CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized, Observer-blind, Active-controlled Study to Evaluate the Safety and Efficacy of mRNA-1010 Candidate Seasonal Influenza Vaccine in Adults 50 Years and Older
Protocol Number:	mRNA-1010-P302
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: 2022-001638-12
Date of Amendment 1:	02 Feb 2023
Date of Original Protocol:	26 May 2022

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by ModernaTX, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed written consent of ModernaTX, Inc. The study will be conducted according to the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance.*

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	A Phase 3, Randomized, Observer-blind, Active-controlled Study to Evaluate the Safety and Efficacy of mRNA-1010 Candidate Seasonal Influenza Vaccine in Adults 50 Years and Older
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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, Observer-blind, Active-controlled Study to Evaluate the Safety and Efficacy of mRNA-1010 Candidate Seasonal Influenza Vaccine in Adults 50 Years and Older" dated 02 Feb 2023 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 IRB/IEC approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment 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 staff 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

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	02 Feb 2023
Original Protocol	26 May 2022

Global Amendment 1, 02 Feb 2023: 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 purpose of this amendment is to prespecify immunogenicity analysis for HAIs and alter the timing of an Interim Analysis. The summary of changes table describes the changes made in Amendment 1, relative to the original protocol, including the sections modified and the corresponding rationales. Minor editorial or formatting changes, including removal of redundant text or text not appropriate for the synopsis, are not included in the summary table. Additional country-specific changes are provided in Section 11.6.

Summary of Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page	Sponsor contact updated.	Administrative change.
Title Page, Signature Page, Protocol Amendment Summary of Changes, Header	Updated the protocol version and date, as applicable.	To reflect the current version.
Section 1.1, Protocol Synopsis, Section 5.1, Inclusion Criteria, Section 5.2, Exclusion Criteria, and Table 2	Updated to clarify that culture-confirmed protocol-defined ILI cases caused by any influenza A or B strains will be included in the endpoint regardless of antigenic match to strains selected for the seasonal vaccine. Added evaluation of humoral immunogenicity to secondary objectives.	To remove redundant language of protocol-defined ILI cases caused by antigenically matched strains in the vaccines that are already summarized in other objectives/endpoints. To allow for earlier timing of sample testing, as it was initially part of an exploratory analysis that was planned for a later time.
Section 1.2, Schedule of Events, Section 4.1, Study Design, and Section 8.9.2, Assessments for Respiratory Viral Infections	Clarified that participants who experience protocol-defined ILI must have an NP swab collected for RT-PCR testing of influenza virus and other respiratory pathogens. In participants who	Clarification based on study site feedback per IRB-notified/approved clarification memo.

Section # and Name	Description of Change	Brief Rationale
	experience ILI symptoms but have not yet fulfilled protocol-defined ILI, Investigators may use their discretion to perform NP swabs when influenza is suspected.	
Section 6.5.2, Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses, and Section 9.4, Analysis Populations	Further information is added to clarify concomitant medications and/or vaccines that may lead to a participant being excluded from the PP Set and analyses: – An authorized or licensed noninfluenza vaccine that is not adjuvanted administered within 14 days before or after the study intervention. – An authorized or licensed adjuvanted, noninfluenza vaccine administered within 28 days after the study intervention. – Any nonstudy influenza vaccine administered during the study period.	To describe details on usage of noninfluenza and influenza vaccines during the study that may result in exclusion from the PP Set.
Section 8.10.2, Serious Adverse Events	Revised definition of serious adverse events as follows: Persistent or significant **disability or** incapacity or substantial disruption of the ability to conduct normal life functions.	To address health authority feedback.
Section 8.15 Biomarkers	Replaced the term, “additional” in front of the word “biomarkers” at the start of the paragraph. Deleted the word “exploratory” and replaced it with the words “future research.”	Clarifications.

Section # and Name	Description of Change	Brief Rationale
	Added the words "from consented participants" at the end of the first paragraph. Shifted statement about "optional blood collections…" from the 1st paragraph to the 2nd paragraph and modified a portion of the statement starting with the following text, "…to research connections between vaccine responses and safet." Added a statement at the end of the 2nd paragraph about NP swab collections.	
Section 9.2 Statistical Hypotheses	Changed "2-sided" to "1-sided" and "5%" to "2.5%". Changed the spending function from "O'Brien-Fleming" to "Pocock."	For noninferiority, the 1-sided P value is more applicable. The Pocock spending function provides a greater chance to achieve success at IA.
Sections 9.2, Statistical Hypotheses, 9.3, Sample Size, 9.5, Statistical Analyses, 9.5.1.1, Analysis of Primary Efficacy Endpoint, 9.6, Planned Analyses, and Table 8	The first IA was removed because of the expected lower power. The alpha spending function was changed to the Lan-DeMets Pocock approximation function to preserve the overall Type I error rate. Statistical considerations were updated because of the revised IA schedule and change in the alpha-spending function. The above success boundaries for hypothesis testing are changed to be in terms of 1-sided P values.	Per prediction, the timing of two IAs will be close. Hence, the Sponsor decided to combine them into one IA. The Pocock spending function provides a greater chance to achieve success at IA. For noninferiority, the 1-sided P value is more applicable.
Section 9.3, Sample Size	Allow the timing of IA based on a specified data cut-off date regardless of number of influenza cases accrued. Updated the power of the PP Set to 93%.	To accommodate DSMB review even if the target number of cases for IA is not reached considering the declining influenza incidence.

Section # and Name	Description of Change	Brief Rationale
	Replaced "2 IAs" with "one IA" and deleted associated text about the percentages of the target total number of cases. Changed "2-sided" to "1-sided" and "5%" to "2.5%". Changed the spending function from "O'Brien-Fleming" to "Pocock."	
Section 9.4, Analysis Populations	The mITT Set definition was revised. Randomized participants who discontinued from the study prior to 14 days after administration of study vaccines will be excluded. The PP Set definition was revised based on edits to the mITT Set. An Immunogenicity Subset and a PP Immunogenicity Subset was added.	The revised definition will include more participants in the mITT Set. In addition, the influenza symptom reporting from 14 days post-vaccination is not required. The additional subsets clarify which participants will be included in the immunogenicity analyses.
Section 9.5.1.1, Analysis of Primary Efficacy Endpoint	Added summary description of how missing data will be handled. Clarified that the randomization strata will be used as strata variables in the statistical model.	To address health authority feedback.
Section 9.5.3, Immunogenicity Analyses	Added summary description of how immunogenicity will be analyzed.	To describe the analysis for immunogenicity.
Section 11.6 APPENDIX 6; Country-specific Requirements	Added new Section displaying all prior country country-specific amendments.	To align with standard operating procedure of incorporating all prior country-specific amendments into a global amendment document.

Abbreviations: DSMB = Data Safety Monitoring Board; IA = Interim analysis; ILI = Influenza-like illness; NP = Nasopharyngeal; PP = Per-protocol.

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Study Intervention: mRNA-1010

Protocol Number: mRNA-1010-P302 Amendment 1

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

Brief Title: A Phase 3 Study to Evaluate the Safety and Efficacy of mRNA-1010 Candidate Seasonal Influenza Vaccine in Adults 50 Years and Older

Regulatory Agency Identifier Number (s): IND: 27460, EudraCT: 2022-001638-12

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 resulting in 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) (Riedel et al 2019). 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 influenza 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 years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2020a). Influenza vaccines based on messenger RNA (mRNA)-technology could provide several benefits compared to 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 as well as improved protection in older adults (Rockman et al 2020).

Objectives and Endpoints

Primary Objectives	Primary Endpoints
• To evaluate the safety and reactogenicity of mRNA-1010 during the treatment period (28 days after study intervention) and follow-up period (period following the treatment period).	• Solicited local and systemic ARs through 7 days after study injection. • Unsolicited AEs through 28 days after study injection.

	• MAAEs from Day 1 to Day 361 (Month 12)/EoS. • AESIs from Day 1 to Day 361 (Month 12)/EoS. • SAEs from Day 1 to Day 361 (Month 12)/EoS. • AEs leading to discontinuation from Day 1 to Day 361 (Month 12)/EoS.
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator against influenza caused by any influenza A or B virus strains using protocol-defined ILI definition.	• First episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any seasonal influenza A or B virus strains regardless of antigenic match to strains selected for the seasonal vaccine.
Secondary Objectives	**Secondary Endpoints**
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains with similarity[a] to the vaccine strains using protocol-defined ILI definition.	• First episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by influenza A or B strains with similarity[a] to those selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains antigenically matched to the vaccine strains[b] using protocol-defined ILI definition.	• First episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6)/end of influenza season caused by influenza A or B strains antigenically matched to the vaccine strains[b] selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains (any strains or similar strains or antigenically matched strains) using CDC-defined ILI definition.	• First episode of RT-PCR confirmed US CDC-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6)/end of influenza season caused by – Any influenza A or B strains; – Influenza A or B strains with similarity to vaccine strains; – Influenza A or B strains that are antigenically matched to vaccine strains.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against culture-confirmed influenza caused by any influenza A or B strains.	• First episode of culture-confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any influenza A or B strains regardless of antigenic match to strains selected for the seasonal vaccine. • First episode of culture-confirmed CDC-defined ILI that begins at least 14 days post

	vaccination through Day 181 (Month 6)/end of influenza season caused by any influenza A or B strains regardless of antigenic match to strains selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator to prevent hospitalizations associated with influenza illness.	• Hospitalizations associated with RT-PCR confirmed protocol defined 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.
• 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 in a subset of participants.	• GMT at Day 29 as measured by HAI assay. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay. • The proportion of participants with a titer ≥ 1:40 at Day 29 as measured by HAI assay. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI assay.

Abbreviations: AE = Adverse events; AESI = Adverse events of special interest ARs = Adverse reactions; CDC = Centers for Disease Control and Prevention; CHF = Congestive heart failure; COPD = Chronic obstructive pulmonary disease; EoS = End of Study; EQ-5D-5L = EuroQoL-5 Dimension 5-Levels; GMFR = Geometric mean fold rise; GMT = Geometric mean titer; HAI = Hemagglutination inhibition; ILI = Influenza-like illness; MAAEs = Medically attended AEs; QoL = Quality of life; RT-PCR = Reverse transcriptase polymerase chain reaction; SAE = Serious adverse events; US = United States; WPAI:ILI = Work productivity and activity impairment questionnaire: Influenza-like illness.

Note: Exploratory objectives may be performed. Refer to Section 3 for further details.

[a] Similarity to strains selected for the seasonal vaccine based on antigenicity testing and/or genomic sequencing.

[b] Antigenically matched to strains selected for the seasonal vaccine based on antigenicity testing.

Overall Study Design:

This study will be a Phase 3, randomized, observer-blinded, active-controlled trial to evaluate the safety and efficacy of mRNA-1010 in adults 50 years and older.

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

Brief summary:

The purpose of this study is to measure relative vaccine efficacy (rVE) of mRNA-1010 as compared to an active comparator to prevent the occurrence of the first episode of reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed protocol-defined influenza-like illness (ILI) caused by any influenza A or B virus strains.

Study details include:

- The study duration will be approximately 27 months (if 2 influenza seasons are required to perform efficacy analyses).

- There will be 6 safety telephone call visits at Days 8, 29 (except for those participants in the immune response biomarker subset which requires a clinic visit on Day 29), 91, 181, 271, and 361 (Month 12)/end of study as specified in the Schedule of Events.
- Approximately 1000 participants will be asked to provide blood samples at baseline and on Day 29 (28 days post vaccination) for assessment of immune responses to the study intervention, including anti-HA antibody responses to vaccine-matched strains (immune response biomarker subset). A clinic visit on Day 29 will be required for these participants.
- All participants will be asked to complete an electronic diary (eDiary) for solicited adverse reactions (ARs) from Day 1 to Day 7.

Number of Participants: Approximately 23,000 participants will be enrolled.

Note: Enrolled means participants' agreement to participate in a clinical trial following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Study Arms and Duration:

- The study will comprise 2 study arms: investigational vaccine (mRNA-1010) group and active comparator (licensed quadrivalent inactivated seasonal influenzas vaccine) group.
- The total study duration (including screening) for each participant is up to 13 months.

Data Safety Monitoring Board:

A Data Safety Monitoring Board (DSMB) will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. Safety data will be reviewed according to intervals defined in the DSMB charter and will also occur as needed.

1.2. Schedule of Events

Table 1: Schedule of Events

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C[1]/SC**	**SC**	**SC**	**SC**	**SC**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**M9**	**M12**	**Up to M12**
Study Visit	**Screening[2]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181**	**D271**	**D361/EoS**	**USV**
Window Allowance (Days)	**-28**	**N/A**	**±2**	**-7 to +3**	**±5**	**±14**	**±14**	**±14**	**N/A**
Informed consent form, demographics, vaccination and, medical history[3]	X								
Inclusion/exclusion criteria	X	X							
Physical examination[4]	X								
Vital signs[5]	X	X							
Pregnancy testing[6]	X	X							
Randomization		X							
Blood collection for immune response biomarkers and/or transcriptomics (optional) subset[7]		X		X					
Blood collection for future research sample (optional)[8]		X							
Study vaccination (including 30-minute post-dosing observation period)[9]		X							
Collection of EFS[10]		X							
NP swab for virus detection[11]									X
Follow-up safety call			X	X[12]	X	X	X	X	
eDiary activation for recording solicited ARs (7 days)[13]		X							
Review of eDiary for solicited ARs[14]			X						
Symptom Reporting eDiary activation[15]		X							
Symptom Reporting eDiary for collection of symptoms of ILI[16]		Twice weekly from Day 1 to Day 181					Once weekly from Day 182 to Day 361		
Review of Symptom Reporting eDiary		Review participant recorded ILI starting on Day 1 through Day 361 (Month 12)/EoS							
Telephone/electronic contacts to remind participants of ILI eDiary reporting[17]		Once weekly from Day 1 to Day 181					Every 2 weeks from Day 182 to Day 361		
eDiary collection of EQ-5D-5L[18]		X			X	X	X	X	X
eDiary collection of WPAI:ILI			eDiary prompts[19]						
Recording of unsolicited AEs		X	X	X					

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C[1]/SC**	**SC**	**SC**	**SC**	**SC**	**C**
Month Timepoint				**M1**	**M3**	**M6**	**M9**	**M12**	**Up to M12**
Study Visit	**Screening[2]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181**	**D271**	**D361/EoS**	**USV**
Window Allowance (Days)	**-28**	**N/A**	**±2**	**-7 to +3**	**±5**	**±14**	**±14**	**±14**	**N/A**
Recording of any SAEs, AESIs, and MAAEs, as well as AEs that led to discontinuation and relevant concomitant medications/procedures[20]		X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[21]		X	X	X	X	X	X	X	
Recording of hospitalizations and outpatient treatment related to or for the treatment of the MAAE or SAE[21]		X	X	X	X	X	X	X	X
Study completion								X	

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

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

1. Day 29 clinic visit is only required for participants in the immune response biomarker subset.
2. The Screening visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening visit may be performed over multiple visits if within the 28-day screening window.
3. Verbal medical history is acceptable.
4. A full physical examination, including height and weight, will be performed at the Screening visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during clinic visits should be reported as an MAAE.
5. Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
6. A point-of-care urine pregnancy test will be performed at the Screening visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening visit. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The participant's follicle-stimulating hormone level may be measured at the Screening visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
7. In a subset of participants, samples will be collected for immunogenicity assessment and immune assessments. Of the people who participate in the subset, an additional blood sample collection for transcriptomics will be optional. Samples on Day 1 must be collected prior to receipt of vaccination.
8. Sample collection for future research, including genomics, is optional. Samples on Day 1 must be collected prior to receipt of vaccination.

9. See Section 4.1 for dose levels and vaccination groups. All participants will be randomized to receive a single IM injection.
10. Assessment of EFS will only be performed for participants aged 65 years and older.
11. The NP swab specimen(s) for pathogens, including influenza virus and other respiratory pathogens (eg, SARS-CoV-2) will be collected any time from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined ILI per the ILI Case Definitions in Section 8.10.5. or if deemed necessary per Investigator's discretion when influenza is suspected. If participants experience ILI symptoms, they will be instructed to contact the clinic to determine if they need an NP swab collected for testing. NP swab collection should occur within 72 hours of symptom onset. NP swabs should be collected prior to any antiviral therapy, if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the eCRF.
12. Only for those participants not in the immune response biomarker subset who otherwise would have a clinic visit this day.
13. The eDiary entries will be recorded at approximately 30 minutes after injection while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and the subsequent 6 days following injection. See Section 8.9.4 for additional details.
14. The site staff will review Symptom Reporting eDiaries daily and if illness symptoms are noted they should follow up with participants to determine if the symptoms warrant the participant providing an NP swab. Follow-up with the participant for symptoms review should be documented in eCRF.
15. The Symptom Reporting eDiary will be activated for collection of ILI symptoms starting at Day 1 and lasting until Day 361 (Month 12)/EoS.
16. Participants will be instructed to report via Symptom Reporting eDiary or telephone calls whether ILI symptoms have been experienced. If participants experience ILI symptoms, they will be instructed to contact the clinic as soon as possible to determine if an NP swab needs to be collected. NP swabs for testing should be collected within 72 hours of symptom onset. NP swabs should be collected prior to any antiviral therapy, if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit.
17. Telephone/electronic contacts are to remind participants of ILI eDiary reporting, not to capture AEs.
18. For participants reporting symptoms of ILI in the Symptom Reporting eDiary, 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. For participants reporting symptoms of ILI in the Symptom Reporting eDiary, the WPAI over the previous 7 days will be collected using the eDiary at 5 days (+1 day) following the start of ILI symptoms reporting in the Symptom Reporting eDiary.
20. Trained study personnel or designee will call all participants to collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESIs, and information on concomitant medications associated with those events. All concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded from Day 1 through Day 361 (Month 12)/EoS.
21. All concomitant medications and non-study vaccinations will be recorded through 28 days after study intervention (including receipt of any authorized or investigational COVID-19 vaccine). Additionally, certain concomitant medications will be recorded through Day 361/EoS (refer to Section 6.5.1).

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

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

Abbreviation or Specialist Term	Definition
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
Ars	Adverse reactions
CDC	Center for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EFS	Edmonton Frail Scale
EoS	End of Study
EQ-5D-5L	EuroQoL-5 Dimension 5-Levels
EQ-VAS	EuroQol visual analogue scale
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLSM	Geometric least square mean
GMP	Good Manufacturing Practice
GMT	Geometric mean Titers
HA	Hemagglutinins
HAI	Hemagglutination inhibition

Abbreviation or Specialist Term	Definition
HCP	Healthcare practitioner
HIV	Human immunodeficiency virus
HR	Hazard ratio
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
ILI	Influenza-like illness
IM	Intramuscular(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
LTFU	Lost to Follow-up
MAAEs	Medically attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRNA	Messenger ribonucleic acid
NH	Northern Hemisphere
NI	Noninferiority
NIM	Noninferiority margin
NP	Nasopharyngeal
PI	Principal Investigator
POCBP	Participants of childbearing potential
PP	Per-protocol
QoL	Quality of life

Abbreviation or Specialist Term	Definition
RT-PCR	Reverse transcriptase polymerase chain reaction
rVE	Relative vaccine efficacy
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	Standard deviation
SH	Southern Hemisphere
SoE	Schedule of Events
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
US	United States
vs.	versus
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 resulting in 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) (Riedel et al 2019). Since influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide 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 influenza 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 years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2020a). Influenza vaccines based on messenger RNA (mRNA)-technology could provide several benefits compared to 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 as well as improved protection in older adults (Rockman et al 2020).

2.2. Background and Overview

The Sponsor has developed a 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 antigen(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.

The Sponsor is using its mRNA-based platform to develop a lipid nanoparticle (LNP) encapsulated mRNA-based seasonal vaccine against disease caused by influenza virus types A and B. The proposed development candidate, mRNA-1010, will be a quadrivalent vaccine containing mRNAs encoding for the hemagglutinins (HAs) of the 4 strains recommended by WHO for cell- or recombinant-based vaccines. Equal amounts of mRNAs will be used for encoding the HA components for each of the 4 different strains. The mRNA-1010 development candidate is administered as a single dose and aims to elicit protection from all seasonal influenza viruses covered by the vaccine.

The Sponsor has enrolled 880 participants in a Phase 1/2 trial with mRNA-1010 in the US and plans to enroll 6000 participants in a Phase 3 immunogenicity trial in the SH in Q2/Q3 2022. The Sponsor is conducting this Phase 3 trial with mRNA-1010 to establish safety and efficacy data to support the licensure for this vaccine.

Details on the mechanism of action and a summary of nonclinical studies of mRNA-1010 can be found in Section 2.2.1.

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

2.2.1. 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 µg 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-good manufacturing practices (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 the vaccine via intramuscular (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 of vaccine 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 hemagglutination inhibition (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 observation with mRNA-1010 vaccine is provided in the Investigator's Brochure (IB).

2.2.2. Clinical Studies

The Sponsor's Phase 1/2 mRNA-1010-P101 trial (NCT04956575) is currently ongoing to provide initial first-in-human safety and immunogenicity data on 3 dose levels of mRNA-1010 encoding strains (CCI µg, CCI µg, or CCI 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 CCI µg and CCI µg dose levels and to test an additional CCI 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 CCI µg and CCI µg) as well as CCI 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 Day 29 by the Data Safety Monitoring Board (DSMB). In the trial, 45 participants in each group received CCI µg, CCI µg, or CCI µg doses of mRNA-1010. The CCI-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 intervention. There was a death due to stage 4 kidney cancer that was unrelated to the study intervention and occurred after the 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 CCI µg dose level were comparable with the titers elicited at higher dose levels.

The interim analysis (IA) from the Phase 2 NH part of mRNA-1010-P101 included data through Day 29 from 498 adults who received the study intervention. The number of participants in the 4 groups were 151 (CCI µg mRNA-1010), 147 (CCI µg mRNA-1010), 147, (CCI 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 intervention. There were no study discontinuations due to AEs, and no AEs that led to a study pause. There was 1 death due to cardiac arrest in a 67-year-old male participant with a relevant medical history of diabetes mellitus, hypertension, and obesity. The event occurred 15 days post 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 to Afluria and similar for 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. Considering the safety and immunogenicity 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, and 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 Centers for Disease Control and Prevention (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 in this study will remain under observation at the clinic for at least 30 minutes after vaccination.

Vasovagal syncope (fainting) can occur before or after any vaccination and 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.

IM injection with other mRNA vaccines manufactured by the Sponsor containing the proprietary SM-102 (heptadecan 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.

IA safety results from the Phase 1/2 portion of mRNA-1010-P101 (data extraction date 07 Oct 2021) demonstrated sporadic abnormalities for chemistry and hematology tests in all groups at 7 days post vaccination, but no trends or safety concerns were identified. There were no Grade 4 laboratory test abnormalities recorded in the study up to Day 29.

The most commonly reported local solicited ARs after interim safety analysis in the mRNA-1010-P101 trial were pain at injection site, axillary swelling, or tenderness. Injection site erythema or swelling was less frequently reported. The most common solicited systemic reactions were headache, fatigue, myalgia, and chills. Fever, nausea and arthralgia were reported less frequently.

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).

Enhanced influenza vaccines (eg, adjuvanted, high dose, or recombinant vaccines) are preferentially recommended and available to the elderly (~65 years of age and older) in some countries. These vaccines are more efficacious in preventing influenza illness compared to standard dose vaccines (eg, the comparator Fluarix®). Moreover, the efficacy of mRNA-1010 is unknown and will be evaluated in this study. Therefore, elderly participants should be made aware of any available alternative option to receive an enhanced influenza vaccine during the consenting process. Nonstudy influenza vaccines are not permitted in the study.

2.3.3. Overall Benefit/Risk Conclusion

Considering the safety and immunogenicity data for mRNA-1010 to date, the Sponsor considers the potential benefits of participation to 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

Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of mRNA-1010 during the treatment period (28 days after study intervention) and follow-up period (period following the treatment period).	• Solicited local and systemic ARs through 7 days after study injection. • Unsolicited AEs through 28 days after study injection. • MAAEs from Day 1 to Day 361 (Month 12)/EoS. • AESIs from Day 1to Day 361 (Month 12)/EoS. • SAEs from Day 1to Day 361 (Month 12)/EoS. • AEs leading to discontinuation from Day 1 to Day 361 (Month 12)/EoS.
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator against influenza caused by any influenza A or B virus strains using protocol-defined ILI definition.	• First episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any seasonal influenza A or B virus strains regardless of antigenic match to strains selected for the seasonal vaccine.
Secondary Objectives	**Secondary Endpoints**
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains with similarity[a] to the vaccine strains, using protocol-defined ILI definition.	• First episode of RT-PCR-confirmed protocol defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by influenza A or B strains with similarity[a] to those selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains antigenically matched to the vaccine strains[b] using protocol-defined ILI definition.	• First episode of RT-PCR confirmed protocol-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6)/end of influenza season caused by influenza A or B strains antigenically matched to the vaccine strains[b] selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against influenza caused by influenza A or B strains (any strains or similar strains or antigenically matched strains) using CDC-defined ILI definition.	• First episode of RT-PCR confirmed US CDC-defined ILI that begins at least 14 days after vaccination through Day 181 (Month 6)/end of influenza season caused by – Any influenza A or B strains; – Influenza A or B strains with similarity to vaccine strains;

Primary Objectives	Primary Endpoints
	– Influenza A or B strains that are antigenically matched to vaccine strains.
• To evaluate relative vaccine efficacy of mRNA-1010 vaccine as compared to an active comparator against culture-confirmed influenza caused by any influenza A or B strains.	• First episode of culture-confirmed protocol-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any influenza A or B strains regardless of antigenic match to strains selected for the seasonal vaccine. • First episode of culture-confirmed CDC-defined ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any influenza A or B strains regardless of antigenic match to strains selected for the seasonal vaccine.
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator to prevent hospitalizations associated with influenza illness.	• Hospitalizations associated with RT-PCR confirmed protocol defined 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.
• 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 in a subset of participants.	• GMT at Day 29 as measured by HAI assay. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI assay. • The proportion of participants with a titer ≥ 1:40 at Day 29 as measured by HAI assay. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI assay.
Exploratory Objectives (may be performed)	
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator to prevent the following events that begin at least 14 days post vaccination through Day 361 (Month 12)/EoS: – All-cause pneumonia. – Pneumonia-related hospitalization. – All-cause hospitalization. – Influenza-related mortality. – All-cause mortality.	
• To evaluate relative vaccine efficacy of mRNA-1010 as compared to an active comparator to prevent the following events that begin at least 14 days post vaccination through Day 361 (Month 12)/EoS:	

Primary Objectives	Primary Endpoints
– Exacerbation of cardiorespiratory diseases (eg, CHF, COPD, asthma, and other chronic cardiorespiratory diseases). – Cardiorespiratory hospitalizations and death.	
• To characterize the effect of mRNA-1010 as compared to an active comparator on other health outcomes including: – Number and frequency of participants aged 65 years and older with first episode of RT-PCR confirmed protocol-defined ILI by baseline frailty status. – EQ-5D-5L health questionnaire utility score at regular intervals as well as for participants with ILI. – WPAI:ILI impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment for participants with ILI.	
• To characterize the effect of mRNA-1010 as compared to an active comparator on prevention or mitigation of the following that are associated with RT-PCR-confirmed ILI or all-cause pneumonia: – Healthcare encounters (outpatient visits, emergency department visits, and hospitalizations). – Duration of hospital encounters including intensive care unit hospitalization, and endotracheal intubation/mechanical ventilation. – Prescriptions for medications (antibiotics, antivirals, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs).	
• Economic Analysis: A separate economic analysis is planned to estimate the impact of vaccination with mRNA-1010 on QoL-adjusted survival and on healthcare costs in real-world practice in one or more geographies. If performed, this analysis would use information on clinical, QoL, and resource use outcomes collected within the study to estimate QoL and costs to a healthcare payer comparing a strategy of vaccination with mRNA-1010 vs. an active comparator. This analysis would be conducted under a separate analysis plan and is intended for submission to health technology assessment and payer audiences to support use of mRNA-1010 following launch.	

Abbreviations: AE = Adverse events; AESI = Adverse events of special interest ARs = Adverse reactions; CDC = Centers for Disease Control and Prevention; CHF = Congestive heart failure; COPD = Chronic obstructive pulmonary disease; EoS = End of Study; EQ-5D-5L = EuroQoL-5 Dimension 5-Levels; GMFR = Geometric mean fold rise; GMT = Geometric mean titer; HAI = Hemagglutination inhibition; ILI = Influenza-like illness; MAAEs = Medically attended AEs; QoL = Quality of life; RT-PCR = Reverse transcriptase polymerase chain reaction; SAE = Serious adverse events; US = United States; WPAI:ILI = Work productivity and activity impairment questionnaire: Influenza-like illness.

a. Similarity to strains selected for the seasonal vaccine: based on antigenicity testing and/or genomic sequencing.

b. Antigenically matched to strains selected for the seasonal vaccine based on antigenicity testing.

4. STUDY DESIGN

4.1. General Design

This study will be a Phase 3, randomized, observer-blinded, active-controlled trial to evaluate the safety and efficacy in preventing seasonal influenza of mRNA-1010 in adults 50 years and older.

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

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

Immunizations are planned during the typical 2022/2023 NH vaccination campaign period. However, if the targeted number of reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed ILI cases observed are not reached, an extension of enrollment over multiple influenza seasons may be required. As a result, vaccines with other seasonal-specific compositions may be used and administered during the relevant typical vaccination campaigns, as appropriate. Additionally, if the interim vaccine effectiveness analyses by public health authorities demonstrate noneffectiveness of licensed influenza vaccines, sample size re-estimation and continuation of enrollment into the next season may be considered.

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

Table 3: Vaccination Groups and Dose Levels

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

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

Clinic visits for all participants will comprise a Screening visit (up to 28 days before the Day 1 visit, or maybe on the same day as the Vaccination Visit on Day 1) and a Vaccination Visit (Day 1) as showed in the schedule of events (SoE, Table 1).

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

Approximately 1000 participants will be asked to provide blood samples at baseline and on Day 29 (28 days post vaccination) for assessment of immune responses to the study intervention

(immune response biomarker subset). A clinic visit on Day 29 will be required for these participants. All participants will be asked to complete an electronic diary (eDiary) for solicited ARs from Day 1 to Day 7. All participants will be asked to provide an optional blood sample for future research use at Day 1.

There will be 6 safety telephone call visits at Days 8, 29 (expect for those participants who are not in the immune response biomarker subset which requires a clinic visit on Day 29), 91, 181, 271, and 361 (Month 12)/EoS as specified in the SoE. The study duration (including screening) is up to 13 months for each participant and the total study duration is approximately 27 months (if 2 influenza seasons are required to perform efficacy analyses).

Participants will be instructed to report whether ILI symptoms have been experienced, via a Symptom Reporting eDiary, twice weekly from Day 1 to Day 181 and once weekly from Day 182 to Day 361 (Month 12)/EoS. If participants experience ILI symptoms, they will be instructed to enter the details in the eDiary and contact the clinic to determine if an NP swab should be collected for RT-PCR testing. NP swabs for testing should be collected within 72 hours of symptom onset. Sites should also reach out to participants if illness symptoms are noted upon review of the eDiary to assess whether the participant is required to provide an NP swab.

NP swab should be collected prior to any antiviral therapy if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the electronic case report form (eCRF).

Unscheduled clinic visits for ILI symptoms and viral respiratory panel testing may be conducted. Participants who manifest protocol-defined ILI or for those participants who experience ILI symptoms but have not yet fulfilled protocol-defined ILI, and based on Investigator's discretion when influenza is suspected, will be evaluated by real-time RT-PCR testing of NP swab specimen(s) for influenza and other respiratory pathogens. NP swabs may be collected as part of a home visit in lieu of a clinic visit.

All participants who report symptoms of ILI will receive eDiary prompts to complete patient-reported outcome questionnaires for EuroQoL 5 Dimension 5-Level (EQ-5D-5L) and Work Productivity and Activity impairment Questionnaire: Influenza-like Illness (WPAI:ILI).

The Investigator might ask a participant to return to the clinical site for an unscheduled visit under certain situations (eg, if an AE is reported). Additional assessments, as necessary, may be conducted at these visits 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. The participant, Investigator, and clinical staff responsible for study assessments/safety will not have access to the treatment assignment during the conduct of the study. The Investigator may be unblinded in the event of an emergency (refer to Section 6.3.7).

4.2. Scientific Rationale for Study Design

This trial is designed as an observer-blind trial. Participants will receive a single dose of either mRNA-1010 vaccine or a licensed quadrivalent seasonal influenza vaccine (an active comparator) in order to assess safety and efficacy of the vaccine.

In this observer-blind trial, 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 trial, will perform study intervention accountability, dose preparation, and study intervention administration.

The NP swab specimen(s) for assessment of pathogens, including influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), will be collected any time from Day 1 through Day 361 (Month 12)/EoS if the participants have protocol-defined ILI (see Section 8.10.5) or if deemed necessary per Investigator's discretion when influenza is suspected. If participants experience these signs or symptoms, they will be instructed to contact the clinic to determine if an NP swab is required to be collected for testing. NP swabs may be collected as part of a home visit in lieu of a clinic visit. If NP swabs during ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the eCRF.

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

The selection of the CCI µg dose level of mRNA-1010 is supported by the data from the Phase 1/2 and the Phase 2 NH interim analyses. First, the CCI µg dose level elicited strong HAI antibody responses. The geometric mean titers (GMTs) exceeded the 1:40 titer threshold for the 2 influenza A strains and 2 influenza B strains tested. This threshold was previously correlated with a 50% reduction in risk of influenza virus infection. This dose generated robust HAI responses for H1N1 and H3N2 strains with Day 29 GMTs that were higher than the licensed comparator. Second, the CCI µg dose level demonstrated an acceptable reactogenicity and safety profile. The frequencies of solicited ARs were lower in the CCI µg dose level than those of the CCI µg and CCI µg dose levels while the immunogenicity was comparable. The reactogenicity and safety profile of the CCI µg dose level was not substantially different to that of the CCI µg dose level, whereas the immunogenicity was higher particularly for adults 50 years and older. In summary, the safety and immunogenicity profile observed from the mRNA-1010-P101 study supports selecting mRNA-1010 at a CCI µg dose level for this study. Further details are provided in the IB.

Fluarix is selected as an active control because it is licensed for the prevention of influenza disease in the adult population in the countries that will take part in this study. Enhanced quadrivalent influenza vaccines have not been considered for the ≥ 65 years old age group because they are not licensed or preferentially recommended in all participating countries.

Improved vaccine efficacy in adults ≥ 50 years old is needed given the increased morbidity and mortality in this population due to declining immunocompetence and increased burden of comorbid medical conditions.

4.4. End of Study Definition

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

The end of study is defined as completion of the last visit of the last participant in the trial or last scheduled procedure as shown in the SoE for the last participant in the trial globally.

5. STUDY POPULATION

Approximately 23,000 participants will be enrolled.

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. At least 50 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. Provide written informed consent for participation in this study, including all evaluations and procedures as specified by this protocol.
4. Females of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal 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. Females 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 study 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 study vaccine administration.

5.2. Exclusion Criteria

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

1. Close contact with someone with laboratory-confirmed influenza infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu®) within the past 5 days prior to the screening visit.
2. Close contact with 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.
3. 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.

4. 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.
5. 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:
   - Human immunodeficiency virus [HIV] positive participants on antiretroviral therapy with cluster of differentiation 4 count ≥ 350 cells/mm^3 and HIV RNA ≤ 500 copies/mL within the past 12 months.
   - Immune-mediated diseases that are stable, for example, Hashimoto's thyroiditis and type 1 diabetes mellitus or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, autoimmune ovarian failure that do not require systemic immunosuppressants per Exclusion Criterion 10.
6. Dermatologic conditions that could affect local solicited AR assessment of the injection site (eg, tattoos, vitiligo or psoriasis patches affecting skin over the deltoid area of the injection site).
7. 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.
8. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
9. 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.
10. Received systemic immunosuppressants for > 14 days in total within 180 days prior to the Screening visit (for glucocorticosteroids, ≥ 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, intra-articular, and topical steroids are allowed.
11. Received any vaccine authorized or approved by local health agency ≤ 28 days prior to study intervention (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after the study intervention.
12. Plans to receive a nonstudy influenza vaccine during the study from Day 1 to Day 181.
13. Is unaware whether they received an influenza vaccine in the previous influenza season.
14. Received a seasonal influenza vaccine or any other investigational influenza vaccine within 180 days prior to the Randomization Visit.
15. Tested positive for influenza by local health authority-approved testing methods within 180 days prior to the Randomization Visit.

16. Has been treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to the Randomization Visit.
17. 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.
18. History of Guillain-Barre syndrome.
19. Received systemic immunoglobulins and long-acting biological therapies that affect immune responses (eg infliximab) or blood products within 90 days prior to the Screening visit or plans to receive them during the study.
20. Donated ≥ 450 mL of blood products within 28 days prior to the Screening visit or plans to donate blood products during the study.
21. 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. *Note: interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary.*
22. Participant is working or has worked as study personnel or is an immediate family member or household member of study personnel, study site 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 trial should defer vaccination with licensed seasonal influenza vaccine until after completion of the 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 trial but are not subsequently randomized. 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 (CONSORT) 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 failures) may be rescreened 1 time if they will be eligible upon rescreening.

6. STUDY TREATMENT

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

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 CCI mg/mL CCI [redacted].

mRNA-1010 will be administered as a single IM injection dose at mRNA total dose level of CCI µg (see Table 4).

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

Table 4: Study Interventions

Vaccination Group	Investigational Vaccine	Active Comparator
Intervention Name	mRNA-1010	Fluarix®/Influsplit®
Type	Vaccine	Vaccine
Unit Dose Strength	CCI µg (mRNA)	CCI µg (protein)
Dosage Level	Single dose of CCI mL	Single dose of CCI mL
Route of Administration	IM	IM
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) system.

Approximately 23,000 participants will be randomized in a 1:1 ratio to receive a single dose of mRNA-1010 at CCI µg total mRNA or a single dose of the active comparator (Table 3). Randomization will be stratified by age categories (≥ 50 to < 65 years or ≥ 65 years) and influenza vaccine status in the previous influenza season (received or not received) at the time of screening. At least 50% of enrollees will be ≥ 65 years old, including at least 10% who will be ≥ 75 years old.

As the appearance of the study interventions differ, enrollment will be observer blinded to the 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 emergency, 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 intervention. 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 study intervention administered until the study database is locked and unblinded for the final analysis. At the interim analyses (see Section 9.6.1), pre-identified Sponsor team members and selected CRO team members will be unblinded to conduct the analyses. Study sites will remain blinded.

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Clinical Study Material Preparation

The study intervention will be prepared for each participant based on their vaccination group assignment. Details of the study interventions are provided in Table 4. Specific instructions for the preparation of mRNA-1010 and active comparator are contained in the Pharmacy Manual.

6.3.2. Clinical Study Material Administration

mRNA-1010 or the active comparator will be administered as a single IM injection into the deltoid muscle in adult participants on Day 1. The study intervention should be administered preferably into the nondominant arm. The dose volume will be held constant at approximately CCI mL per injection.

Participants will be monitored for at least 30 minutes after administration of the study intervention. 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 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 study intervention. The study intervention will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

All study interventions 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, GMP 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. 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 study intervention accountability, site 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 study intervention that was not temperature controlled during shipment or storage. Such study intervention will be retained for inspection by the monitor and disposed of according to approved methods. 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 study intervention accountability staff maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study intervention, 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 a Sponsor-selected third party, as appropriate.

Clinical study material 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 the Pharmacy Manual.

6.3.7. Unblinding

Except in the case of medical emergency, 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 (see Section 11.6 for country-specific amendment

affecting this paragraph). In the event of a medical emergency requiring identification of individual treatment assignment, the Investigator must promptly contact the CRO clinical research associate 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 will be tracked via an audit trail in IRT and documented in the final study report.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

At each 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 and Concomitant Vaccinations

The following concomitant medications and vaccines must be recorded in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the study intervention and through Day 361/EoS.
- All concomitant medications taken through 28 days after the study intervention. 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 the study intervention.
- Any authorized influenza vaccine administered since August 2021.
- Systemic steroids (≥ 10 mg/day prednisone or equivalent), immunosuppressants, immunoglobulins and long-acting biological therapies that affect immune responses (eg infliximab), and/or blood products administered at any time during the study period after the study intervention.
- 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 to record in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after the study intervention, 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.

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) Set. Analysis sets are described in Section 9.4.

- Any investigational or nonregistered product (drug or vaccine) other than the study intervention used during the study period.
- Immunosuppressants administered chronically (ie, more than 14 days in total) during the study period. For glucocorticosteroids, this will mean that prednisone ≥ 10 mg/day or the equivalent is not permitted. Inhaled, nasal, intra-articular, and topical steroids are allowed.
- An authorized or licensed noninfluenza vaccine that is not adjuvanted administered within 14 days before or after the study intervention.
- An authorized or licensed adjuvanted, noninfluenza vaccine administered within 28 days after the study intervention.
- Any non-study influenza vaccine administered during the study period.
- Immunoglobulins and long-acting biological therapies that affect immune responses (eg, infliximab) and/or any blood products administered during the study period.

6.6. Continuous Access to Study Intervention After the End of the Study

There will be no access to study intervention following the end of the study.

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 foreseen 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 relative 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
- Physician decision (specify)
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs or solicited ARs) 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 a result of an AE, SAE, or solicited AR until resolution or stabilization of the event.

If a participant withdraws from the study, they 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. 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 Lost to Follow-up (LTFU) if the participant repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study 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 lost to follow up, the Investigator or designee must make an 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 locally 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, the participant will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence, as described above, has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

The study SoE can be found in Table 1.

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

8.1. Screening

At the Screening visit (up to 28 days before the Day 1 visit), all screening requirements, including the Screening Status eCRF to indicate if a participant is either a screen failure or not, must be completed.

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

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, ethnicity, and race will be recorded at Screening on the appropriate eCRF page.

8.4. Medical History

Medical history (including verbal history) from each participant will be collected and recorded on the appropriate eCRF page. Significant findings that were present prior to study vaccination must be included in the Medical History eCRF page.

8.5. Randomization

Study intervention group and study intervention assignment allocation will be performed on Vaccination Visit (Day 1) as described in Section 6.2. The confirmation for study vaccine administration must be recorded on the Injection eCRF page.

8.6. Physical Examination and Vital Signs

A full physical examination will be performed at the Screening visit (according to standard medical practice, including assessment of height and weight). Vital sign measurements must include the assessment of body temperature (oral being the preferred route), systolic and diastolic blood pressures, heart rate, and respiratory rate. The information collected will be recorded in the eCRF.

Vital signs will be measured by study site staff at the Day 1 visit prior to vaccination and approximately 30 minutes after vaccination, prior to discharge of the participant.

Symptom-directed physical examinations will be performed at all other scheduled timepoints as specified in the SoE (Table 1). Interim physical examinations may be performed at the discretion of the Investigator.

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

Treatment of any abnormality observed during physical examination should be performed according to local medical practice outside the study or by referral to an appropriate healthcare provider at the discretion of the Investigator.

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 intervention will be administered via a single 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 administration of the study intervention, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions.

8.8. Efficacy Assessments

Assessment will be conducted to document RT-PCR-confirmed protocol-defined-ILI that begins at least 14 days post vaccination through Day 181 (Month 6)/end of influenza season caused by any influenza A or B virus strains or by strains similar to or antigenically matched to the strains selected for the seasonal vaccine.

Participants who develop symptoms consistent with protocol-defined ILI will have NP swabs collected for testing and ILI symptoms assessed. The initial test on the NP swab 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, additional assays such as genetic sequencing of the virus genes and/or virus culture with subsequent antigenicity testing will be performed to determine vaccine match or similarity.

8.9. Safety Assessments

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

- Solicited local and systemic ARs (Section 8.10.3) that occur through the 7 days following the study intervention (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiary (Section 8.9.4).
- Unsolicited AEs (Section 8.10.1) observed or reported through the 28 days following the study intervention (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 8.10.1.

- 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. MAAEs are defined in Section 8.10.4.
- AESIs from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study. AESIs are defined in Section 8.10.6.
- SAEs from Day 1 through Day 361 (Month 12)/EoS or withdrawal from the study. SAEs are defined in Section 8.10.2.
- Vital signs measurement.
- Details of all pregnancies in female participants will be collected after the start of study intervention and until the end of their participation in the study (Section 8.9.5). All pregnancies must be followed to determine the outcome; however, pregnancy related-data received after the end of the study may not be collected in the clinical database.

Planned time points for all safety assessments are provided in the SoE (Table 1).

8.9.1. Pregnancy Screen and Testing

A pregnancy test via 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 8.9.5.

8.9.2. Assessments for Respiratory Viral Infections

The NP swab specimen(s) for pathogens, including influenza virus, will be collected any time from Day 1 to Day 361 (Month 12)/EoS if participants have protocol-defined ILI (Section 8.10.5) or if deemed necessary per Investigator's discretion when influenza is suspected. If participants experience these signs or symptoms, they will be instructed to contact the clinic to determine if they need an NP swab collected for testing. NP swab collection should occur within 72 hours of symptom onset. Sites may follow up with participants for symptom review if illness symptoms are noted upon review of the Symptom Reporting eDiary to assess whether the participant is required to provide an NP swab. NP swab should be collected prior to any antiviral therapy, if possible. NP swabs may be collected as part of a home visit in lieu of a clinic visit. In the event that NP swabs during ILI cannot be collected, any available influenza testing results performed outside of the study should be captured in the eCRF.

Participants who experience protocol-defined ILI (Section 8.10.5) must have NP swabs collected for RT-PCR testing of influenza virus and other respiratory pathogens. For participants who experience ILI symptoms but have not yet fulfilled protocol-defined ILI definition, Investigators may use their discretion to perform NP swabs when influenza is suspected. If Investigator

discretion is applied, participant should be followed-up for any new symptoms following NP swab collection.

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

All cases that meet the definition of RT-PCR-confirmed influenza infection should be captured as MAAEs along with relevant concomitant medications, hospitalizations, outpatient medical care, and details about severity, seriousness, and outcome.

If an unscheduled visit for assessment of protocol-defined ILI occurs within the first 28 days post study injection, the event should be captured as an unsolicited AE on the Adverse Event eCRF page. If such an unscheduled visit occurs after Day 29, it should be captured as an AE only if it meets MAAE definition (additional medical evaluation, including examinations/testing not required per protocol, and/or treatment is provided during the visit) **OR** if the participant meets RT-PCR confirmed influenza infection (RT-PCR with positive result for influenza) (Section 8.10.5).

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 nonstudy vaccinations. 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 (for 7-day reactogenicity). The local and systemic ARs that will be solicited by the eDiary are described in Table 5.

Solicited local and systemic reactogenicity ARs will be collected on the day of study intervention and during the 7 days after study intervention (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.10.3.

At the dosing visit, participants will record data into the eDiary starting approximately 30 minutes after dosing under supervision of the site staff to ensure successful entry of assessments. The 30-minute observation period is an opportunity for site staff to train the participant on eDiary completion requirements. The site staff will perform any retraining as necessary throughout the study.

At the dosing visit, participants will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same side as the injection arm[s]) during the 7 days after study injection. Daily

oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the site staff.

The participant will be trained on how to complete the eDiary questions according to the SoE (Table 1) and also reminded to call the site immediately if they experience any condition. If eDiary questions result in identification of relevant safety events according to the study period or symptoms of ILI, a follow-up call will be triggered. The results of the call should be recorded in the appropriate source documentation.

If a participant does not respond to the eDiary questions according to the SoE, site staff will follow-up with the participant.

8.9.5. 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 study participants are not pregnant and do not become pregnant during the course of the study. Female individuals who have a positive pregnancy test at the Screening visit should not be enrolled; participants who have a positive pregnancy test at Day 1 must not receive the study intervention and should be withdrawn from the study. Female participants who become pregnant at any time during the study after receiving the study intervention should be asked to 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.

Pregnancies reported in female participants will be collected after the start of study intervention 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 administration of study intervention 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 study site 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.

8.9.6. 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 study intervention (ie, the day of injection and 6 subsequent days). Other (unsolicited) AEs will be collected from Day 1 through 28 days after the study intervention (ie, the day of injection and 27 subsequent days).

MAAEs, 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).

8.9.7. Reporting Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study intervention 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 study intervention, 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.

Refer to Section 8.9.9 for reporting of medical occurrences that begin before the start of study intervention administration but after obtaining informed consent.

8.9.8. Reporting Serious Adverse Events

Any AE considered serious by the Investigator or that meets SAE criteria (Section 8.10.2) 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 study intervention caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. 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 paper SAE/AESI Report Form distributed to the study sites should be completed and sent via email or fax as provided on the form.

Regulatory reporting requirements for SAEs are described in Section 8.9.11.

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 study intervention or study procedures, or that caused the participant to discontinue the study.

8.9.9. Time Period and Frequency for Collecting AE and SAE Information

Medical occurrences that begin before the start of study intervention 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 study intervention 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 8.10.2. 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 intervention or study participation, the Investigator must promptly notify the Sponsor.

8.9.10. Method of Detecting AEs and SAEs

eDiary has specifically been designed for this study by the Sponsor to collect solicited ARs. Refer to Section 8.9.4 for further details on the use of eDiary. Details on recording of solicited ARs in an eDiary are included in Section 8.10.3.

The Investigator is responsible for the documentation of AEs regardless of vaccination group or suspected causal relationship to the study intervention. 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.

8.9.11. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a 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, IRB/IEC, and Investigators.

Safety reports must be prepared for suspected unexpected serious adverse reactions and will be forwarded to Investigators according to local regulatory requirements and Sponsor policy.

An Investigator who receives a 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.

8.9.12. Blood Sampling Volumes

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

8.9.13. 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 eDiary.

8.10. Safety Definitions

8.10.1. Adverse Event

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

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

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.
- New conditions detected or diagnosed after the first dose of study intervention 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 unsolicited AE is any AE reported by the participant that is not specified as a solicited AR (Section 8.10.3) 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 the study intervention).

8.10.2. Serious Adverse Events

An AE (including a solicited AR) is considered a SAE if it results in any of the following outcomes:

- **Results in Death**
- **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 1 overnight stay as an inpatient for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. 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 disability or 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 (see Section 11.6 for country-specific amendment affecting this paragraph).
- **Congenital anomaly or birth defect**
- **Medically important event**
  An AE is medically important if, per the medical judgment of the Investigator or the Sponsor, it is determined that 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.

8.10.3. Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration. An eDiary will prompt daily participant reporting of solicited ARs using a structured checklist (Section 8.9.4). Participants will record such occurrences in the eDiary on the day of administration of study intervention and on each of the 6 days after dosing.

Severity grading of reactogenicity events will be automatically assigned upon participant entry into the eDiary based on the grading scales presented in Table 5, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

If a participant reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study staff 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 that started after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF. Causality for these events will be determined per assessment by the Investigator.

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

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

Table 5: Solicited Adverse Reactions and Grades

Reaction	Grade 1	Grade 2	Grade 3	Grade 4[1]
Injection site pain	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room (ER) visit or hospitalization
Injection site erythema (redness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis

Reaction	Grade 1	Grade 2	Grade 3	Grade 4[1]
Injection site swelling/induration (hardness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection*	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Headache	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Nausea/vomiting	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Fever (oral)	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

Abbreviation: ER = Emergency room.

Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event reported on the AE page will be determined per assessment by the Investigator.

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

Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

8.10.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study clinic for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up) and visits to HCPs external to the study clinic (eg, emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured on the AE page of the eCRF.

An unscheduled visit for assessment of protocol-defined ILI (symptoms assessment and NP swab) is not considered an MAAE unless additional medical evaluation, including examinations/testing not required per protocol, and/or treatment is provided during the visit, **OR** if the participant meets RT-PCR confirmed influenza infection (RT-PCR with positive result for influenza) (Section 8.10.5).

8.10.5. Influenza-like Illness Case Definitions

Protocol-defined ILI:

A protocol-defined ILI is defined as body temperature ≥ 37.5°C [≥ 99.5°F]) accompanied by at least 1 respiratory illness symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing).

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 Influenza Infection:

An RT-PCR-confirmed influenza infection is defined as a positive influenza result on a respiratory sample by RT-PCR within 7 days of onset of protocol- or CDC-defined ILI performed at any setting during the study period.

Culture-confirmed Influenza Infection:

Culture-defined ILI is defined as a positive influenza result by viral culture following a positive influenza result by RT-PCR. Viral cultures will only be done on samples with a positive influenza result by RT-PCR.

Similarity to Strains Selected for the Seasonal Vaccine:

A laboratory-confirmed isolate is deemed similar to one of the vaccine components if determined by antigenic testing of the cultured virus using specific antisera and/or by genetic sequencing of the HA segments showing identity of key antigenic residues with vaccine strain-like strains.

Antigenic Matched to Strains Selected for the Seasonal Vaccine

Culture-confirmed viruses are deemed to be antigenically similar to vaccine strains by antigenic testing of the cultured virus using specific antisera.

8.10.6. Adverse Events 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.

AESIs for this protocol are described in Section 11.4.

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 should report this information on the paper SAE/AESI Report Form provided to the study site via email or fax as provided on the form (Section 8.9.8).

8.10.6.1. Anaphylaxis

All suspected (ie, related to study intervention) 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 8.9.8. 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.

8.10.6.2. 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 8.9.8).

An independent Cardiac Event Adjudication Committee (CEAC) will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Section 8.11.2).

The CDC Working Case Definitions are provided in Section 11.5 as guidance.

8.10.7. Assessment of Intensity/Severity

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 8.9.8), 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 Preventative Vaccine Clinical Trials (DHHS 2007) 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 8.10.3.

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.

Study 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. 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.

8.10.8. Assessment of Causality

The Investigator will assess causality (ie, whether there is a reasonable possibility that the study intervention 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 study intervention. Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention.

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

8.11. Safety Oversight

8.11.1. Data and Safety Monitoring Board

A DSMB will be used throughout the conduct of this study. This committee will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. Safety data will be reviewed according to intervals defined in the DSMB charter and will also occur as needed.

8.11.2. Independent Cardiac Event Adjudication Committee

An independent Cardiac Event Adjudication Committee (CEAC) of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then make a final decision on whether to suspend further enrollment and/or study dosing based on an assessment of the overall potential risk to study participants.

The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

8.12. Treatment of Overdose

As the study intervention is to be administered by a HCP, it is unlikely that an overdose will occur.

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

1. Contact the Medical Monitor 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.

8.13. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.14. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.15. Biomarkers

Additional biomarkers may be evaluated as part of future research objectives and development. Biomarker assessments may be evaluated as part of the study, which may include serum antibody levels, genomic and transcriptomics studies from consented participants.

According to the ICF (Section 11.1.6), serum from biomarker 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). Optional blood collections for DNA and mRNA sequencing may be performed to research connections between vaccine responses and safety.

NP swabs collected in the study may be used for assay development purposes.

8.16. 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).

8.16.1. Patient-reported Outcome Measures

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

8.16.1.1. EFS

At Day 1, the EFS will be collected by clinical staff for participants aged 65 years and older. This scale is a brief, valid, and reliable tool for assessment of frailty across 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.

8.16.1.2. EQ-5D-5L

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

For all participants, responses to the EQ-5D-5L will be collected using the eDiary 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 symptoms reporting (+1 day), and 5 days (+1 day) later.

8.16.1.3. WPAI

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

8.16.2. Medical Resource Utilization

8.16.2.1. Hospitalization

For hospital stay (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)

8.16.2.2. Outpatient Medical Resource Utilization

For participants reporting MAAEs, outpatient medical resource utilization will be collected, where available. Options that will be 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 study intervention administered until the study database is locked and unblinded, with the following exceptions:

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than the study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded clinic personnel will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned interim analyses (Section 9.5.4). Sponsor team members will be pre-specified to be unblinded to the interim analyses 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 trial participants and to help ensure the integrity of the study.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the study intervention in a secure location that is not accessible or visible to other clinic staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as mRNA-1010 will look different from the 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 primary efficacy objective of this study is to evaluate relative vaccine efficacy (rVE) of mRNA-1010 as compared to an active comparator, to prevent the occurrence of the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.

The null hypothesis to be tested first is that the rVE of mRNA-1010 as compared to an active comparator is inferior, using a 10% noninferiority margin (NIM), (ie, H_0^1: rVE$\leq$ -10%). The rVE

is defined as the percent of reduction in the hazards of the primary endpoint (mRNA-1010 vs. active comparator). Equivalently, the null hypothesis is: H_0^1: hazard ratio (HR) ≥ 1.1

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1010 and the active comparator at a 1-sided 2.5% significance level, using the PP Set.

The trial will be considered to meet the primary efficacy objective by demonstrating noninferiority (NI) of mRNA-1010 to the active comparator if the *p-value* for rejecting HR ≥ 1.1 is less than the nominal *p-value* based on the Lan-DeMets Pocock approximation spending function at the IA or final analysis, on the PP Set. Cases will be counted starting 14 days after the vaccination.

Once NI is demonstrated, the rVE will be further evaluated using the same endpoint for superiority. The null hypothesis to be tested is H_0^2: rVE ≤ 0%. Equivalently, the null hypothesis is: H_0^2: HR ≥ 1.

Superiority of mRNA-1010 versus (vs.) the active comparator on the primary efficacy endpoint will be concluded if the *p-value* for rejecting HR ≥ 1 is less than the nominal *p-value* based on the Lan-DeMets Pocock approximation spending function, on the mITT Set.

9.3. Sample Size

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

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1010 and active comparator, a total of 365 cases on the PP Set will provide at least 93% power to establish a NI claim with a selected NIM = 10%, ie, rejecting the null hypothesis H_0^1: rVE ≤ -10%, with one IA using the Lan-DeMets Pocock boundary for efficacy and a log-rank test statistic with an overall 1-sided Type I error rate of 2.5%.

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

The total number of cases pertains to the PP Set accruing at least 14 days after study intervention.

Approximately 23,000 participants will be randomized with the following assumptions:

- The target rVE of mRNA-1010 to the active comparator is 25% to prevent the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.
- An attack rate of 2% in the active comparator for the primary endpoint.
- One IA in the middle of February 2023 with approximately 75% of total target cases expected across 2 study intervention groups in the PP Set.

- A dropout rate ~ 10% (not evaluable for the PP Set).
- Type I error rate will be adjusted using the Lan-DeMets Pocock boundary.

If the IA is conducted exactly at 75% of total target cases, the nominal 1-sided Type I error rate will be 2.07% at IA and 1.2% at final analysis for NI testing, respectively.

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

- The target rVE of mRNA-1010 to the active comparator is 25% to prevent the first episode of RT-PCR confirmed protocol-defined ILI caused by any influenza A or B virus strains.
- An attack rate of 2% in the active comparator for the primary endpoint.
- An IA in the middle of February 2023 with approximately 290 cases expected (75% of total target cases) across 2 study intervention groups in the mITT Set (defined in Section 9.4).
- A dropout rate ~ 4% (not evaluable for the mITT Set).
- Type I error rate will be adjusted using the Lan-DeMets Pocock boundary.

The total number of cases pertains to the mITT Set accruing at least 14 days after the study intervention. If the IA is conducted exactly at 75% of total target cases, the nominal 1-sided Type I error rate will be 2.07% at IA and 1.2% at final analysis, respectively.

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

9.4. Analyses Populations

Table 6: Populations for Analyses

Analysis Sets	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received any study intervention. Participants will be analyzed according to the group to which they were randomized.
Modified Intent-to-Treat Set (mITT)	All participants in the FAS except those who discontinued from the study prior to 14 days following administration of study intervention. The mITT Set will be used as the primary analysis set for efficacy endpoints evaluating superiority. Participants will be analyzed according to the group to which they were randomized.
Per-Protocol (PP) Set	All participants in the mITT, excluding those with significant protocol deviations that could adversely impact efficacy (eg, disease or

Analysis Sets	Description
	therapeutic intervention that might cause suboptimal response to the study intervention). The PP Set will be used as the primary analysis set for efficacy endpoints evaluating noninferiority. Participants will be analyzed according to the group to which they were randomized.
Immunogenicity Subset	All participants in the biomarker subset who are in the FAS and have baseline and Day 29 antibody assessment via HAI assay. Participants will be analyzed according to the group to which they were randomized.
PP Immunogenicity Subset	The PP Immunogenicity Subset includes all participants in the Immunogenicity Subset who received the planned dose of IP, complied with the immunogenicity testing schedule, and had no major protocol deviations that impact the immunogenicity assessment. Participants with RT-PCR–confirmed influenza between Days 1 to 29 will be removed from the PP Immunogenicity 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	The Solicited Safety Set consists of all randomized participants who received any study intervention and contributed to any solicited adverse reaction (AR) data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study intervention that they actually received.
Safety Set	All randomized participants who received any study intervention. The Safety Set will be used for all analyses of safety except for the solicited ARs, and participants will be included in the vaccination group corresponding to the study intervention that they actually received.

9.5. Statistical Analyses

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

The overall Type I error rate for the primary endpoint at the IAs and the final analysis is strictly controlled at 2.5% (1-sided) based on the Lan-DeMets Pocock spending function (see Section 9.6 for details). The primary efficacy results that will be considered statistically significant after consideration of the strategy for controlling the Type I error is described in Section 9.5.1. Statistical significance of the primary efficacy endpoint for the primary objective can be achieved at either IA or at the final analysis.

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

efficacy objectives (endpoints) will only be tested at the planned IA or final analysis, whichever is applicable, when the primary efficacy endpoint for the primary objective achieves statistical significance. In that case, refer Section 9.6.2 for the multiplicity adjustments among the efficacy objectives (endpoints).

9.5.1. Efficacy Analyses

Efficacy analyses will be performed using the FAS, mITT Set, and PP Set, and participants will be included in the study intervention group to which they are randomized.

9.5.1.1. Analysis of Primary Efficacy Endpoint

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

The rVE is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs. active comparator) and will be estimated using 1-HR estimand. A stratified Cox proportional hazard model with study intervention group as a fixed effect will be used based on the PP Set to estimate the HR (mRNA-1010 vs. active comparator). The stratification factors at randomization, ie, age group ($\geq$ 50 to < 65 years or $\geq$ 65 years) and influenza vaccine status in the previous season (received or not received), will be applied as the strata variables. The Efron's method will be used to handle ties.

For the primary efficacy endpoint, participants without RT-PCR confirmed protocol-defined ILI will be censored at the last study assessment date. Potential intercurrent events may include:

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

In the estimand of the primary analysis on the primary endpoint, a hypothetical strategy will be used to address the intercurrent events in the primary analysis based on the PP Set. The details are presented in Section 11.3.

Participants without RT-PCR confirmed protocol-defined ILI will be censored at Day 181 (Month 6) or end of influenza season (whichever occurs later), or at the date of early discontinuation or death unrelated to influenza, whichever is earlier. Participants with early RT-PCR confirmed protocol-defined ILI up to 14 days after the study vaccination will be censored at the start date of the early RT-PCR confirmed protocol-defined ILI (see Section 11.6 for country-specific amendment affecting this paragraph.

The trial will be considered to meet the primary efficacy objective if the *p-value* for rejecting H_0^1: rVE $\leq$ -10% is less than the nominal *p-value* based on the Lan-DeMets Pocock boundaries, on the PP Set. The nominal alpha at the IA and final analysis will be 2.07% at IA and 1.2% at final analysis.

Analyses of the primary endpoint will be also performed based on the mITT Set using the same methods as described above.

To support the primary analysis, rVE will also be estimated by 1 minus the ratio of incidence rates adjusting for person-time, and the 95% CI of rVE will be computed using the exact method, conditional upon the total number of cases adjusting for person-time.

In addition, Kaplan Meier curve will be used to plot the estimated cumulative incidence rates over time by vaccine group. Participants without a case for the primary endpoint identified will be censored at Day 181/Month 6 or end of influenza season, whichever ends later.

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

9.5.1.2. Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints that are defined in Section 3 will be analyzed in a similar way as for the primary efficacy endpoint. More details can be found in the SAP.

9.5.2. 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.

9.5.2.1. Adverse Events

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

Unsolicited AEs will be coded by system organ class and preferred term according to the MedDRA terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used in this study.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and any solicited AR during the 7-day follow-up period after the study intervention 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 for each vaccination group.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, AESIs, severe AEs, and AEs leading to discontinuation from the study will be summarized. Numbers of events of unsolicited AEs, SAEs, MAAEs, and AESIs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 7 summarizes analysis strategy for safety parameters. Further details will be described in the SAP.

Table 7: 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 AESI	X	
Any Unsolicited MAAE	X	
Any Unsolicited Treatment-Related AE	X	
Any Treatment-Related SAE	X	
Discontinuation due to AE	X	
Any Grade 3 and above AE	X	
Any Treatment-Related Grade 3 and above AE	X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically-attended adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by system organ class and preferred term coded by MedDRA.

9.5.2.2. Baseline Descriptive Statistics

Demographic variables (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, height, weight, and body mass index) will be summarized by study intervention group in descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables).

9.5.3. Immunogenicity Analyses

The primary analysis population for immunogenicity will be the PP Immunogenicity Subset, unless specified otherwise.

For each of the 4 strains, the GMT of HAI titers with corresponding 95% CI will be provided at each timepoint. The 95% CIs will be calculated based on the *t*-distribution of the log-transformed values then back-transformed to the original scale. The GMFR of HAI titers with corresponding 95% CI at each postbaseline timepoint over baseline will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

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, and 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 95% CI will be provided to assess the treatment difference. The

corresponding 2-sided 95% CI of GMR will be provided to assess the difference in immune response between the mRNA-1010 group compared with the active comparator group at Day 29.

For each strain, seroconversion is defined as either a prevaccination HAI titer < 1:10 and a postvaccination titer ≥ 1:40 or a prevaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in postvaccination HAI antibody titer.

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 95% CI for the difference in seroconversion rates. The seroconversion rate difference with the corresponding 95% CI at Day 29 will be provided for each strain.

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

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

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

9.5.4. Exploratory Analyses

Exploratory endpoints evaluating the rVE will be assessed by similar analysis methods as used for the analysis of the primary efficacy endpoint.

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

9.5.5. Subgroup Analyses

If sufficient case numbers of the primary and key secondary endpoints in a subgroup (ie, age, race, etc.) are available, subgroup analysis may be performed.

9.6. Planned Analyses

9.6.1. Interim Analyses

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

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

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

Table 8 summarizes the timing, number of cases, and decision guidance at each IA and final analysis.

Table 8: Interim Boundaries Using Lan-DeMets Pocock Spending Function, Calculation Based on the PP Set for the Endpoint Supporting the Primary Objective

Information Fraction (% of total #cases)	Number of Cases	Nominal Alpha (1-sided) ±	Efficacy Boundary Rejecting H_0: rVE ≤ -10%	Cumulative Probability (Crossing Efficacy Boundary if the True rVE = 25%)
IA (75% cases assumed)	274	2.07%	rVE ≥ 14.0% (HR ≤ 0.860)	87.1%
Final Analysis (100%)	365	1.2%	rVE ≥ 13.2% (HR ≤ 0.868)	93.7%

Abbreviations: HR = hazard ratio; IA: interim analysis; PP = per-protocol; rVE = relative vaccine efficacy.
±: actual nominal alpha may be adjusted based on the actual information fraction at individual IA(s).

The study will be considered positive (rVE has been demonstrate) if the *p-value* for rejecting HR ≥ 1.1 is less than 2.07% based on the Lan-DeMets Pocock alpha spending function, provided that the IA is conducted exactly at 75% information fraction. The final analysis will be performed when approximately 365 cases have been observed in the PP Set. In the case that the early study success is not achieved, the study will be considered positive at the final analysis if the 1-sided *p-value* for rejecting HR ≤1.1 is less than 1.2%.

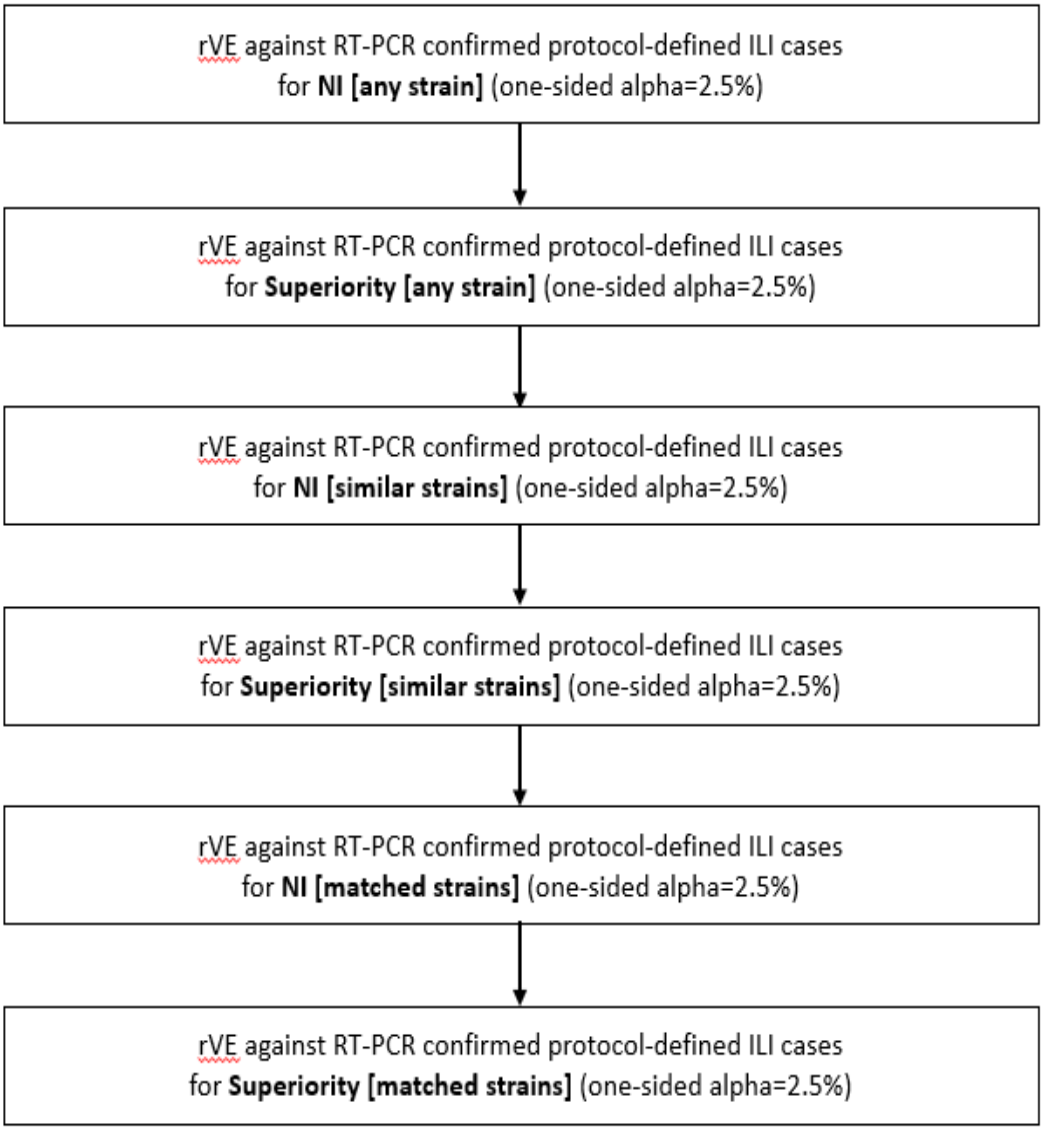
If NI is demonstrated, superiority will be evaluated using the same endpoint based on the mITT Set, following the test sequence illustrated in Figure 1. Upon successful demonstration of the NI claim at the IA, the second null hypothesis to support the superiority objective of the primary efficacy endpoint, (ie, H_0^2: HR ≥ 1 [equivalently, rVE ≤ 0%]), will be tested in the mITT Set. The superiority is successful at the IA if the 1-sided P value for rejecting HR ≥ 1 is less than 2.07% using the Lan-DeMets Pocock alpha spending function. Otherwise, the superiority test will be conducted again at the final analysis, given that the NI claim has been successfully demonstrated (either at the IA or final analysis). The superiority test is successful at the final analysis if the 1-sided P value for rejecting HR ≥ 1 is less than 1.2% based on the Lan-DeMets Pocock alpha spending function.

Approximately 290 cases and 386 cases are expected to be observed at the IA and the final analysis, respectively, in the mITT Set.

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 efficacy endpoints (Figure 1).

Figure 1: Testing Sequence of the Primary and Secondary Endpoints



Noninferiority of mRNA-1010 vs. the active comparator on the primary efficacy endpoint will be declared if the *p-value* for rejecting HR ≥ 1.1 is less than the nominal *p-value* based on the Lan-DeMets Pocock approximation spending function, on the PP Set. The nominal alpha levels (1-sided) are 2.07% at IA and1.2% at the final analysis, respectively, if the IA is conducted when 75% of total target cases are accumulated across the 2 groups.

Once the NI criteria is met for the primary efficacy endpoint, superiority of mRNA-1010 relative to the active comparator will be tested on the mITT Set. The superiority of rVE will be considered demonstrated if the *p-value* for rejecting HR ≥ 1 is less than the nominal *p-value* based on the Lan-DeMets Pocock approximation spending function, on the mITT Set. For this superiority testing, the nominal 1-sided alpha level will be 2.07% at the planned IA and at 1.2%

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

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

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

The testing sequence can only continue to the next level only if all tests at the higher level achieve statistical significance at the 1-sided 2.5% alpha level. If a test at the higher level fails to demonstrate statistical significance, then the testing sequence will stop, and all testing thereafter will not be conducted.

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

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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 (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (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 ModernaTX, Inc. or its representatives will perform a remote or onsite visit with the investigational study 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 ModernaTX, Inc. or its representatives. This will be documented in a Clinical Study Agreement between ModernaTX, Inc., 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 ModernaTX, Inc. 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 a study intervention 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 ModernaTX, Inc. 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 study intervention 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

ModernaTX, Inc., 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 ModernaTX, Inc., their designee(s), the IRB/IEC, or regulatory authorities to inspect the study intervention storage area, study intervention stocks, study intervention records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of ModernaTX, Inc., 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, International Council for Harmonisation Good Clinical Practice (ICH GCP E6 [R2]), and any applicable regulatory requirements. The Investigator should contact ModernaTX, Inc. immediately if contacted by a regulatory agency about an inspection.

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB 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 study site 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 study site 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 meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 IEC/IRB 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 IEC/IRB 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 the participant in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The Investigator or their 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 their 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 they are 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.

The ICF will contain a separate section/consent form(s) that addresses the use of remaining mandatory 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 decline 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 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 to 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 study site 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 their 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 their medical records may be examined by Clinical Quality Assurance 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 their 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.

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 Sponsor may store samples for the time frame specified in the ICF to achieve study objectives. 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.

11.1.11. 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.

11.1.12. Dissemination of Clinical Study Data

ModernaTX, Inc. 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.

11.1.13. 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 on the electronic CRF (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, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 quality assurance representative from 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.

11.1.14. 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 World Health Organization – Drug Reference List.

11.1.15. 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 CRF 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.

ModernaTX, Inc. or its designee requires that the Investigator prepare and maintain adequate and accurate records for each participant treated with the study intervention. 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.

11.1.16. 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 ModernaTX, Inc. 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.

11.1.17. 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 contract research organization(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 study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The Investigator may initiate study-site 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 study site 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.

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

11.1.18. 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 ModernaTX, Inc.

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 (see Section 11.6 for country-specific amendment affecting this section). 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. The above applies to females of child-bearing potential who are sexually active with male partners and not to females with same sex partners or those who are not sexually active as their usual lifestyle.

11.3. APPENDIX 3: Estimands and Estimand Specifications

Table 9: Intercurrent Event Types

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

Abbreviation: IcEv: intercurrent event, PP: per-protocol, FAS: full analysis set, mITT: modified intent-to-treat.

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

Objective: To demonstrate the efficacy of mRNA-1010 to prevent influenza	
Estimand Description	Vaccine efficacy will be measured using 1 – HR (mRNA-1010/ Fluarix) from 14 days after study intervention. A hypothetical strategy will be used for early discontinuation (eg, withdrawal consent, deaths unrelated to influenza) or early infection in participants in PP Set.
Target Population	Adults aged 50 years and older
Variable/Endpoint	Time to first episode of RT-PCR confirmed protocol-defined ILI, censoring at early discontinuation, early infection, or last assessment for an event not being observed, whichever comes earlier.
Treatment Condition(s)	Test: mRNA-1010 Reference: Active Comparator (Fluarix®)
Estimand Label	**Estimand 1**
Population-Level Summary	Vaccine efficacy defined as 1 - HR of mRNA-1010/active comparator
Intercurrent Event Strategy	
IcEv1 (Early discontinuation or unrelated death):	Hypothetical
IcEv2 (early infection):	Hypothetical
Rationale for Strategy(s)	Hypothetical: early discontinuation (including unrelated death) censored at time of discontinuation (or at time of death), and early case will be censored at the time at case onset, handled with independent censoring.

Abbreviation: HR = Hazard ratio; IcEv: intercurrent event; ILI = Influenza like illness; RT-PCR = Reverse transcription polymerase chain reaction

11.4. APPENDIX 4: Adverse Events of Special Interest Terms

Investigators should report all events that fall into the categories presented in Table 11 as an AESI per the reporting processes in Section 8.9.8. 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 11: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome • Acute disseminated encephalomyelitis • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis as defined per protocol (Section 8.10.6.1) • Follow reporting procedures in Section 8.9.8
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

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

11.5. APPENDIX 5: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Table 12: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	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.	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. • tachypnea. • lethargy.	**OR,** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • Irritability. • vomiting. • poor feeding. • tachypnea. • 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¶.	**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.

Acute pericarditis**	Presence of ≥ 2 new or worsening of the following clinical features: • acute chest pain††. • pericardial rub on exam. • 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 Center for Disease Control and Prevention 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 treatment. 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) AV 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).

11.6. APPENDIX 6: Country-specific Requirements

11.6.1. Protocol Amendment DNK-1 (Danish Country-specific Requirements), 26 Oct 2022

Country-specific requirements for the Danish Medicines Agency are as follows:

- Section 5.1, Inclusion Criteria, and Appendix 2, Contraception Guidance, changed the term “adequate contraception” to “highly effective contraceptive methods.”
- Section 8.10.2, Serious Adverse Events, revised the definition of serious adverse events as follows: Persistent or significant **disability or** incapacity or substantial disruption of the ability to conduct normal life functions.
- Section 9.5.1.1, Analysis of Primary Efficacy Endpoint, now includes the following summary description for how missing data will be handled: Participants without RT-PCR–confirmed protocol-defined ILI will be censored at Day 181 (Month 6) or end of influenza season (whichever occurs later), or at the date of early discontinuation or death unrelated to influenza, whichever is earlier. Participants with early RT-PCR–confirmed protocol-defined ILI up to 14 days after the study vaccination will be censored at the start date of the early RT-PCR–confirmed protocol-defined ILI.

11.6.2. Protocol Amendment GBR-1 (United Kingdom Country-specific Requirements), 22 Sep 2022

Country-specific requirements for the Medicines and Healthcare products Regulatory Agency are as follows:

- Section 6.3.7, Unblinding, removed text that stated the requirement of the Investigator to promptly contact the CRO clinical research associate with an explanation for unblinding within 24 hours of opening the code.

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