21 and Day 42 followed by H1N1 challenge on Day 42. Mice received a single dose via IM injection, antibody responses were measured at Day 21, and the animals were challenged that day with either an H1N1 or H3N2 virus.

In both animal models, serological analyses demonstrated that HAI antibody titers were detectable against the 4 viral strains after the first immunization with mRNA-1010 and in the case of ferrets, titers were further boosted by the second immunization. In addition, the HAI antibody titers induced by mRNA-1010 were as robust as the titers induced by the adjuvanted influenza vaccine (FLUAD).

Upon live virus challenge, ferrets that were vaccinated with mRNA-1010 had lower detectable viral loads compared to the placebo group across different tissues. Compared to FLUAD, mRNA-1010 performed equally well and reduced viral loads to lower levels in the nose, throat, and nasal turbinates. No virus was detected in the lung 4 days after challenge.

Upon H3N2 live virus challenge, mice that were vaccinated with mRNA-1010 lost less weight and showed fewer clinical symptoms as compared to animals that received FLUAD or animals in the control group. Upon (H1N1)pdm09-like virus challenge, animals that received mRNA-1010 or FLUAD were fully protected against morbidity and showed no scorable clinical symptoms.

In conclusion, vaccination with mRNA-1010 induces strong antibody responses in mice and ferrets and confers protective efficacy against live virus challenge.

A detailed review of the nonclinical experience with mRNA-1010 vaccine will be provided in the investigator's brochure (IB).

2.2.3 Clinical Studies

The Sponsor's Phase 1/2 mRNA-1010-P101 study (NCT04956575) is currently ongoing to provide initial first-in-human safety and immunogenicity data on 3 dose levels of mRNA-1010 encoding strains (50, 100, or 200 µg total mRNA) recommended by the WHO for the 2021 SH. An amendment to mRNA-1010-P101 includes a Phase 2 NH portion to the study to increase the size of the safety database for the 50 µg and 100 µg dose levels and to test an additional 25 µg dose level of mRNA-1010 as well as a licensed seasonal influenza vaccine as an active comparator. A Phase 2 Extension portion to this trial is ongoing to study additional dose levels of mRNA-1010 (6.25 µg and 12.5 µg) as well as 25 µg of mRNA-1010 and an active comparator.

No significant safety concerns have been observed in the ongoing Phase 1/2 mRNA-1010-P101 study upon review of safety data up to 29 days by the Data Safety Monitoring Board (DSMB). In

that study, 45 participants in each group received 50 µg, 100 µg, or 200 µg doses of mRNA-1010. The 50-µg dose of mRNA-1010 showed a preferable reactogenicity profile. The local and systemic adverse reactions (ARs) were mostly mild to moderate in severity. There were no Grade 4 ARs or serious adverse events (SAEs) assessed by the investigator as related to the study vaccine. There was a death due to stage 4 kidney cancer that was unrelated to the study vaccine and occurred after Day 29 visit. Vaccination with mRNA-1010 elicited HAI antibodies in both younger and older adults against all strains at all dose levels. HAI titers elicited at the 50 µg dose level were comparable with the titers elicited at higher dose levels.

The interim analysis from the Phase 2 NH part of mRNA-1010-P101 included data through Day 29 from 498 adults who received study injection. The number of participants in the 4 groups were 151 (25 µg mRNA-1010), 147 (50 µg mRNA-1010), 147 (100 µg mRNA-1010) and 53 (Afluria). No significant safety concerns were identified. The frequency and severity of the reports of solicited ARs in the mRNA-1010 groups increased in a dose-dependent manner particularly in the older age groups but were acceptable across all dose levels. The solicited ARs were higher in the mRNA-1010 groups than in the Afluria group. Local and systemic solicited ARs were mostly mild to moderate in severity without any Grade 4 ARs, adverse events of special interest (AESIs) or SAEs assessed to be related to the study vaccines. There were no study discontinuations due to AEs, and no AEs that led to a study pause. There was one death due to cardiac arrest in a 67-year-old male participant with a relevant history of diabetes mellitus, hypertension, and obesity. The event occurred 15 days after study vaccination and was assessed by the investigator to be unrelated to the study intervention. mRNA-1010 elicited high levels of HAI antibodies on Day 29 across all dose levels, substantially exceeding the 1:40 threshold associated with a 50% reduction in risk of infection. Antibody responses induced by mRNA-1010 against the influenza A strains H1N1 and H3N2 were higher compared with those against Afluria and were similar to the influenza B strains.

A description of the immunogenicity and safety of mRNA-1010 is provided in the IB.

2.3 Benefit/Risk Assessment

2.3.1 Known Potential Benefits

The mRNA-1010 vaccine may be effective against seasonal influenza strains as defined by the WHO for the 2022 SH influenza season.

Considering the safety data for mRNA-1010 to date, the Sponsor considers the potential benefits of participation to exceed the risks.

Participants will obtain medical advice about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination, vital signs measurement, nasopharyngeal [NP] swabs testing).

Participants will be contributing to the process of developing a new potentially prophylactic measure in an area of unmet medical need.

2.3.2 Risks From Study Participation and Their Mitigation

As with all injectable vaccines, immediate systemic allergic reactions to vaccination, ranging from mild allergic reactions (eg, urticaria) to systemic allergic reactions (eg, anaphylaxis) can

occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). Since the authorization of the mRNA-1273 vaccine for coronavirus disease 2019 (COVID-19), the US CDC estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precautionary measure, all participants will remain under observation at the clinic for at least 30 minutes after vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection, and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the proprietary SM-102 (44eptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate) lipid formulation have commonly resulted in transient and self-limiting local inflammatory reactions. These typically included pain, erythema (redness), or swelling (hardness) at the injection site, which were mostly mild to moderate in severity and usually occurred within 24 hours of injection.

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection have been observed in early phase clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown.

In a recently completed Phase 3 study of the mRNA-1273 vaccine for COVID-19 in 30,420 healthy adults, the most commonly reported local reactions included pain, swelling, and erythema at the injection site. Most of these reactions were Grade 1 or 2 in severity and resolved within 3 to 4 days of onset. The most commonly reported systemic reactions were headache, myalgia, arthralgia, fatigue, chills, and fever. In most cases, the reactions resolved spontaneously within several days (Baden et al 2021).

Similarly, safety results from Phase 1 studies conducted by the Sponsor on 2 mRNA vaccines containing the HA glycoproteins from the H10N8 and H7N9 avian influenza viruses were well tolerated, although the Sponsor's LNP/mRNA platform has since been updated (eg, SM-102 is used in mRNA-1010 and mRNA-1273; Feldman et al 2019).

In the post authorization setting, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Investigators and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

Further details are provided in the current IB.

2.3.3 Overall Benefit/Risk Conclusion

Considering the safety data for mRNA-1010 to date, the Sponsor considers the potential benefits of participation exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 2.

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains at Day 29	• GMT at Day 29 as measured by HAI assay • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay
• To evaluate the safety and reactogenicity of mRNA-1010	• Frequency and grade of each solicited local and systemic reactogenicity AR during a 7-day follow-up period post vaccination • Frequency and severity of any unsolicited AEs during the 28-day follow-up period post vaccination • Frequency of any SAEs, AESIs, MAAEs, and AEs leading to discontinuation from Day 1 through Day 361 (Month 12)/EoS
Secondary	
• To further evaluate the immunological response of mRNA-1010 (for superiority) relative to an active comparator against vaccine-matched influenza A virus strains at Day 29	• GMT at Day 29 as measured by HAI assay • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay
• To evaluate relative vaccine efficacy to prevent influenza caused by any strain of influenza virus	• First episode of RT-PCR–confirmed protocol-defined ILI that begins at least 14 days postvaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine • First episode of RT-PCR–confirmed Centers for Disease Control and Prevention (CDC)–defined ILI that begins at least 14 days postvaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of

Objectives	Endpoints
	antigenic match to the strains selected for the seasonal vaccine • First episode of RT-PCR–confirmed protocol-defined ILI cases that begin at least 14 days postvaccination through Day 181 (Month 6)/end of influenza season caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine, in participants aged 50 years and older or 65 years and older
• To evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29	• The proportion of participants with a titer ≥ 1:40 at Day 29 as measured by HAI assay • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI assay
Exploratory (May Be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 to that of an active comparator against vaccine-matched or vaccine-mismatched influenza A and B strains, including the use of alternative methods	• GMT and GMFR of nAbs by assays such as MN and/or HAI assays or alternative methods against vaccinematched or vaccinemismatched strains on Day 29 compared with Day 1 (Baseline) • GMT and GMFR of anti-HA antibody titers against vaccine-matched and mismatched strains on Day 181 and Day 361, as measured by HAI assay • The proportion of participants with seroconversion and the proportion of participants with a titer ≥ 1:40 at Day 181 and Day 361, as measured by HAI assay
• To further characterize the immune response to mRNA-1010 and active comparator	• Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses

Objectives	Endpoints
• To describe the occurrence of clinical influenza cases throughout the study period	• Number of cases of RT-PCR–confirmed protocol-defined ILI cases that begin at least 14 days postvaccination through Day 361/EoS caused by any strain of influenza virus regardless of antigenic match to the strains selected for the seasonal vaccine

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; ILI = influenza-like illness; MAAE = medically attended adverse event; MN = microneutralization; nAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event.

Other exploratory objectives are as follows:

- To explore the number and percentage of participants aged 65 years and older with first episode of protocol-defined ILI by baseline frailty status.
- To describe EuroQoL 5-dimension 5-levels (EQ-5D-5L) health questionnaire utility score at regular intervals as well as for participants with protocol-defined ILI.
- To describe Work Productivity and Activity Impairment Questionnaire: Influenza-like Illness (WPAI:ILI) v2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with protocol-defined ILI.

4. STUDY DESIGN

4.1 General Design

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

The mRNA-1010 vaccine to be tested includes mRNAs encoding for the surface HAs of the influenza strains recommended by the WHO for 2022 SH cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019 (A/H1N1)like virus;
- A/Darwin/6/2021 (A/H3N2)like virus;
- B/Michigan/01/2021 (B/Victoria lineage)like virus; and
- B/Phuket/3073/2013 (B/Yamagata lineage)like virus.

Study vaccine administration is planned prior to or during the typical SH influenza vaccination campaign period. Medically stable adults, aged 18 years and older, will be screened and enrolled. A complete list of inclusion and exclusion criteria is provided in Section 5.

The Sponsor's Phase 1/2 mRNA-1010-P101 study is currently ongoing to provide initial first-in-human safety and immunogenicity data on 3 dose levels of mRNA-1010 encoding strains (50, 100, or 200 µg total mRNA) recommended by the WHO for the 2021 SH. An amendment to mRNA-1010-P101 includes a Phase 2 NH portion to the study to increase the size of the safety database for the 50 µg and 100 µg dose levels and to test an additional 25 µg dose level of mRNA-1010 as well as a licensed seasonal influenza vaccine as an active comparator. mRNA-1010 encoding strains for the 2021 to 2022 NH will be used in the Phase 2 NH portion. A Phase 2 Extension portion is assessing additional dose levels of 6.25 µg and 12.5 µg mRNA-1010 as well as 25 µg mRNA-1010 and an active comparator. The interim analysis of safety data through Day 29 of 180 healthy adults in the Phase 1/2 portion of mRNA-1010-P101 showed preferable reactogenicity profile for the 50 µg dose of mRNA-1010. The Phase 2 NH interim analysis of safety data through Day 29 demonstrated no significant safety concerns of the dose levels tested (25, 50, and 100 µg).

Approximately 6000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 vaccination groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Tetra, Table 3). Randomization will be stratified by age categories (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) and influenza vaccine status in the prior 12 months (received or not received) at Screening. At least 50% of participants enrolled will be ≥ 50 years old, including approximately 20% who will be ≥ 65 years old. The Sponsor anticipates approximately 300 participants will be ≥ 75 years old.

Table 3: Vaccination Groups and Dose Levels

Vaccination Group	Vaccination Received	mRNA/Antigen	Total Dose (µg)	Number of Participants
		HA (each) (µg)		
1	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	3000
2	Active Comparator (Fluarix Tetra)	15 (of protein)	60 (of protein)	3000

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

Table 1 displays the study Schedule of Events (SoE). Clinic visits will consist of a Screening Visit (up to 28 days before the Day 1 visit), a Vaccination Visit on Day 1 (may be on the same day as the Screening Visit), a clinic visit on Day 29, and subsequent clinic visits in a subset of participants (approximately the first 1000 participants) on Day 181 and Day 361 (Month 12)/end of study (EoS), with up to 13 months of study participation for each participant. There will also be 1 optional visit on Day 4. Contact by electronic means or telephone calls will proceed as specified in the SoE (Table 1). Unscheduled clinic visits for potential influenza like- illness (ILI) symptoms and viral respiratory panel testing will also be conducted.

All participants will provide blood samples at baseline and on Day 29 (28 days post vaccination) for assessment of geometric mean titer (GMT), geometric mean fold rise (GMFR), and seroconversion, as measured by HAI assay. In addition, approximately the first 1000 randomized participants will also provide humoral immunogenicity blood samples at Day 181 and Day 361, a subset of which will be used for immunogenicity analysis. There will be an optional visit on Day 4 at which blood will be drawn for future biomarker assessment.

Participants who manifest protocol-defined ILI will be evaluated by real-time reverse transcription polymerase chain reaction (RT-PCR) testing of NP swab specimen(s) for influenza (and other respiratory pathogens).

Participants will be instructed to report once weekly from Day 1 to Day 361 (Month 12)/EoS via Symptom Reporting electronic diary (eDiary) or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms occur, the investigator must contact the participant to assess symptoms and ensure an NP swab is collected within 72 hours of symptom onset. If possible, NP swabs should be collected prior to initiation of antiviral therapy. If there is no response to an eDiary prompt for 2 consecutive entries, the clinic staff will attempt to contact the study participant by telephone. All participants who report symptoms of ILI will receive eDiary prompts to complete PRO questionnaires for EQ-5D-5L and WPAI:ILI.

For participants aged 65 years and older, the frailty status will be assessed by clinic staff at baseline using the Edmonton Frail Scale (EFS).

There may be situations in which the investigator asks a participant to report for an unscheduled visit following the report of an adverse event (AE). Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

All personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding, except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors. Neither the participant nor the investigator nor clinical staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study. The investigator may unblind in the event of an emergency (refer to Section 6.3.7).

4.2 Scientific Rationale for Study Design

This study is designed as an observer-blind study. Participants will receive a single dose of either mRNA-1010 vaccine or a licensed quadrivalent seasonal influenza vaccine (an active comparator) to assess noninferior immunogenicity.

In this observer-blind study, participants, clinic staff involved in participant assessment, and Sponsor personnel (or its designees) will be blinded to participant vaccine allocation. A limited number of Sponsor and/or contract research organization (CRO) personnel will be unblinded to conduct safety data analyses for the DSMB safety data reviews (as described in the DSMB charter) and perform the primary analysis. Unblinded study personnel, who will not participate in any other aspect of the study, will perform investigational product (IP) accountability, dose preparation, and IP administration.

The NP swab specimen(s) for assessment of pathogens, including influenza virus and SARS-CoV-2, will be collected any time from Day 1 through Day 361 (Month 12)/EoS if the participants have protocol-defined ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection at the investigator's discretion (see Section 8.11.5). If participants experience these signs or symptoms, they will be instructed to contact the clinic to have an NP swab collected for testing. Nasopharyngeal swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected by the study staff, any available influenza and/or SARS-CoV-2 testing results performed by a certified laboratory outside of the study should be captured in the eCRF.

4.3 Justification for Dose, Control Product, and Choice of Study Population

The Sponsor's Phase 1/2 mRNA-1010-P101 study is currently ongoing to provide initial first-in-human safety and immunogenicity data on 3 dose levels of mRNA-1010 encoding strains (50, 100, or 200 µg total mRNA) recommended by the WHO for the 2021 SH. An amendment to mRNA-1010-P101 includes a Phase 2 NH portion to the study to increase the size of the safety database for the 50 µg and 100 µg dose levels and to test an additional 25 µg dose level of mRNA-1010 as well as a licensed seasonal influenza vaccine as an active comparator (Fluarix Tetra). Fluarix Tetra was selected as an active comparator because it is licensed for the prevention of influenza disease caused by vaccine-matched strains in the target population (≥ 18 years old) in SH countries. A Phase 2 Extension portion is ongoing to study additional dose levels of mRNA-1010 (6.25 µg and 12.5 µg) as well as 25 µg of mRNA-1010 and an active comparator.

No significant safety concerns have been observed in the ongoing Phase 1/2 mRNA-1010-P101 study upon review of safety data up to 29 days by the DSMB. The 50-µg dose of mRNA-1010 showed a preferable reactogenicity profile. Vaccination with mRNA-1010 elicited HAI

antibodies in both younger and older adults against all strains at all dose levels. HAI titers elicited at the 50 µg dose level were comparable with the titers elicited at higher dose levels.

The interim analysis from the Phase 2 NH part of mRNA-1010-P101 through Day 29 demonstrated no significant safety concerns at any dose level (25, 50, or 100 µg) (further details are provided in the current IB).

4.4 End of Study Definition

A participant is considered to have completed the study if they complete the final visit on Day 361 (Month 12) as shown in the SoE (Table 1).

The EoS is defined as completion of the last visit of the last participant in the study or last scheduled procedure as shown in the SoE (Table 1) for the last participant in the study.

5. STUDY POPULATION

Approximately 6000 participants will be enrolled in a 1:1 ratio to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine (Fluarix Tetra) as an active comparator (approximately 3000 participants in each vaccination group).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Individual is at least 18 years of age at the time of consent (Screening Visit).
2. Investigator has assessed that the participant understands and is willing and physically able to comply with protocol mandated follow-up, including all procedures.
3. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified by this protocol.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as post-menopausal or permanently sterilized. Follicle-stimulating hormone (FSH) may be measured at the discretion of the investigator to confirm postmenopausal status (see additional information in Section 11.2).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at the Screening Visit and on the day of vaccination prior to vaccine dose being administered on Day 1.
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1). Adequate female contraception is defined as consistent and correct use of a local health authority-approved contraceptive method in accordance with the product label.
    - Has agreed to continue adequate contraception through 90 days following vaccine administration.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant has had close contact to someone with SARS-CoV-2 infection or COVID-19 as defined by the US CDC or has had a positive SARS-CoV-2 test in the past 10 days prior to the Screening Visit.

2. Participant is acutely ill or febrile (temperature ≥ 38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window and will retain their initially assigned participant number.
3. Participant has a history of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 60 days prior to the Screening Visit and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
4. Reported history of congenital or acquired immunodeficiency, immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    a) Participants who are HIV positive and on antiretroviral therapy with cluster of differentiation 4 count ≥ 350 cells/mm^3 and HIV RNA ≤ 500 copies/mL within the past 12 months.
    b) Participants with immune-mediated diseases which are stable (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or autoimmune ovarian failure which do not require systemic immunosuppressants per Exclusion Criterion 9.
5. Dermatologic conditions that could affect local solicited adverse reaction (AR) assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
6. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA or influenza vaccines or any components of the mRNA or influenza vaccines, including egg protein.
7. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
8. Any medical, psychiatric, or occupational condition, including reported history of substance abuse, that, in the opinion of the investigator, may pose additional risk due to participation in the study or that could interfere with the interpretation of study results.
9. Participant has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 180 days prior to the Screening Visit (for corticosteroids, ≥ 10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed.

10. Participant has received any vaccine authorized or approved by local health agency ≤ 28 days prior to study injection (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after the study injection.
11. Participant is not aware whether they have received an influenza vaccine in the past 12 months.
12. Participant has received a seasonal influenza vaccine or any other investigational influenza vaccine within 180 days prior to Day 1.
13. Participant has tested positive for influenza by local health authority-approved testing methods within 180 days prior to the Screening Visit.
14. Participant has a history of myocarditis, pericarditis, or myopericarditis within 60 days prior to the Screening Visit. Participants who have not returned to baseline after their convalescent period will also be excluded.
15. Participant has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to the Screening Visit, or plan to receive them, are also excluded.
16. Participant has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
17. Participant has participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.
18. Participant is an immediate family member or household member of study personnel, clinic staff, or Sponsor personnel.

5.3 Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. Participants in the study should defer vaccination with licensed seasonal influenza vaccine until after completion of their Day 29 visit, and ideally until Day 181 Visit, if seasonal influenza vaccine is available, and they have discussed with the investigators and have chosen to receive it.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated

Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, screen failure details, eligibility criteria, and information on any SAE which may have occurred from the time informed consent was obtained to the time of withdrawal.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time if they will be eligible upon rescreening.

6. STUDY TREATMENT

6.1 Investigational Product and Active Comparator Administered

The term "IP" refers to the mRNA-1010 vaccine and to the licensed seasonal influenza vaccine (the "active comparator") administered in this study. The vaccines to be administered in this study are described in Table 4.

The mRNA-1010 vaccine to be tested includes mRNAs encoding for the surface Has of the influenza strains recommended by the WHO for 2022 SH cell- or recombinant-based vaccines:

- A/Wisconsin/588/2019 (A/H1N1)-like virus;
- A/Darwin/6/2021 (A/H3N2)-like virus;
- B/Michigan/01/2021 (B/Victoria lineage)-like virus; and
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

mRNA-1010 is formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). The mRNA-1010 injection is provided as sterile liquid for injection and is a white-to-off-white dispersion at a concentration of 0.1mg/mL in CCI Tris buffer containing CCI sucrose and CCI sodium acetate at pH 7.0 – 8.0.

The mRNA-1010 vaccine will be administered as a single 0.5 mL IM injection at an mRNA total dose level of 50 µg to participants according to the vaccination group assignment (Table 4).

The active comparator administered in this study is a licensed quadrivalent inactivated seasonal influenza vaccine (Fluarix Tetra) administered as a single 0.5 mL IM injection (Table 4).

Table 4: Investigational Product and Active Comparator Administered

Vaccination Group:	**Investigational Product**	**Active Comparator**
Intervention Name:	mRNA-1010	Fluarix Tetra (S-Hemisphere)
Type	Vaccine	Vaccine
Dosage Level(s):	50 µg (mRNA)	60 µg (protein)
Route of Administration:	IM injection	IM injection
Physical Description:	Sterile liquid for injection, white-to-off-white dispersion	Sterile, colorless, and slightly opalescent suspension
Source:	Provided centrally by the Sponsor	Hybrid – Potentially Centrally and Locally

Packaging and Labeling:	mRNA-1010 will be provided in 2R glass vials. Each vial will be labeled as required per country requirement.	Active comparator will be provided in a prefilled syringe in a carton. Each carton will be labeled as required per country requirement.

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid.

6.2 Randomization and Blinding

Randomization will be performed using an interactive response technology (IRT). Approximately 6000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Table 3). Randomization will be stratified by age categories (18 to < 50 years old, ≥ 50 to < 65 years old, or ≥ 65 years old) and influenza vaccine status in the prior 12 months (received or not received) at Screening. At least 50% of enrolled participants will be ≥ 50 years old, including approximately 20% who will be ≥ 65 years old. The Sponsor anticipates that approximately 300 participants will be ≥ 75 years old.

As the appearance of the study vaccines differ, enrollment will be observer blinded as to treatment assignment.

Dose preparation, administration, and accountability will be performed by designated unblinded site personnel who will not participate in any of the clinical study evaluations. The unblinded site personnel will prepare the dose out of view of the participant and the blinded site personnel.

The laboratory personnel in charge of immunogenicity testing will be blinded to the treatment assignment of the samples tested throughout the course of the study.

Except in the case of medical necessity, a participant's treatment should not be unblinded without the approval of the Sponsor. The treatment code should be broken only if the investigator in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine. Instructions regarding emergency unblinding will be provided to the investigator and are discussed in Section 6.3.7.

The investigator, clinic 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 for the final analysis. At the primary analysis and the 6-month analysis (see Section 9.6), pre-identified Sponsor team members and selected CRO team members will be unblinded to conduct the analyses. Clinics will remain blinded.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Clinical Study Material Preparation

The IP will be prepared for each participant based on their vaccination group assignment. The mRNA-1010 vaccine injection will have a volume of 0.5 mL and will contain mRNA-1010 at a dose of 50 µg. The active comparator will be administered at a volume of 0.5 mL. The mRNA-1010 and active comparator preparation instructions are detailed in the Pharmacy Manual.

6.3.2 Clinical Study Material Administration

The study vaccine (mRNA-1010 or the active comparator) will be administered as a single IM injection into the deltoid muscle on Day 1. Preferably, the IP should be administered into the nondominant arm.

Participants will be monitored for a minimum of 30 minutes after administration of the study injection. Assessments will include vital sign measurements and monitoring for local or systemic reactions as shown in the SoE (Table 1).

The clinic will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either onsite resuscitation equipment and personnel or appropriate protocols for the rapid transport of a participant to a resuscitation area or facility are required.

Further instructions for the preparation and administration of mRNA-1010 and active comparator are described in the mRNA-1010 Pharmacy Manual.

6.3.3 Clinical Study Material Packaging and Labeling

The Sponsor will provide the investigator (via the clinic pharmacy) with adequate quantities of the IP. Sterile mRNA-1010 for this study will be packaged in 2R glass vials with a 0.7 mL fill volume. The IP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner

All Ips used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.3.4 Clinical Study Material Storage

mRNA-1010 must be stored at the clinical site at 2°C to 8°C in a secure area with limited access and must be protected from moisture and light until it is prepared for administration (Section 6.3.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. The refrigerator should be connected to a backup generator. In addition, for IP accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The clinic is responsible for reporting any IP that was not temperature controlled during shipment or storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods. Please note that the mRNA-1010 will be stored at -25°C to -15°C at the depots and during shipments to the clinical sites.

The active comparator should be stored in its original container and in accordance with the instructions in the Pharmacy Manual.

6.3.5 Clinical Study Material Accountability

The investigator is responsible for ensuring the IP accountability staff maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study vaccines, and the return to the Sponsor or alternative disposition of used/unused product(s) in a drug accountability

log. Drug accountability will be noted by the site monitor during site visits and at the completion of the study. For further direction, refer to the Pharmacy Manual.

6.3.6 Clinical Study Material Handling and Disposal

A site monitor will reconcile the clinical study material during study conduct and at the end of the study for compliance. Once fully reconciled at the site, the clinical study material can be destroyed at the investigational site or Sponsor-selected third party, as appropriate.

Study products may be destroyed at the clinic only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be obtained and sent to the Sponsor or designee. For further direction, refer to Pharmacy Manual.

6.3.7 Unblinding

Except in the case of medical necessity, a participant's treatment assignment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the investigator will make every attempt to contact the CRO CRA to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblinding's will be tracked via an audit trail in IRT and documented in the final study report.

6.4 Study Intervention Compliance

All vaccinations will be administered by qualified and trained study personnel to ensure that all vaccine doses administered comply with those planned. Study vaccine doses administered will be recorded in the eCRF. Administration data will be reconciled with site accountability records to determine compliance.

6.5 Concomitant Therapy

At each clinic visit, the site personnel should question the participant regarding any medications taken and vaccinations received and record the information as specified in Section 6.5.1.

6.5.1 Recording of Concomitant Medications, Concomitant Vaccinations, and Concomitant Procedures

The following concomitant medication(s) and vaccine(s) must be recorded in the eCRF:

- Any vaccine (authorized or investigational) administered in the prior 12 months.
- All concomitant medications and non-study vaccines taken through 28 days after the IP injection. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.

- Any authorized or investigational COVID-19 vaccine at any time before or during the study period after the IP injection.
- Any authorized influenza vaccine at any time during the study period after the IP injection.
- All concomitant procedures/surgeries at any time during the study period after the IP injection.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) and systemic steroids (≥ 10 mg/day prednisone or equivalent) , administered at any time during the study period after the IP injection.
- Immunoglobulins and long-acting biological therapies that affect immune responses (eg, infliximab) and/or any blood products administered during the study period.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or medically attended AE (MAAE) from Day 1 through Day 361 (Month 12)/EoS.
- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after the IP injection, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the clinic staff during the clinic visits after vaccination or via other participant interactions (eg, telephone calls).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Global.

If a participant takes a prohibited drug therapy, the investigator and the CRO's medical monitor will make a joint decision about continuing or withholding the study vaccination of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

6.5.2 Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant From Per-protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 10 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.

- An authorized or licensed vaccine administered within 28 days after the study vaccination.
- Immunoglobulins and long-acting biological therapies that affect immune responses (eg, infliximab) and/or any blood products administered during the study period.

6.6 Intervention After the End of the Study

Any AE occurring after the end of the study and considered to be caused by the study vaccine must be reported to the Sponsor.

7. DELAY OR DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Participant Discontinuation/Withdrawal From the Study

Participants who withdraw or are withdrawn from the study will not be replaced.

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If a participant desires to withdraw from the study because of an AE, the investigator will attempt to obtain agreement to follow-up with the participant until the event is considered resolved or stable and will then complete the EoS section of the eCRF.

All data collected until the date of withdrawal or last contact of the participant will be used for the analysis.

Information related to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify)
- SAE (specify)
- Solicited AR or reactogenicity event (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs, solicited ARs, or reactogenicity events) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study as result of an AE, SAE, solicited AR, or reactogenicity event until resolution of the event.

A participant withdrawing from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (see Section 11.1.6).

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

7.2 Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the clinic. The following actions must be taken if a participant fails to return to the clinic for a required clinic visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- Should the participant continue to be unreachable or noncompliant with clinic visits or procedures, he or she will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

The study SoE can be found in Table 1.

8.1 Screening

Before performing any study procedures, all potential participants will sign an informed consent form (ICF; Section 11.1.6).

At the Screening Visit (up to 28 days for the Day 1 visit), all screening requirements, including reason for screen failure if a participant is not randomized, must be completed. The Enrollment Page in the eCRF must also be completed.

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

8.2 Confirm Inclusion and Exclusion Criteria

All inclusion and exclusion criteria described in Section 5.1 and Section 5.2 must be met before randomization (Day 1 visit).

8.3 Demographic and Baseline Data

Demographic information relating to the participant's sex, age, race, ethnicity, height, weight, and body mass index will be recorded at the Screening Visit on the appropriate eCRF page.

8.4 Medical History

Medical history will be collected and recorded from each participant on the appropriate eCRF page. Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page.

8.5 Randomization

Vaccination group and vaccine assignment allocation will be performed at the Day 1 visit as described in Section 6.2. The confirmation for study vaccine administration must be recorded on the Injection page of the eCRF.

8.6 Physical Examination and Vital Signs

A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as an MAAE (Section 8.11.4).

Vital sign measurements include the assessment of systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once prior to vaccination and once

30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.

The information collected will be recorded in the eCRF.

8.7 Study Vaccine Administration

A single-dose vaccination (mRNA-1010 or active comparator) will be administered to all participants.

After completing all prerequisite procedures prior to vaccination, the study vaccine will be administered via IM injection into the deltoid muscle. A detailed description of the vaccine administration procedure is provided in Section 6.3.2.

The participants will be observed closely (via clinical assessment including measurement of vital signs) for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions.

8.8 Efficacy and Immunogenicity Assessments

8.8.1 Sampling for Efficacy Assessments

Assessment of clinical efficacy may be performed in this study.

8.8.2 Sampling for Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE (Table 1). The following analytes will be measured:

- Serum antibody level as measured by HAI assay.
- Serum neutralizing antibody level as measured by microneutralization assay or similar methods may also be performed.

Measurement of antibody levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 11.1.6), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to influenza vaccines, additional assay development, and the immune response across influenza viruses (Section 11.1.10).

8.9 Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant, according to the SoE (Table 1):

- Solicited local and systemic ARs (Section 8.11.3) that occur during the 7 days following the study injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 8.9.4).

- Unsolicited AEs observed or reported during the 28 days following the study injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 8.11.1.
- AEs leading to discontinuation from study participation from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study.
- MAAEs from Day 1 through Day 361(Month 12)/EoS or withdrawal from the study. Medically attended AEs are defined in Section 8.11.4.
- SAEs (Section 8.11.2) and AESIs (Section 8.11.6) from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study.
- Details of all pregnancies in female participants will be collected after the start of study vaccine and until the end of their participation in the study (Section 8.11.7). All pregnancies must be followed to determine the outcome.

8.9.1 Pregnancy Screen and Testing

A pregnancy test via blood or point-of-care urine test will be performed for all female participants of childbearing potential 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. Additional pregnancy testing during the study may also be performed if required by local regulatory requirements. The participant's FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the investigator, to confirm postmenopausal status (Section 11.2).

Further details on reporting and follow-up of pregnancy are provided in Section 8.11.7.

8.9.2 Assessments for Respiratory Viral Infections

The NP swab specimen(s) for pathogens, including influenza virus and SARS-CoV-2, will be collected any time from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined ILI or symptoms suggestive of COVID-19 or other upper or lower respiratory infection, as defined in the ILI Case Definitions (Section 8.11.5). If participants experience these signs or symptoms, they will be instructed to contact the clinic to have an NP swab collected for testing. Nasopharyngeal swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza and/or SARS-CoV-2 testing results performed outside of the study should be captured.

Symptoms reporting for ILI will be conducted between Day 1 through Day 361 (Month 12)/EoS as described in Section 8.9.4.

All RT-PCR-confirmed influenza (Section 8.11.5) and RT-PCR-confirmed symptomatic COVID-19 infections will be recorded as MAAEs along with relevant concomitant medications, hospitalizations, outpatient medical care, and details about severity, seriousness, and outcome. Asymptomatic RT-PCR-confirmed COVID-19 infections are not to be recorded as MAAEs.

8.9.3 Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls will follow a schedule for each participant, as shown in the SoE (Table 1). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to withdrawal from study participation, concomitant medications associated with those events, and any non-study vaccinations (Section 8.11.14). All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone contact. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

8.9.4 Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary using either an application downloaded to their own device or using a device that is provided at the time of enrollment. Before enrollment on Day 1, the participants will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 8.11.3). Participants will also use the eDiary to record any ILI symptoms (as part of active surveillance) that they experience after vaccination from Day 1 through Day 361 (Month 12)/EoS.

Participants will be instructed on Day 1 on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment of localized axillary swelling or tenderness on the same side as the injection arm.

Participants will record data into the eDiary starting approximately 30 minutes after injection under supervision of the clinic staff to ensure successful entry of assessments. The clinic staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection, and for 6 days following injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic ARs, as defined in Section 8.11.3, that occur on the day of vaccination and during the 7 days after vaccination (ie, the day of injection and 6 subsequent days).
- Symptom reporting of ILI. Participants will be instructed to report via Symptom Reporting eDiary or by contacting the site if ILI symptoms have been experienced from Day 1 to Day 361 (Month 12)/EoS. If symptoms are reported, the investigator must contact the participant to assess symptoms and ensure an NP swab is collected within 72 hours of symptom onset. If possible, NP swabs should be collected prior to initiation of antiviral therapy. If there is no response to an eDiary prompt for 2 consecutive entries, the clinic staff will attempt to contact the participant by telephone call (Section 8.9.2).

- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the clinic. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler provided by the clinic.
- Any medications taken to treat or prevent pain or fever on the day of injection and for the next 6 days.
- Patient-reported outcome questionnaires, as defined in Section 8.17. All participants will receive eDiary prompts to complete the EQ-5D-5L questionnaire on Day 1, Day 91, Day 181, Day 271, and Day 361 (Month 12)/EoS, and participants who report symptoms of ILI will receive eDiary prompts to complete EQ-5D-5L and WPAI:ILI questionnaires.

The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of the solicited ARs.

Clinic staff will review eDiary data with participants at a visit 7 days after the injection.

8.9.5 Blood Sampling Volumes

The maximum planned volumes of blood sampled per participant will not exceed 450 mL for the complete study.

8.9.6 Ancillary Supplies for Participant Use

Clinics will distribute Sponsor-provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions, for recording solicited ARs in the eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

8.10 Clinical Assessments

Participants who develop symptoms consistent with protocol-defined ILI (Section 8.11.5) and/or COVID-19 will have NP swabs collected for testing. The initial test will be a real-time, RT-PCR-based assay, to determine if either influenza A and/or B strains, as well as other respiratory viruses such as SARS-CoV-2, are present in the clinical sample. For samples that test positive for influenza in the RT-PCR assay, further testing by PCR-based genetic sequencing of the HA segments and/or other influenza virus genes may be performed to identify the specific subtype of the influenza strain. The RT-PCR positive samples may be cultured. Cultured viruses may be used to evaluate similarity (match) to the current year's vaccine strains using ferret

antisera to determine antigenic similarity to vaccine strains. See Section 8.11.5 for how to capture these illnesses.

8.11 Safety Definitions

8.11.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug/vaccine in humans, whether or not considered related to the drug/vaccine.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to IP or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, after the IP injection
- New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study

Events NOT Meeting the Adverse Event Definition

- Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure)
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

An AR is any AE for which there is a reasonable possibility that the IP caused the AE (Section 8.11.3). For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study vaccine and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol; is specified as a solicited AR in the protocol; or is specified as a solicited AR in the protocol but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after each dose of IP).

8.11.2 Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator

during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to IP.

- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.11.3 Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs

using a structured checklist (Section 8.9.4). Participants will record such occurrences in an eDiary on the day of each IP injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entries into the eDiary according to the grading scales presented in Table 5, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b).

If a participant reported a solicited adverse reaction during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity page of the eCRF.

If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event on the Reactogenicity page of the eCRF. If the participant reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF. All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 5: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[1] (Life-threatening)
Local					
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Any use of prescription pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic					

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[1] (Life-threatening)
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	> 40.0°C > 104.0°F

Grading of Grade 4 events will be determined per investigator and assessment is recorded on the reactogenicity event page in the electronic case report form.

Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator. Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b).

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

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

8.11.4 Medically Attended Adverse Events

An MAAE is an AE that leads to an unplanned visit to a HCP for medical evaluation (examinations/testing) and/or treatment that is not required per study protocol. The visit may be with an HCP at the clinical trial site or at another facility (eg, medical office, urgent care, emergency room). Investigators will review all AEs for the occurrence of MAAEs.

In addition, all RT-PCR–confirmed influenza and RT-PCR–confirmed symptomatic COVID-19 infections will be recorded as MAAEs and reported on the participant's AE eCRF from Day 1 through the EoS.

8.11.5 Influenza-like Illness Case Definitions

Protocol-defined ILI

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

Table 6: Respiratory and Systemic Symptoms for Protocol-defined Influenza-like Illness

Respiratory symptoms	Systemic symptoms
1. Sore throat 2. Cough/rhinorrhea/nasal congestion (≥1 of the 3 symptoms count as 1 respiratory symptom) 3. Sputum production 4. Wheezing	1. Body temperature > 37.2°C [> 99°F] 2. Chills 3. Tiredness 4. Headache 5. Myalgia 6. Nausea/vomiting

Respiratory symptoms	Systemic symptoms
5. Difficulty breathing	7. Diarrhea

CDC-defined ILI

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

RT-PCR-confirmed Protocol-defined Influenza Infection

An RT-PCR-confirmed protocol-defined influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR performed at the Global Central Laboratory and/or a local certified laboratory within 7 days of onset of protocol-defined ILI symptoms at any time during the study period.

RT-PCR–confirmed CDC-defined Influenza Infection

An RT-PCR–confirmed CDC-defined influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR performed at Global Central Laboratory and/or a local certified laboratory within 7 days of onset of CDC-defined ILI symptoms at any time during the study period.

Through Day 28, any illness assessed for protocol-defined ILI/suspected SARS-CoV-2 and reports of asymptomatic RT-PCR–confirmed COVID-19 events should be captured as an AE in the AE eCRF. Starting on Day 29, asymptomatic COVID-19 events should no longer be captured as AEs, and illnesses assessed for protocol-defined ILI/suspected SARS-CoV-2 should only be captured as AEs if they have RT-PCR–confirmed influenza or RT-PCR–confirmed symptomatic COVID-19 infections (must be recorded as MAAEs), or if they otherwise meet the criteria for reporting as an SAE (Section 8.11.2), MAAE (Section 8.11.4), or event leading to discontinuation from the study. An event should not be recorded as an MAAE based on visits to the clinical trial site for protocol-required assessment of ILI symptoms and NP swab collection.

8.11.6 Adverse Event of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the Sponsor are required. Such events may require further investigation to characterize and understand them.

AESI for this protocol are described in Section 11.3.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the electronic data capture system. If a site received a report of a new AESI from a participant or receives updated information on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on the paper SAE/AESI form provided using the SAE Mailbox.

Anaphylaxis

All suspected cases of anaphylaxis should be recorded as MAAEs and AESIs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, per Section 8.11.12. The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitive reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:
  - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes
  - **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation
  - **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea
  - **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting

Myocarditis/Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC Working Case Definitions. The event should also be reported as an SAE if it meets seriousness criteria (see Section 8.11.2).

An independent Cardiac Event Adjudication Committee (CEAC) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for “probable” or “confirmed” events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study vaccine assignment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

The CDC Working Case Definitions are provided in Section 11.4 as guidance.

8.11.7 Recording and Follow-up of Pregnancy

The effects of mRNA-1010 on the unborn child and on the newborn baby are not known. Because of this, it is important that research study participants are not pregnant and do not become pregnant during the course of the research study. Female individuals who have a positive pregnancy test at the Screening Visit should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with IP but should remain in the study and be followed-up for safety. Pregnancy testing is scheduled to occur at the Screening Visit and Day 1 (Table 1). Additional pregnancy testing during the study may also be performed if required by local regulatory requirements.

Details of all pregnancies in female participants will be collected after the start of study vaccine and until Day 361 (Month 12)/EoS.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to the Sponsor or designee within 24 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the clinic to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

8.11.8 Recording and Follow-up of an AE and/or SAE

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected from Day 1 through 7 days after the vaccine dose (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected from Day 1 through 28 days after the vaccine dose (ie, the day of injection and 27 subsequent days).

Medically attended AEs, SAEs, and AESIs will be collected from participants as specified in the SoE (Table 1) from Day 1 until the end of their participation in the study.

At every clinic visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including surveillance for respiratory viral infection symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any non-study vaccinations.

In addition to participant observations, physical examination findings and other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.2).

8.11.9 Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.11.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.11.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Clinic staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.11.10 Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

8.11.11Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes, type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Medical occurrences that begin before the start of IP administration but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; However, if the condition worsens at any time after IP administration, it will be recorded and reported as an AE.

8.11.12Reporting Serious Adverse Events

Any AE considered serious by the investigator or that meets SAE criteria (Section 8.11.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as required per applicable regulations. The investigator is responsible for notifying the institutional review board (IRB) or independent ethics committee (IEC) directly.

If the eCRF is unavailable at the time of the SAE, the SAE/AESI paper form provided by the Sponsor is to be used for SAE reporting.

Regulatory reporting requirements for SAEs are described in Section 8.11.16.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the participant to discontinue the study.

8.11.13Time Period and Frequency for Collecting AE and SAE Information

Medical occurrences that begin before the start of IP administration but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time after IP administration, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant
- Questioning the participant in an unbiased and nonleading manner

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of becoming aware of the event, as indicated in Section 8.11.2. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (EoS). However, if an investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and considers the event to be reasonably related to the study IP or study participation, the investigator must promptly notify the Sponsor.

8.11.14Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. At the time of consent, the participants must confirm they will be willing to complete the eDiary via an application downloaded to their smartphone or via a device that is provided at the time of enrollment. Prior to enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of vaccination group or suspected causal relationship to the IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE or AESI requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.11.15Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All AEs, SAEs, and AESIs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.2).

8.11.16Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.12 Safety Oversight

Safety monitoring for this study will include the blinded study team members, inclusive of at a minimum, the Sponsor medical monitor and CRO medical monitor, as well as safety reviews by an unblinded DSMB. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the DSMB of potential safety signal events. The DSMB, composed of external, independent subject matter experts, including an unblinded statistician, will conduct unblinded reviews of safety data on a periodic basis, as defined in a DSMB charter, or as otherwise requested by the study team.

8.13 Treatment of Overdose

As the study vaccine is to be administered by a healthcare professional, it is unlikely that an overdose will occur.

However, in the event of an overdose, the investigator should:

1. Contact the Medical Monitor SAE Hotline immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the last safety follow-up visit.
3. Report any signs or symptoms associated with the overdose as an AE and record details in the relevant AE/SAE sections in the eCRF.
4. Document the quantity of the excess dose in the eCRF.

8.14 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study**.**

8.15 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.16 Biomarkers

Biomarker assessments (to be determined) will be evaluated as part of the study, which may include genomic and transcriptomic studies. Optional blood collections for DNA and mRNA sequencing will be performed and may be used for potential biomarker research. Samples for humoral immunogenicity on Day 181 and 361 (Month 12)/EoS will be collected and assessed in a subset, which will require a clinic visit on those days.

8.17 Patient -reported Outcomes and Medical Resource Utilization

Exploratory objectives related to patient-reported outcomes (PROs) and medical resource utilization are listed in Section 3.

Patient-reported outcomes and medical resource utilization associated with symptoms of ILI will be assessed at time points specified in the SoE (Table 1).

Concomitant medication use collection is detailed in Section 6.5.1.

8.17.1 Patient-reported Outcome Measures

Patient-reported outcome measures will include the following questionnaires: EQ-5D-5L scale, WPAI:ILI, and the EFS.

EQ-5D-5L

The EQ-5D-5L consists of both the EQ-5D descriptive system questionnaire and the EQ visual analogue scale (EQ-VAS).

For all participants, the EQ-5D-5L will be collected by eDiary at Day 1 (Baseline), Day 91, Day 181, Day 271, and Day 361 (Month 12)/EoS. For participants reporting ILI symptoms, the EQ-5D and EQ-VAS will be collected using the eDiary on the day of the symptoms reporting (+1 day) and 5 days (+1 day) later.

WPAI:ILI

The participant will be prompted to report productivity or activity impairment related to their ILI symptoms. For participants reporting ILI symptoms, the WPAI over the previous 7 days will be collected by eDiary 5 days (+1 day) after the start of ILI symptoms reporting. The list of the ILI symptoms that is part of their reporting of symptoms is the specific health problem to be considered.

Edmonton Frail Scale

The EFS will be collected for participants aged 65 years and older at Day 1 (Baseline) by clinic staff.

8.17.2 Medical Resource Utilization

Hospitalization

Where hospital stay information is available (new hospitalization or prolongation of existing hospital stay), the following information will be collected for confirmed influenza cases from SAE and MAAE reports:

- Admission date
- Discharge date
- Intensive care unit stay (yes or no)

Outpatient Medical Resource Utilization

For participants reporting MAAEs, outpatient medical resource utilization will be collected, where available. Options provided are: outpatient/physician visit; emergency room/urgent care visit; and telemedicine visit.

9. STATISTICAL CONSIDERATIONS

9.1 Blinding and Responsibility for Analyses

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

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the IP for all participants. These personnel will have no study functions other than IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded clinic personnel will administer the IP. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned primary analysis and the 6-month analysis (Section 9.6). Sponsor team members will be prespecified to be unblinded to the primary analysis and the 6-month analysis results and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants.
- The DSMB may review data, as appropriate, to safeguard the interests of clinical study participants and to help ensure the integrity of the study.

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

Procedures for breaking the blind in the case of a medical emergency are provided in Section 6.3.7.

9.2 Statistical Hypotheses

The null hypothesis H^1_0: immunogenicity response to mRNA-1010, as measured by GMT or by seroconversion rate at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for A strains (ie, H1N1, H3N2). Four coprimary immunogenicity endpoints will be tested for noninferiority of mRNA-1010 vs. active comparator for A strains at a two-sided 0.025 level.

The null hypothesis H^2_0: immunogenicity response to mRNA-1010, as measured by GMT or by seroconversion rate at Day 29 using HAI assay, is inferior compared to that in participants who received the active comparator for B strains (ie, B/Victoria, B/Yamagata). Four coprimary immunogenicity endpoints will be tested for non-inferiority of mRNA-1010 vs. active comparator for B strains at a two-sided 0.025 level.

At Day 29, for each individual influenza virus strain,

- The noninferiority in GMT in participants who received mRNA-1010 compared to that of participants who received the active comparator will be demonstrated by the lower bound of the 97.5% confidence interval (CI) of the GMT ratio (geometric mean ratio [GMR]) ruling out 0.667 (lower bound > 0.667) using a noninferiority margin of 1.5. The GMR is the ratio of the GMT of HAI titer in those receiving mRNA-1010 compared with the GMT of those receiving the active comparator.
- The noninferiority in seroconversion rate in the mRNA-1010 group compared to that of the active comparator group will be demonstrated by the lower bound of the 97.5% CI of the seroconversion rate difference (mRNA-1010 vs. active comparator) ruling out -10% (lower bound > -10%) using a noninferiority margin of 10%.

The success criteria of non-inferiority for A strains are met if H^1_0 is rejected at two-sided 0.025 level on all four co-primary endpoints. Similarly, the success criteria of non-inferiority for B strains are met if H^2_0 is rejected at two-sided 0.025 level on all four co-primary endpoints.

Once the noninferiority success criteria of the coprimary endpoints for A strains are met, the following endpoints will be tested in a sequential order to support secondary objectives:

The following endpoints will be tested at a two-sided α_1=5% level if noninferiority is demonstrated for both A and B strains; and at a α_1=2.5% level if non-inferiority is only demonstrated for A strains.

The null hypothesis H^3_0: immunogenicity response to mRNA-1010 compared to that in participants who received the active comparator, as measured by GMR at Day 29 using HAI assay, is ≤ 1 for each individual A strain (H1N1 and H3N2). The superiority in GMT in participants who received mRNA-1010 compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α) CI of the GMR ruling out 1 (lower bound > 1) for both individual A strains.

Once the success criteria of hypothesis H^3_0 are met, the next null hypothesis to be tested is H^4_0: immunogenicity response to mRNA-1010 compared to that in participants who received the active comparator, as measured by GMR at Day 29 using HAI assay, is ≤ 1.5 for each individual A strain (H1N1 and H3N2). The super-superiority in GMT in participants who received mRNA-1010 compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α) CI of the GMR ruling out 1.5 (lower bound > 1.5) for both individual A strains.

If the success criteria of hypothesis H^4_0 are met, the last null hypothesis to be tested is H^5_0: immunogenicity response to mRNA-1010 compared to that in participants who received the

active comparator, as measured by seroconversion rate difference at Day 29 using HAI assay, is ≤ 10% for each individual A strain (H1N1 and H3N2). The super-superiority of seroconversion rate in the mRNA-1010 group compared to that in the active comparator group will be demonstrated by the lower bound of the (100%- α) CI of the seroconversion rate difference ruling out 10% (lower bound > 10%) for both individual A strains.

9.3 Sample Size Determination

With approximately 3000 participants exposed to IP in the mRNA-1010 group, the study has an approximately 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate.

Assuming approximately 15% of randomized participants will be excluded from the PP Immunogenicity Set, with approximately 5100 participants in the PP Immunogenicity Set (1:1 ratio; approximately 2550 in each vaccine group), the study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by the GMT in participants receiving mRNA-1010 compared with that in the active comparator group, at a 2-sided 0.025 level, assuming an underlying GMR of 0.9 in all 4 strains and a noninferiority margin of 1.5. The standard deviation of the natural log-transformed levels is assumed to be 1.5.

The study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by seroconversion rate in the mRNA-1010 group compared with that in the active comparator group, at a 2-sided 0.025 level, assuming a seroconversion rate of 70% in influenza A strains and 60% in influenza B strains, respectively, in the mRNA-1010 group (a true rate difference is 0 compared to the active comparator group), and a noninferiority margin of 10%.

9.4 Analyses Populations

The analysis sets are defined in Table 7.

Table 7: Populations for Analyses

Population	Description
Randomization Set	All participants who are randomly assigned to treatment, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All participants randomly assigned to treatment who received any study vaccination. Participants will be analyzed according to the group to which they were randomized.

Population	Description
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who provide any follow-up for ILI beginning at least 14 days following administration of study intervention. Participants will be analyzed according to the group to which they were randomized.
PP Set for Efficacy	A subset of participants in the mITT Set who do not have significant protocol deviations that could adversely impact efficacy, eg, disease or therapeutic intervention that might cause suboptimal response to the study intervention. Participants will be analyzed according to the group to which they were randomized.
Immunogenicity Set	All participants in the FAS who have baseline and Day 29 antibody assessment via HAI assay. Participants will be analyzed according to the group to which they were randomized.
PP Immunogenicity Set	The PP Immunogenicity Set includes all participants in the Immunogenicity Set who received planned dose of IP, complied with the immunogenicity testing schedule, and had no major protocol deviations that impact key or critical data. Participants with RT-PCR-confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity Set. The PP Immunogenicity Set will be used for all analyses of immunogenicity unless specified otherwise. Participants will be analyzed according to the group to which they were randomized.
Solicited Safety Set	All randomized participants who received any study vaccination and contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs, and participants will be included in the vaccination group corresponding to the vaccination that they actually received.
Safety Set	All participants randomly assigned to treatment who received any study vaccination. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the IP that they actually received.

Abbreviations: AR = adverse reaction; IP = investigational product; PP = Per-protocol; RT-PCR = reverse transcription polymerase chain reaction.

9.5 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the pre-planned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1 Immunogenicity Analyses

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

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

An analysis of covariance model (ANCOVA) will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, vaccination group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The geometric least square mean (GLSM), and its corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale, as an estimate of the GMT. GMR, estimated by the ratio of GLSM and the corresponding 2-sided 97.5% CI will be provided to assess the treatment difference. The corresponding 2-sided 97.5% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 compared to the active comparator group at Day 29. For each strain, the noninferiority of GMT will be considered demonstrated if the lower bound of the 97.5% CI of the GMR is > 0.667 based on a noninferiority margin of 1.5.

The number and percentage of participants with seroconversion due to vaccination will be provided with 2-sided 95% CI using the Clopper-Pearson method at Day 29. To compare the seroconversion rates between the vaccination groups, the Miettinen-Nurminen's method will be used to calculate the 97.5% CI for the difference in seroconversion rates. The seroconversion rate difference with the corresponding 97.5% CI at Day 29 will be provided. For each strain, the noninferiority of seroconversion rate will be considered demonstrated if the lower bound of the 97.5% CI of the seroconversion rate difference is > -10% based on a noninferiority margin of 10%.

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

Subgroup analysis for the coprimary immunogenicity endpoints will be conducted as appropriate.

Once the noninferiority success criteria are met for A strains, superiority of mRNA-1010 relative to the active comparator for A strains may be further evaluated. More details about the testing sequence can be found in Section 9.6.2.

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

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

For summarizations of GMTs, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

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

9.5.2 Efficacy Analyses

The primary analysis population of efficacy is the mITT Set.

To evaluate the incidence of first episode of RT-PCR-confirmed protocol-defined ILI after vaccination with mRNA-1010 or the active comparator, the incidence rate will be calculated as the number of participants with a case (ie, first occurrence of ILI at least 14 days after the study injection through Day 181/end of influenza season) divided by the number of participants at risk adjusted by person-time (years). The person-time is calculated as the time from randomization to the date of the first episode for participants with a case, or the time from randomization to the date of discontinuation or death or Day 181/end of influenza season, whichever occurs first, for participants without a case. Person-time, incidence rate, and 95% CI for incidence rate will be provided by vaccination group. Relative vaccine efficacy will be estimated by 1- ratio of incidence rate (mRNA-1010 vs. active comparator) adjusting for person-time, and the 95% CI will be computed using the exact method conditional upon the total number of cases adjusting for person-time.

Sensitivity analyses may be performed on the PP Set for Efficacy.

RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed CDC-defined ILI in participants aged 50 years and older or 65 years and older will be analyzed similarly.

9.5.3 Safety Analyses

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. Participants will be included in the vaccination group corresponding to what they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, and AEs leading to discontinuation.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7-day follow-up period after the injection will be summarized. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation will be summarized. Unsolicited AEs will be coded according to the MedDRA and presented by MedDRA system organ class and preferred term.

Solicited ARs will be coded by system organ class and preferred term according to the MedDRA for AR terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b) will be used in this study with modification for rash, solicited ARs, and vital signs.

The number of events of unsolicited AEs, SAEs, AESIs, and MAAEs will be reported in summarization tables accordingly.

Table 8 summarizes the analysis strategy for safety parameters. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Table 8: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	X	X
Any unsolicited AE	X	–
Any SAE	X	–
Any unsolicited MAAE	X	–
Any unsolicited AESI	X	–
Any unsolicited treatment-related AE	X	–
Any treatment-related SAE	X	–
Any unsolicited AE leading to withdrawal from study participation	X	–
Any severe unsolicited AE	X	–
Any treatment-related severe unsolicited AE	X	–

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; SAE = serious adverse event.
Note: 95% CI using the Clopper-Pearson method. X = results will be provided.

9.5.4 Exploratory Analyses

Any protocol-defined and/or CDC-defined ILI cases will be presented by vaccination group.

The number and percentage of participants aged 65 years and older with first episode of protocol defined ILI will be presented by baseline frailty status for each vaccination group.

Analyses of the other exploratory endpoints will be described in the SAP.

9.6 Planned Analyses

9.6.1 Interim Analyses

The primary analysis of safety and immunogenicity will be performed after all participants have completed the Day 29 visit. All data relevant to the primary study analysis through the Day 29

visit will be cleaned and locked for the primary analysis (ie, data that are as clean as possible) and a report may be generated.

A 6-month analysis may be performed once all participants complete the Day 181 Visit or the influenza season ends, whichever occurs later. All of safety, immunogenicity, and efficacy data will be cleaned and locked for the analysis. Additional safety analyses at other time points may be performed.

The above 2 analyses will be performed by a separate team of unblinded programmers and statisticians. More details can be found in the study data blinding plan.

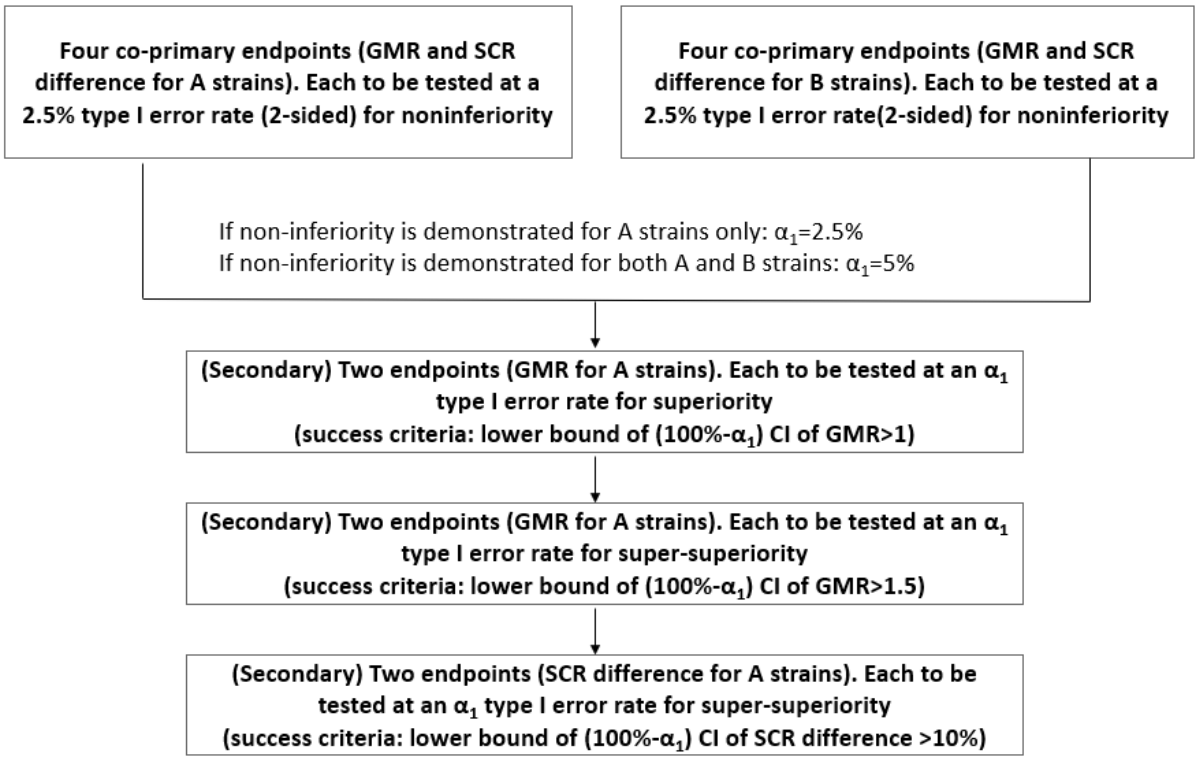
Final analysis of all safety, immunogenicity and efficacy data will be performed once all participants complete the Day 361 (Month 12)/EoS Visit.

The SAP will describe the planned analyses in greater detail.

9.6.2 Multiplicity

To control the overall Type I error for the study, a hierarchical testing strategy will be used to test the primary and secondary immunogenicity objectives (Figure 1).

Figure 1: Testing Sequence of the Primary and Secondary Objectives



At the first step in the testing sequence as demonstrated in Figure 1, the noninferiority of mRNA-1010 compared with active comparator for A strains and for B strains will be tested at a type I error rate of 2.5% (2-sided) respectively.

If noninferiority is demonstrated for A strains only at the first step, the superiority testing for A strains will be tested following the order of testing sequency at a type I error rate of 2.5% (2-sided).

If non-inferiority is demonstrated for both A and B strains at the first step, the type I error rate for the following test will be 5% (2-sided).

The testing sequence can only continue to the next level if the tests at the higher level meet the success criteria (as specified in Section 9.2). If a test at the higher level fails to meet the success criteria for that level, the testing sequence will stop, and all testing thereafter will not be conducted.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 APPENDIX 1: Study Governance Considerations

11.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.1.2 Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Moderna or its representatives will visit the investigational clinic to:

- Determine the adequacy of the facilities.

- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Moderna or its representatives. This will be documented in a Clinical Study Agreement between Moderna, designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and Moderna in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB/IEC review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from Moderna or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.1.3 Audits and Inspections

Moderna, their designee(s), the IRB/IEC, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow Moderna, their designee(s), the IRB/IEC, or regulatory

authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of Moderna, a regulatory authority, and any IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements. The investigator should contact Moderna immediately if contacted by a regulatory agency about an inspection.

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study, including the participant consent form and recruitment materials, must be maintained by the investigator and made available for inspection.

11.1.4 Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the clinic are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the clinic are not financially responsible for further treatment of the disease under study.

11.1.5 Recruitment Strategy

Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate.

Participant recruitment and retention initiatives will be incorporated into the trial. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical trial sites, participant support services such as concierge, and trial information and support collateral for both the participant and the site. Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant, should be submitted to the Sponsor for approval. All documents must be approved by the IRB/IEC.

11.1.6 Informed Consent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center. All consent documents will be approved by the appropriate IRB/IEC. The actual ICF used at each center may differ, depending on local regulations and IRB/IEC requirements. However, all versions must contain the standard

information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB/IEC prior to the form being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him or her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his or her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate.

The participant must be made aware of and give consent to direct access to his or her source medical records by study monitors, auditors, the IRB/IEC, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant should also be informed that he or she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial screening period).

The ICF will contain a separate consent form(s) that addresses the use of remaining optional samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. A participant will be told that they are free to refuse participation and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document agreement to allow any remaining specimens to be used for exploratory research. A participant who declines to participate in this optional research will not provide this separate signature.

11.1.7 Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s)/IEC(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed to by the investigator(s), and approved by the relevant IRB(s)/IEC(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s)/IEC(s) must be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigator(s), and notified to the IRB(s)/IEC(s).

11.1.8 Protocol Deviations

The noncompliance may be either on the part of the participant, the investigator, or the clinic staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within in a timely manner of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Sponsor and the study medical monitor. Protocol deviations must be sent to the reviewing IRB/IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements.

11.1.9 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his or her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his or her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

- The contract between the sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

11.1.10 Sample Retention and Future Biomedical Research

Samples may be used for purposes related to this research. The samples may be stored until the study team has determined that specimens are no longer needed, and the decision has been made that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the participant.

These samples could be used to address further scientific questions related to mRNA-1010 or anti-respiratory virus immune response, to research the complications associated with influenza and other conditions for which individuals with influenza are at increased risk, and to improve treatment. During the study or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity to seasonal influenza to include humoral and cellular immune assay methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. A decision to perform such exploratory research may arise from new scientific findings related to the drug/vaccine class or disease, as well as reagent and assay availability.

11.1.10.1 Data and Safety Monitoring Board

A DSMB will be used throughout the conduct of this study. The DSMB will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. The data to be reviewed will be unblinded. Safety data will be reviewed according to intervals defined in the DSMB charter and as needed if potential safety concerns are identified.

11.1.10.2 Dissemination of Clinical Study Data

Moderna shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), etc., as well as some national registries.

11.1.11 Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed, and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

11.1.12 Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the investigational site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using the WHO-drug reference list.

11.1.13 Source Documents

Source documents are original documents or certified copies and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent/assent forms, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the case report form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Moderna or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts and the signed ICFs are to be included in the investigator's files with the participant's study records.

11.1.14 Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from

any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for Moderna or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.15 Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the clinic or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate clinic closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a clinic by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further mRNA-1010 development.

Clinics will be closed upon study completion. A clinic is considered closed when all required documents and study supplies have been collected and a clinic closure visit has been performed.

11.1.16 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to Moderna.

11.2 APPENDIX 2: Contraceptive Guidance

Definitions: Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

A **postmenopausal state** is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods (for the purpose of this study) include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- Documented tubal ligation
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of a regulatory agency-approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap)
- Intrauterine device

- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

11.3 APPENDIX 3: Adverse Events of Special Interest

Investigators should report all events which fall into the categories presented in Table 9 as an AESI per the reporting processes specified in Section 8.11.6. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines.

Table 9: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150 x 10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
New onset of or worsening of the following neurologic diseases	• Guillain-Barre syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per protocol (Section 0) • Following reporting procedures in Section 8.11.6
Myocarditis/pericarditis	• Myocarditis • Pericarditis • Myopericarditis

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

11.4 APPENDIX 4: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 10 as guidance.

Table 10: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
	Probable Case	**Confirmed Case**
Acute myocarditis	Presence of ≥ 1 new or worsening of the following clinical symptoms:* • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope **OR** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • Irritability • Vomiting • Poor feeding • Tachycardia • Lethargy **AND** ≥ 1 new finding of: • Troponin level above upper limit of normal (any type of troponin) • Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§ • Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis	Presence of ≥ 1 new or worsening of the following clinical symptoms:* • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope **OR** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • Irritability • Vomiting • Poor feeding • Tachycardia • Lethargy **AND** ≥ 1 new finding of: • Histopathologic confirmation of myocarditis† • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	AND • No other identifiable cause of the symptoms and findings	**AND** • No other identifiable cause of the symptoms and findings

Condition	Definition	
	Probable Case	Confirmed Case
Acute pericarditis**	Presence of ≥ 2 new or worsening of the following clinical features: • Acute chest pain†† • Pericardial rub on examination • New ST-elevation or PR-depression on EKG • New or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Abbreviations: CDC = Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

Note: An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study vaccine assignment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† Using the Dallas criteria (Aretz et al 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of: 1) ST-segment or T-wave abnormalities; 2) paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) atrioventricular nodal conduction delays or intraventricular conduction defects.

¶ Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon
** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Reference: Gargano et al 2021.

11.5 APPENDIX 5: Protocol Amendment History

11.5.1 Amendment 1, 10 Feb 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Main Rationale for the Amendment:

The main rationale for this amendment is to enhance clarity and implement additional protocol administrative corrections.

The summary of changes table provided below describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol. Minor grammar and formatting corrections were made throughout the document to enhance clarity and readability (which did not affect the conduct of the study).

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Global	Changed “active surveillance” to “Symptom Reporting eDiary”.	To enhance clarity.
1.1 Protocol Synopsis	Changed “April 2022” to “May 2022” for first participant in and “June 2022” to “July 2023” for the estimated date last participant completed.	To correct an administrative error.
1.1 Protocol Synopsis	Changed “ruling out 10% (lower bound > 10%)” to “ruling out -10% (lower bound > -10%)” for the noninferiority in seroconversion rate. Note: The negative sign was also added to > 10% in the Immunogenicity Analyses section of the synopsis.	To correct an administrative error in statistical analysis.
1.1 Protocol Synopsis, 4.1 General Design, and 6.1 Investigational Product and Active Comparator Administered	Updated the 2022 Southern Hemisphere strains.	To reflect the actual formulation of mRNA-1010.
1.1 Protocol Synopsis, 4.1 General Design, and 6.2 Randomization and Blinding	Added “at the time of screening” to the stratification factors.	To enhance clarity.

1.1 Protocol Synopsis, 4.1 General Design, and 6.2 Randomization and Blinding	Changed “and” to “including”.	To enhance clarity.
1.1 Protocol Synopsis, 4.1 General Design, 8.9.2 Assessments for Respiratory Viral Infections, and 8.9.4 Use of Electronic Diaries	Removed passive surveillance from the protocol. Participants will be instructed to contact study sites if they have ILI symptoms outside the Symptom Reporting eDiary period.	To improve compliance in eDiary reporting. By removing passive surveillance, prompts for the participants to complete the Symptom Reporting eDiary can be programmed.
1.1 Protocol Synopsis, 1.2 Schedule of Events (SoE), 4.1 General Design, and 8.9.4 Use of Electronic Diaries	Changed active surveillance/Symptom Reporting eDiary from: • 3 to 4 times weekly from Day 1 to Day 29 and twice weekly from Day 91 to Day 361/EoS to once weekly from Day 1 to Day 361	To reduce participant fatigue and improve compliance in eDiary reporting.
1.1 Protocol Synopsis and 5.2 Exclusion Criteria	For exclusion criterion 1: • Changed requirement for no close contact with someone with SARS-CoV-2 infection from 14 to 10 days and removed the stipulation about being fully vaccinated. • Removed the requirement for absence of confirmed SARS-CoV-2 infection 30-180 days prior to enrollment.	To reflect the changing COVID-19 landscape and transmissibility of new variants as well as new Center for Disease Control and Prevention guidance on SARS-CoV-2.
1.1 Protocol Synopsis and 5.2 Exclusion Criteria	Added exclusion of participants who is not aware if they have received an influenza vaccine in the past 12 months.	To allow stratification at randomization by influenza vaccine status.
1.1 Protocol Synopsis and 8.11.5 Influenza-like Illness Case Definitions	• Changed “Influenza-like Illness” to “Influenza-like Infection” for the definition of RT-PCR confirmed. • Added “respiratory sample” and “within 7 days of onset of protocol-defined ILI”.	• To correct an error. • To enhance clarity.
1.1 Protocol Synopsis and 9.4 Analyses Populations	• Added a statement that the selection for the Immunogenicity Subset can	• To enhance clarity.

	be found in a detailed sampling plan. • Deleted the statement that the selection for the PP Immunogenicity Subset can be found in a detailed sampling plan.	
1.1 Protocol Synopsis and 9.5.1 Immunogenicity Analyses	Deleted redundant text on the noninferiority criteria in the Immunogenicity Analyses section of the synopsis.	To enhance clarity.
1.1 Protocol Synopsis and 9.3 Sample Size Determination	Reduced the sample size for immunogenicity analyses from 4,000 to 3,000 (2,000:1,000 mRNA-1010:active comparator).	Due to a revisit of the secondary endpoints.
9.5.1 Immunogenicity Analyses	Added that HAI titer ≥ 1:40 post-injection due to vaccination will be provided with 2 sided 95% CI using the Clopper Pearson method	To correct an omission.
1.2 SoE	Deleted Screening from the SoE for: 1) Recording of SAEs/AESIs and concomitant medications relevant to or for the treatment of SAEs/AESIs; 2) Recording of concomitant medications and nonstudy vaccinations; and 3) Recording of hospitalizations and outpatient treatment-related to or for the treatment of the MAAE or SAE to reflect these will be captured beginning with Day 1.	To correct an error.
1.2 SoE, 4.2 Scientific Rationale for Study Design, and 8.9.2 Assessments for Respiratory Viral Infections	Added that in the event that NP swabs during ILI cannot be collected, any available influenza and/or SARS-CoV-2 testing results performed outside of the study should be captured in the eCRF.	To capture all instances of influenza/SARS-CoV-2 infections.
1.2 SoE and 8.9.4 Use of Electronic Diaries	Changed the time frame for reporting eDiary entries from “1 hour” to “30 minutes” after injection.	To be consistent with other Phase 3 studies.

1.2 SoE and 8.17.1 Patient-reported Outcome Measures	Adapted the timing of eDiary prompts for participants reporting the symptoms of ILI: • For EQ-5D-5L from prompting on the day of the report and 7 and 14 days after (±1 day window for all time points) to on the day of report (+1 day) and 5 days (+1 day) after. • For WPAI from prompting on day 7 and 14 (±1 day window for both time points) after the report to only 5 days (+1 day) after.	To get QOL data with immediacy for any ILI event but to avoid generation of multiple QOLs appearing on a given calendar day.
1.2 SoE, 8.9.1 Pregnancy Screen and Testing, and 8.11.7 Recording and Follow-up of Pregnancy	Added that a point-of-care blood or urine pregnancy test will be performed at the Screening Visit and that additional pregnancy testing may be performed if required by local regulatory requirements.	To specify that local regulatory requirements regarding pregnancy testing should be followed.
2.2.3 Clinical Studies, 4.1 General Design, and 4.3 Justification for Dose, Control Product, and Choice of Study Population	• Added text on vaccination with mRNA-1010 on antibodies. • Added text on the planned Phase 2 extension study. • Added text on the interim data in the Northern Hemisphere from a Phase 2 study.	To add supportive data.
6.3.3 Clinical Study Material Packaging and Labeling	Changed the fill volume from 0.8 mL to 0.7 mL.	To correct an error.
6.3.4 Clinical Study Material Storage	Added a statement on storage conditions at the depots and during shipping.	To provide additional details.
11.2 Appendix 2: Contraception Guidance	Updated the definition of “women of childbearing potential” and the definition of “nonchildbearing potential”.	To align with the updated protocol template text.
11.2 Appendix 2: Contraception Guidance	Deleted “used in conjunction with spermicide”.	To clarify what constitutes adequate contraception, that is consistent with contraceptive methods used in participating Southern Hemisphere countries.

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