CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older
Protocol Number:	mRNA-1010-P303
Amendment Number:	2
Date of Amendment	11 Dec 2023
Date of Amendment 1:	10 Oct 2023
Date of Original Protocol:	28 Feb 2023
Compound:	mRNA-1010
Brief Title:	A Phase 3 study to evaluate the immunogenicity and safety of mRNA-1010 candidate seasonal influenza vaccine in adults
Study Phase:	3
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number(s):	**Registry** **ID** FDA IND 27460

Sponsor Signatory:

See e-Signature and date signed on last page of the document.

Sponsor Signatory and Contact Information will be provided separately.

CONFIDENTIAL

This document contains confidential information, which should not be copied, referred to, released to, or published by anyone without written approval from ModernaTX, Inc.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled A Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older, dated 11 Dec 2023 and the most recent version of the mRNA-1010 IB.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, ICH, E6(R2) GCP Guidance, and all applicable local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB 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 Subinvestigator. 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. 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, 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 2	11 Dec 2023
Amendment 1	10 Oct 2023
Original Protocol	28 Feb 2023

Global Amendment 2, 11 Dec 2023: Current Amendment

This amendment is considered to be substantial.

Main Rationale for the Amendment:

The main purpose of this amendment is to update the objectives and endpoints in Part B by moving immunogenicity objectives with corresponding endpoints from exploratory to primary (for noninferiority) and to secondary (for superiority). The summary of changes table describes these changes, including sections that are affected by these changes.

Summary of Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature Page, Protocol Amendment Summary of Changes, Header	Updated the protocol version and date, as applicable.	To reflect the current version.
Section 2.9.5.1 (Immunogenicity Analysis, Part A)	Immunogenicity analysis (paragraph 6) was changed from, "The primary analyses will be repeated using the Immunogenicity Set as a sensitivity analysis" to, "The primary analyses will be repeated using the Immunogenicity Set as a supplementary analysis".	To align with the FDA E9(R1) for Estimands.
Section 3.1 (Protocol Synopsis, Part B)	Section 3.1 (Protocol synopsis) was updated to align with changes in the relevant sections of Part B.	To align with changes in relevant sections of Part B.
Section 3.2 (Objectives and Endpoints, Part B)	Added to primary objectives (Part B): • To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults 18 to <65 years old	To align with the change to establish immunogenicity of mRNA-1010 candidate seasonal influenza vaccine.

Section # and Name	Description of Change	Brief Rationale
	Moved from exploratory to secondary objectives (Part B): • To evaluate the immunological response of mRNA-1010 (for superiority) relative to a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza A and B strains at Day 29. • To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29.	
Sections 3.3.1 and 4.3.1 (Overall Design): Table 9 (Part B), and Table 13 (Part C)	Amount of mRNA/Antigen for treatment group 3 (Table 9) and treatment group 5 (Table 13) changed from 50 µg to 12.5 µg, and for treatment group 6 (Table 13) from 15 µg to 60 µg.	To correct an error in dose calculation of mRNA/antigen.
Section 3.3.2 (Scientific Rationale for Study Design, Part B)	Updated scientific rationale for study design in Part B.	To align with updated objectives and endpoints.
Section 3.9.2 (Statistical Hypothesis), and Section 3.9.3 (Sample Size Determination, Part B)	Statistical hypothesis and the sample size determination were updated in Part B.	To align with the needed analyses for updated endpoints
Section 3.9.7 (Multiplicity, Part B)	Multiplicity adjustment criteria were updated. Figure 1 was moved from Section 4.9.7 to Section 3.9.7.	To align with testing noninferiority and superiority hypotheses in Part B.
Section 3.4.2 (Exclusion Criteria, Part B) and Section 4.4.2 (Exclusion Criteria, Part C)	Updated the exclusion criteria # 10 in Part B and Part C of the study.	To provide clarity on heart muscle inflammation exclusion in Parts B and C.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or Specialist Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
AFAB	Assigned female at birth
ANCOVA	Analysis of covariance
AR	Adverse reaction
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSR	Clinical study report
DHHS	Department of Health and Human Services
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EoS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	Geometric least square mean
GMFR	Geometric mean fold rise
GMR	Geometric mean ratio
GMT	Geometric mean titer
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HCP	Healthcare practitioner
HD	High dose
HIV	Human immunodeficiency virus

Abbreviation or Specialist Term	Definition
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILI	Influenza-like illness
IM	Intramuscular(ly)
IND	Investigational new drug
IRB	Institutional Review Board
IRT	Interactive response technology
IST	Internal safety team
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
(m)RNA	(Messenger) ribonucleic acid
NH	Northern Hemisphere
NP	Nasopharyngeal
POCBP	Person of childbearing potential
PONCBP	Person of nonchildbearing potential
PP	Per-protocol
QTLs	Quality tolerance limits
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SCR	Seroconversion rate
SD	Standard dose
SH	Southern Hemisphere
SoA	Schedule of Activities
WHO	World Health Organization

1. INTRODUCTION

Seasonal influenza viruses are estimated by the WHO to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year, which is a severe challenge to public health (WHO 2023). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the NH and SH, respectively (Riedel et al 2019). Since influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto 2018). Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice a year (once for the NH and once for the SH). Influenza A and B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages) (WHO 2023a, WHO 2023b).

Currently licensed seasonal influenza virus vaccines rarely exceed 60% overall effectiveness and are poorly effective during the years when circulating viruses do not match the strains selected for the vaccine antigens (CDC 2023a). Influenza vaccines based on mRNA technology could provide several benefits compared with current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, and improved protection in older adults (Rockman et al 2020).

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

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

1.1. Study Rationale

The Sponsor is conducting this Phase 3 study (mRNA-1010-P303) of its seasonal influenza mRNA vaccine (mRNA-1010) in 3 parts (Part A, Part B, and Part C), to establish immunogenicity and safety in support of licensure. The design of this study will include immunogenicity objectives for HAI, a surrogate endpoint of prevention of influenza illness and its complications. The rationale for this approach is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016). The Sponsor has optimized mRNA-1010, previously studied, to CCI [redacted]

CCI

1.2. Background

mRNA-1010 is an LNP-encapsulated, mRNA-based, prophylactic vaccine containing 4 mRNAs in an equivalent mRNA mass ratio that encode membrane-bound HA of the 4 different influenza strains, recommended by the WHO for 2022 to 2023 (Part A) and 2023 to 2024 (Parts B, and C) NH cell or recombinant-based vaccines.

The Sponsor has completed a Phase 1/2 study of mRNA-1010 (mRNA-1010-P101, NCT04956575) at dose levels up to 200 µg and is now conducting two Phase 3 studies at a 50-µg dose level: mRNA-1010-P301, a safety and immunogenicity study (NCT05415462) and mRNA-1010-P302, a safety and efficacy study (NCT05566639).

Data from study mRNA-1010-P101 Phase 2 NH suggest an improved and more durable immune response against influenza A strains compared to a licensed seasonal influenza vaccine at Day 29, Day 91, and Day 181. No safety concerns were identified. The 50-µg dose was chosen for the Phase 3 studies based on the observed reactogenicity and immunogenicity profile. Interim results at Day 29 from the Phase 3 mRNA-1010-P301 study indicate no safety concerns. Compared to licensed influenza vaccine, mRNA-1010 achieved superiority on seroconversion rates for A/H3N2 and A/H1N1, as well as superiority on geometric mean titer ratios for A/H3N2 and non-inferiority on geometric mean titer ratios for A/H1N1. Noninferiority was not met for either endpoint for the influenza B/Victoria- and B/Yamagata-lineage strains. In order to improve the immune response to the influenza B strains, the Sponsor has since optimized mRNA-1010 (see Section 1.1).

Additional details of mRNA-1010 are provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Risk Assessment

There have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 vaccines, including mRNA vaccines. The majority of the cases have been reported in adolescent and young adult persons assigned male at birth 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 (Gargano et al 2021). Investigators and participants should be alert to the signs and symptoms of myocarditis and pericarditis (see Section 5.5). The risk of myocarditis or pericarditis after administration of non-coronavirus disease mRNA vaccines is unknown.

Safety and reactogenicity data from a Phase 1/2 study of mRNA-1010 (mRNA-1010-P101, NCT04956575) with dose levels up to 200 µg revealed no safety concerns. Additional details are provided in the IB.

1.3.2. Benefit Assessment

Participants will obtain information about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination, vital signs measurement).

Participants will be contributing to the process of developing a new potentially prophylactic measure for influenza infection.

1.3.3. Overall Benefit/Risk Conclusion

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

2. PART A

2.1. Protocol Summary

2.1.1. Synopsis (Part A)

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

Brief Title: A Phase 3 study to evaluate the immunogenicity and safety of mRNA-1010 candidate seasonal influenza vaccine in adults.

Regulatory Agency Identifier Number(s):

Registry	ID
FDA	IND 27460

Rationale:

The Sponsor is conducting Part A of this Phase 3 study of its candidate seasonal influenza mRNA vaccine (mRNA-1010), mRNA-1010-P303, to establish immunogenicity and safety in support of licensure. The design of this study will include immunogenicity objectives for HAI, a surrogate endpoint of prevention of influenza illness and its complications. The rationale for this approach is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016). The Sponsor has optimized mRNA-1010, previously studied in 2 previous Phase 3 trials, CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix® Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the reactogenicity and safety of mRNA-1010.	• Solicited local and systemic ARs through 7 days after study intervention dosing. • Unsolicited AEs through 28 days after study intervention dosing. • MAAEs from Day 1 to Day 181/EoS. • AESI from Day 1 to Day 181/EoS. • SAEs from Day 1 to Day 181/EoS. • AEs leading to discontinuation from study participation from Day 1 to Day 181/EoS.

Objectives	Endpoints
Secondary	
• To further evaluate the humoral immunogenicity of mRNA-1010 against 4 vaccine-matched influenza virus A and B strains at Day 29.	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 181/EoS.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator against vaccine-matched or vaccine-mismatched A and B strains, including the use of alternative methods.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).
• To assess the occurrence of clinical influenza in study participants and characterize their immune response to infection and viral isolates.	• Frequency of RT-PCR-confirmed ILI and assessment of immune responses in participants with RT-PCR-confirmed ILI.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; AR = adverse reactions; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; ILI = influenza-like illness; MN = microneutralization; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; nAb=neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event.

Overall Design Synopsis:

mRNA-1010-P303 Part A is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older.

Approximately 2400 medically stable adults at least 18 years of age inclusive, at the time of signing the ICF will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Quadrivalent) at Day 1. Randomization will be stratified by age categories (18 to <50 years old, ≥50 to <65 years old, or ≥65 years old) and influenza vaccine status in the prior 12 months (received or not received).

Brief Summary:

The study aims to demonstrate noninferiority of mRNA-1010 versus a licensed quadrivalent seasonal influenza vaccine (an active comparator) in the immune response, as measured by GMT and by seroconversion rate at Day 29, using HAI assay, for each of the 4 vaccine-matched influenza virus A and B strains.

Study details include:

- There will be 4 clinic/in-person visits (Screening Visit and at Days 1, 29 and Day 181 (Month 6)/EoS) and 2 safety phone calls at Days 8 and 91 as specified in the SoA. The Screening Visit and Day 1 may be performed on the same day or a different day.
- All participants will be asked to complete an eDiary for solicited ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days).
- Detection of all AEs will be through 28 days after study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Detecting MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Day 181 (Month 6)/EoS.

Number of Participants: Approximately 2400 participants will be enrolled in Part A.

Study Arms and Duration:

- The study will comprise 2 study arms: investigational vaccine (mRNA-1010) group and active comparator (a licensed quadrivalent seasonal influenza vaccine) group.
- The total study duration (including Screening) for each participant is up to 7 months.

2.1.2. SoA (Part A)

Table 1: Schedule of Activities (Part A)

Visit Number		1	2	3	4	5	USV	Notes
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**	
Month Timepoint				**M1**	**M3**	**M6**	**Up to M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	**N/A**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	**N/A**	
Informed consent form, demographics, concomitant medications, medical history[b]	X							
Inclusion/exclusion criteria	X	X						Refer to Section 2.4.1 and Section 2.4.2
Physical examination[b]	X							Refer to Section 2.8.3.1
Vital signs measurements	X	X						Refer to Section 2.8.3.2
Pregnancy testing	X	X						Prior to study intervention dosing on Day 1 Refer to Section 2.8.3.3
Randomization		X						Refer to Section 2.6
Blood collection for future research sample (optional)		X						Prior to study intervention dosing Refer to Section 2.8.6 and Section 5.1.3
Blood collection for transcriptomics (optional)		X		X				Prior to study intervention dosing on Day 1 Refer to Section 2.8.7

Visit Number		**1**	**2**	**3**	**4**	**5**	**USV**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**	
Month Timepoint				**M1**	**M3**	**M6**	**Up to M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	**N/A**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	**N/A**	
Study intervention dosing (including 30-minute, postdose observation period)[c]		X						One IM injection in the deltoid muscle Refer to Section 2.5.2.2
Blood collection for humoral immunogenicity		X		X		X		Prior to study intervention dosing on Day 1
NP swab for virus detection[d]		X					X	Prior to study intervention dosing on Day 1 Refer to Section 2.8.3.4 and Section 2.8.3.11.3
eDiary activation for recording solicited ARs (7 days)[e]		X						Refer to Section 2.8.3.6
Review of solicited ARs eDiary		X	X					
Follow up safety call[f]			X		X			Refer to Section 2.8.3.5
Recording of unsolicited AEs		X	X	X			X[g]	Refer to Section 2.8.3.8 and Section 5.3

Visit Number		**1**	**2**	**3**	**4**	**5**	**USV**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**	
Month Timepoint				**M1**	**M3**	**M6**	**Up to M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	**N/A**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	**N/A**	
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[h]		X	X	X	X	X	X[g]	
Recording of concomitant medications[i]		X	X	X				Refer to Section 2.6.6.2
Recording of concomitant procedures/surgeries		X	X	X	X	X	X[g]	Refer to Section 2.6.6.2
Recording of non-study vaccinations[j]		X	X	X	X	X		Refer to Section 2.6.6.2
Study completion						X		

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

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

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

c. See Section 2.5.1, Table 3 for dose levels and treatment groups.

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

2.2. Objectives and Endpoints (Part A)

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

Table 2: Objectives and Endpoints (Part A)

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the reactogenicity and safety of mRNA-1010.	• Solicited local and systemic ARs through 7 days after study intervention dosing. • Unsolicited AEs through 28 days after study intervention dosing. • MAAEs from Day 1 to Day 181/EoS. • AESI from Day 1 to Day 181/EoS. • SAEs from Day 1 to Day 181/EoS. • AEs leading to discontinuation from study participation from Day 1 to Day 181/EoS.
Secondary	
• To further evaluate the humoral immunogenicity of mRNA-1010 against 4 vaccine-matched influenza virus A and B strains at Day 29.	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 181/EoS.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed active comparator against vaccine-matched or vaccine-mismatched A and B strains, including the use of alternative methods.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched or vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

Objectives	Endpoints
• To assess the occurrence of clinical influenza in study participants and characterize their immune response to infection and viral isolates.	• Frequency of RT-PCR-confirmed ILI and assessment of immune responses in participants with RT-PCR-confirmed ILI.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; AR = adverse reactions; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; ILI = influenza-like illness; MAAE = medically attended adverse events; MN = microneutralization; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event.

2.3. Study Design (Part A)

2.3.1. Overall Design (Part A)

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

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

Medically stable adults (see Part A Exclusion Criterion # 3), aged 18 years and older, will be screened and enrolled. A complete list of inclusion and exclusion criteria is provided in Section 2.4.

Approximately 2400 participants will be randomly assigned (see Section 2.6) to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Quadrivalent, Table 3).

Table 3: Treatment Groups and Dose Levels (Part A)

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

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid

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

All participants will provide blood samples for assessment of GMT, GMFR, and seroconversion, as measured by HAI (Table 1 and Section 2.8.2). There will be optional blood draws for future research (including genomics) and transcriptomics (Table 1, Section 2.8.6 and Section 2.8.7).

An NP swab for viral respiratory panel testing will be collected at Baseline (Day 1) (prior to study intervention dosing) from all participants and at unscheduled clinic visits if participants have symptoms suggestive of ILI (Section 2.8.3.4). Table 1 displays the time periods for collecting solicited ARs via eDiary (Section 2.8.3.6) and unsolicited AEs. MAAEs, SAEs, and AESIs will be collected from Day 1 to Day 181 (Month 6)/EoS.

There may be situations in which the Investigator asks a participant to report for an unscheduled visit following the report of an AE as shown in the SoA (Table 1). The eCRF should be completed for each unscheduled visit.

This is an observer-blind study (refer to Section 2.6.1 for details). The Investigator may unblind in the event of an emergency (refer to Section 2.5.2.7 for details).

An IST and CEAC will be involved (refer to Section 5.1.6 for details).

2.3.2. Scientific Rationale for Study Design

The study aims to demonstrate noninferiority of mRNA-1010 versus a licensed quadrivalent seasonal influenza vaccine (an active comparator) in the immune response for all 4 strains as measured by GMT and by seroconversion rate.

The rationale for using HAI as a surrogate endpoint of prevention of influenza illness and its complications is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016).

2.3.3. Justification for Dose

The Sponsor has completed a Phase 1/2 study of mRNA-1010 (mRNA-1010-P101, NCT04956575) at dose levels up to 200 µg and is now conducting three Phase 3 studies at a 50 µg dose level: mRNA-1010-P301, a safety and immunogenicity study (NCT05415462), mRNA-1010-P302, a safety and efficacy study (NCT05566639), and an mRNA-1010-P303 Part A (NCT05827978). No safety concerns were identified with dose levels up to 200 µg. The 50-µg dose was chosen for the Phase 3 studies based on the observed reactogenicity and immunogenicity profile (refer to Section 1.2 for details).

2.3.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure for the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or last scheduled procedure.

2.4. Study Population (Part A)

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

2.4.1. Inclusion Criteria (Part A)

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

Age

1. At least 18 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Investigator has assessed that the participant understands and is willing and physically able to comply with protocol mandated follow-up, including all procedures.

Sex and Contraceptive/Barrier Requirements

3. Participants AFAB are eligible to participate if they are not pregnant or breastfeeding/chestfeeding/bodyfeeding, and one of the following conditions applies:
   - Is a PONCBP as defined in Section 5.6.
   - Is a POCBP and using an acceptable contraceptive method as described in Section 5.6 from at least 28 days before the dose of study intervention and during the study intervention period (at a minimum until 90 days after the dose of study intervention). The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the dose of study intervention.
   - A POCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at the Screening Visit and before the dose of study intervention, if Day 1 is not on the same day as the Screening Visit (see Section 2.8.3.3).
     – If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
   - Additional requirements for pregnancy testing during and after study intervention are located in Section 2.8.3.3.
   - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a person with an early undetected pregnancy.

Informed Consent

4. Capable of giving signed informed consent as described in Section 5.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2.4.2. Exclusion Criteria (Part A)

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

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window.
2. 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 Day 1.
3. 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 Day 1 and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
    - Asymptomatic conditions and conditions with no clinically significant end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, if they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the Investigator.
    - Participants who have undergone surgical procedures within 7 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention dosing are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Participants who are HIV positive and on antiviral therapy with cluster of differentiation 4 count ≥350 cells/mm^3 and HIV RNA ≤500 copies/mL within the past 12 months.
    - Participants with immune-mediated diseases which are stable (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or auto-immune ovarian failure, which do not require systemic immunosuppressants per Part A Exclusion Criterion # 13.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos; psoriasis patches affecting skin over the deltoid areas).
6. Participant has tested positive for influenza by local health authority-approved testing methods within 150 days prior to Day 1.
7. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of mRNA vaccines or any components of the mRNA-1010 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. Diagnosis of malignancy within the previous 2 years (excluding nonmelanoma skin cancer).
10. History of myocarditis, pericarditis, or myopericarditis within onset of 180 days prior to Day 1 or have not returned to Baseline clinical status. Participants who have not returned to Baseline after their convalescent period will also be excluded.
11. History of Guillain-Barre syndrome.
12. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.

Prior/Concomitant Therapy

13. Participant has received systemic immunosuppressants for >14 days in total within 180 days prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study intervention dosing.
14. Participant has received any vaccine authorized or approved by local health agency ≤28 days prior to study intervention dosing (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after study intervention dosing.
15. Participant has received a licensed seasonal influenza vaccine within 5 months (150 days) prior to Day 1.
16. Participant has participated in any investigational seasonal influenza vaccine study within 12 months prior to Day 1.
17. Participant is not aware whether they have received an influenza vaccine in the most recent influenza season (in the prior 12 months).
18. Participant has been treated with antiviral therapies for influenza (eg, Tamiflu) within 150 days prior to Day 1.
19. Participant has received systemic immunoglobulins or blood products within 90 days prior to Day 1 or plans to receive systemic immunoglobulins or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to Day 1, or plan to receive them, are also excluded.
20. Participant has donated ≥450 mL of blood products within 28 days prior to Day 1 or plans to donate blood products during the study.

Other Exclusion Criteria

21. Participant has participated in an interventional clinical study within 28 days prior to Day 1, based on the medical history interview or plans to do so while participating in this study. Participants may continue in prior interventional study follow-up activities, as long as it does not involve further investigational treatment other than the study intervention described in this protocol (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.

2.4.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time.

2.4.4. Criteria for Temporarily Delaying the Day 1 Visit

Body temperature (oral preferred) must be measured on the study intervention visit before dosing. The following events constitute criteria for delay of study intervention dosing, and if any of these events occur at the time scheduled for dosing, the participant may receive the study intervention dosing at a later date within the time window specified in the SoA (Table 1), or the participant may be discontinued from dosing at the discretion of the Investigator (Section 2.7):

- Acute moderate or severe infection with or without fever at the time of study intervention dosing.
- Fever, defined as body temperature ≥38.0°C/≥100.4°F at the time of study intervention dosing.

Participants with a fever of ≥38.0°C/≥100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the Investigator determines that the participant's health on the day of dosing temporarily precludes study intervention, the visit should be rescheduled within the allowed interval for that visit.

2.5. Study Intervention(s) and Concomitant Therapy (Part A)

Study intervention(s) refers to the mRNA-1010 vaccine (intervention label: mRNA-1010.6) and to the licensed seasonal influenza vaccine (the "active comparator") intended to be administered to the study participants during the study conduct.

2.5.1. Study Intervention(s) Administered

The study intervention(s) to be administered and the treatment groups in the study are provided in Table 4.

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

The active comparator administered in this study is a licensed quadrivalent seasonal influenza vaccine administered as a single 0.5 mL IM injection.

Table 4: Study Intervention(s) Administered

Intervention Label	**mRNA-1010.6**	**Fluarix**
Treatment Group Type	Experimental	Active comparator
Intervention Name	mRNA-1010	Fluarix Quadrivalent
Intervention Description	mRNA-1010 contains LNP dispersion encoding the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2022 to 2023 NH cell- or recombinant-based vaccines. All mRNAs are formulated in LNPs composed of 4 lipids and provided as a sterile liquid for injection, white-to-off white dispersion in appearance, at a concentration of 0.10 mg/mL in 20 mM Tris buffer with 87 g/L sucrose, and 2.2 mM sodium acetate at pH 7.5.	Licensed quadrivalent seasonal vaccine Fluarix Quadrivalent contains the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2022 to 2023 NH egg-based vaccines.
Type	Vaccine	Vaccine
Dosage Level(s)	50 µg of mRNA Single dose	60 µg of proteins Single dose
Route of Administration	IM	IM
Use	Experimental	Active control

Intervention Label	mRNA-1010.6	Fluarix
IMP and AxMP	IMP	IMP
Sourcing	By Sponsor	By Sponsor
Packaging and Labeling	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

Abbreviations: AxMP = auxiliary medicinal product; CFR = Code of Federal Regulations; GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; HA = hemagglutinin; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IM = intramuscular(ly); IMP = investigational medicinal product; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; NH = Northern Hemisphere; WHO = World health Organization.

2.5.2. Preparation, Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized clinic staff may supply, prepare, or administer study intervention.

All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized clinic staff.

The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

2.5.2.1. Study Intervention(s) Preparation

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

2.5.2.2. Study Intervention(s) Administration

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

Participants will be monitored for a minimum of 30 minutes after administration of the study intervention. Assessments will include vital sign measurements and monitoring for solicited ARs as shown in the SoA (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.

2.5.2.3. Study Intervention(s) Packaging and Labeling

The Sponsor will provide the Investigator (via the clinic pharmacy) with adequate quantities of the study intervention(s). The study intervention(s) 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, CFR Title 21, Good Manufacturing Practice guidelines, ICH, and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

2.5.2.4. Study Intervention(s) Storage

mRNA-1010 must be stored at the clinical site at 2°C to 8°C in a secure area with limited access and must be protected from moisture and light until it is prepared for administration (Section 2.5.2.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. The refrigerator should be connected to a backup generator. In addition, for study intervention accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The clinic is responsible for reporting any 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. Please note that 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.

2.5.2.5. Study Intervention(s) 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 study intervention in a study intervention accountability log. Study intervention 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.

2.5.2.6. Study Intervention(s) Handling and Disposal

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

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

2.5.2.7. Unblinding

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

2.6. Assignment to Study Intervention (Part A)

Randomization will be performed using an IRT. Approximately 2400 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as an active comparator (Fluarix Quadrivalent, Table 3). Randomization will be stratified by age categories (18 to <50 years old, ≥50 to <65 years old, or ≥65 years old) and influenza vaccine status in the prior 12 months (received or not received). Approximately 50% of participants (1200) enrolled will be ≥50 years old, including approximately 20% (480) who will be ≥65 years old. The Sponsor anticipates approximately 200 participants enrolled in the ≥65 years old age group will be ≥75 years old.

2.6.1. Blinding

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

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

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.

Neither the participant nor the Investigator nor clinic staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study.

Except in the case of medical necessity, a participant's treatment should not be unblinded without the approval of the Sponsor. The treatment code should be broken only if the Investigator in charge of the participant feels that the case cannot be treated without knowing the identity of the study intervention. Instructions regarding emergency unblinding will be provided to the Investigator and are discussed in Section 2.5.2.7.

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 primary analysis (see Section 2.9.6), pre-identified Sponsor team members and selected CRO team members will be unblinded to conduct the analyses. Clinics will remain blinded.

2.6.2. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of the dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the clinic staff other than the person administering the study intervention.

2.6.3. Dose Modification

Not applicable.

2.6.4. Continued Access to Study Intervention After the End of the Study

Continued access to the study intervention will not be available after the end of the study.

2.6.5. Treatment of Overdose

The study intervention will be provided in a single dose vial and is to be administered by a healthcare provider. It is unlikely that an overdose will occur. Should overdose occur, careful monitoring and follow-up must be performed.

2.6.6. Prior and Concomitant Therapy

Medications administered within the period starting 28 days before the study intervention must be recorded in the eCRF.

2.6.6.1. Prohibited Therapy

Medications prohibited for the duration of the study are:

- Systemic immunosuppressive treatment (for corticosteroids, ≥10 mg/day of prednisone or equivalent). Intra-articular and epidural steroids are not allowed within 28 days before and/or after study intervention dosing. Inhaled, nasal, and topical steroids are allowed.
- Systemic immunoglobulins or blood products.
- Long-acting biological therapies that affect immune responses (eg, infliximab).

The Investigator should contact the medical monitor with questions regarding potential prohibited medications and to determine eligibility for the study. It is the Investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

2.6.6.2. Recording of Concomitant Medications, Concomitant Vaccinations and Concomitant Procedures

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

- Any vaccine (authorized or investigational) administered in the prior 12 months. For authorized influenza vaccines, detailed information regarding which vaccine was administered should be provided if available.
- All prohibited therapies (Section 2.6.6.1) at the time of the Day 1 Visit.
- All concomitant medications taken at the time of the Day 1 Visit through 28 days after study intervention dosing. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- All non-study vaccines taken through 181 days after study intervention dosing.
- 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 MAAE from Day 1 through Day 181 (Month 6)/EoS.
- The participant will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after study intervention dosing, including the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the clinic staff during the clinic/in-person visit and safety phone call after study intervention dosing or via other participant interactions (eg, telephone calls).
- All concomitant procedures/surgeries at any time during the study period after study intervention dosing.

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

2.6.6.3. 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 PP analysis (analysis sets are described in Section 2.9.4):

- 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 corticosteroids, this will mean that prednisone ≥10 mg/day or the equivalent is not permitted. Intra-articular and epidural steroids are not allowed within 28 days before and/or after study intervention dosing. Inhaled, nasal, and topical steroids are allowed.
- Long-acting, immune-modifying drugs administered at any time during the study period (eg, infliximab).
- An authorized or licensed vaccine administered within 28 days of study intervention dosing.
- Immunoglobulins and/or any blood products administered during the study period.

2.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal (Part A)

Discontinuation of specific sites or of the study as a whole are detailed in Section 5.1.10.

2.7.1. Discontinuation of Study Intervention

Not applicable.

2.7.1.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study, if possible, the Investigator will request that the participant complete all study procedures pending at the time of withdrawal, as shown in the SoA (Table 1).

The participant will be permanently discontinued from the study participation at that time.

A participant who withdraws from the study will not be replaced.

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.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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).

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. All data collected until the date of withdrawal or last contact of the participant will be used for the analysis. A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

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 a participant, or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse event
- Death
- LTFU
- Noncompliance with study procedures
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by participant
- Withdrawal due to solicited AR/reactogenicity
- Other

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study because of an SAE or AE until resolution of the event.

2.7.1.2. Lost to Follow-up

A participant will be considered LTFU if the participant repeatedly fails to return for scheduled visits 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 LTFU, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and certified letter) 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 be not considered LTFU until due diligence has been completed.

2.7.2. Pause Rules

Not applicable.

2.8. Study Assessments and Procedures (Part A)

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (Section 2.4). The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

Study results that could unblind the study will not be reported to investigative sites or other blinded clinic staff until the study database is locked and unblinded.

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 by local regulations.

Sample collection on Day 1 (ie, blood and NP swab) must be performed prior to study intervention dosing.

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.

All study visits with the exception of the Screening Visit and Day 1 Visit can take place at the study site or mobile site or at the home of the participant, where allowed by local regulations, and upon written Sponsor approval. If a visit cannot be scheduled within the indicated allowable window and/or the participant misses the visit, this is considered a protocol deviation. However, the visit should still be completed, if possible, to collect study data. Subsequent visits should be scheduled at the originally planned number of days after Day 1 defined in the SoA (Table 1).

2.8.1. Demography

Demographic information relating to the participant's sex, age, and race will be recorded at Screening in the eCRF.

Medical history of each participant will be collected and recorded in the eCRF. Significant findings that were present prior to the signature of the informed consent will also be included in the eCRF.

2.8.2. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Table 1). The following analytes will be measured:

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

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

Serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to influenza vaccines, additional assay development, and the immune response across influenza viruses.

2.8.3. Safety Assessments

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

- Solicited local and systemic ARs that occur during the 7 days following the study intervention dosing (ie, the day of study intervention dosing and 6 subsequent days). Solicited ARs will be recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following the study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol defined solicited ARs.
- AEs leading to discontinuation from study participation from Day 1 (poststudy intervention dosing) through Day 181 (Month 6)/EoS.
- MAAEs from Day 1 through Day 181(Month 6)/EoS.
- AESIs from Day 1 through Day 181 (Month 6)/EoS.
- SAEs from Day 1 through Day 181 (Month 6)/EoS.
- Details of pregnancies in participants may be collected after the start of study intervention dosing (see Section 2.8.3.8.5); however, pregnancy related data received after the end of the study may not be collected in the clinical database.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and non-study vaccinations.
- Concomitant procedures.
- Pregnancy testing.

2.8.3.1. Physical Examinations

A complete physical examination will be performed at the Screening Visit. A complete physical examination will include, at a minimum, assessments of skin, head, ears, eyes, nose, throat, neck,

thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. Height and weight will also be measured and recorded. Any clinically significant finding identified during the Screening Visit should be reported as medical history.

Symptom-directed physical examinations will be performed at other clinic/in-person visits, at the discretion of the Investigator, except at Screening where a full physical examination will be performed (Table 1). Any clinically significant finding identified during a symptom-directed physical examination should be reported as an AE.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

2.8.3.2. Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature will be measured at the timepoints indicated in the SoA (Table 1). Vital signs may be collected at other clinic/in-person visits in conjunction with a symptom-directed physical examination. The preferred route of temperature assessment is oral.

The participant will be seated for at least 5 minutes before all measurements are taken. On Day 1, vital sign measurements will be collected once before study intervention dosing and at least 30 minutes after study intervention dosing (before participants are discharged from the study site). If vital signs are clinically concerning, participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection.

Febrile participants on the study intervention dosing day (fever is defined as a body temperature ≥38.0°C/100.4°F) may be rescheduled within the relevant window periods. Criteria for delay of study intervention dosing are provided in Section 2.4.4.

An abnormal vital sign measurement should be assessed to determine if it meets AE reporting criteria per protocol and reported as an AE in the EDC, if appropriate. The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at Baseline, is considered stable, or until the Investigator determines that follow-up is no longer medically necessary.

2.8.3.3. Pregnancy Testing

Refer to Section 2.4.1 for pregnancy testing entry criteria and to Section 5.2 Appendix 2 for clinical laboratory tests.

A pregnancy test either via blood or point-of-care urine test will be performed at the Screening Visit and before study intervention dosing 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 FSH level may be measured at the Screening Visit, as necessary and at the discretion of the Investigator, to confirm postmenopausal status.

2.8.3.4. Assessments for Respiratory Viral Infections (Part A Only)

NP swab specimen(s) for viral respiratory pathogens will be collected prior to study intervention dosing on Day 1. The participant will be instructed to contact the study site if they have symptoms suggestive of ILI throughout the study up to Day 181 (Month 6)/EoS. An unscheduled visit for symptom assessment and NP swab will be conducted if a participant reports protocol-

defined ILI that is within 7 days from symptom onset. Participants who manifest protocol-defined ILI will be evaluated by RT-PCR testing of NP swab specimen(s) for influenza (and other respiratory pathogens) (Section 2.8.3.11.3). NP swabs may be collected as part of a home visit in lieu of a clinic/in-person visit, according to site procedures and prior Sponsor approval. 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.

2.8.3.5. Safety Phone Calls

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

2.8.3.6. 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 16.

Solicited local and systemic reactogenicity ARs will be collected on the day of study intervention dosing and during the 7 days after study intervention dosing (ie, the day of study intervention dosing and 6 subsequent days). Details on the recording of solicited local and systemic ARs are included in Section 2.8.3.9.

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

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 intervention dosing. Daily oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the clinic staff.

The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1). If eDiary questions result in identification of relevant safety events according to the study period or symptoms, a follow-up safety call will be triggered. The results of the safety call should be recorded in the appropriate source documentation.

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

2.8.3.7. 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. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

2.8.3.8. AEs, SAEs, and Other Safety Reporting

The definitions of AEs, SAEs, solicited ARs, and unsolicited AEs can be found in Section 5.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 5.3.

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

All SAEs, AESI, MAAE, and AEs leading to discontinuation from study participation will be collected from the start of study intervention dosing until Day 181 (Month 6)/EoS or withdrawal from the study at the timepoints specified in the SoA (Section 5.3).

All solicited local and systemic ARs will be collected from the start of study intervention and during the 7 days following the study intervention (ie, the day of study intervention dosing and 6 subsequent days).

All unsolicited AEs will be collected from the start of study intervention and during the 28 days following the study intervention (ie, the day of study intervention and 27 subsequent days).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs; however, if the condition worsens at any time after study intervention administration, it will be recorded and reported as an AE.

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 5.3. 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 information on AEs or SAEs after the study completion Visit. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

2.8.3.8.2. Method of Detecting AEs and SAEs

An electronic diary has specifically been designed for this study by the Sponsor for collection of solicited adverse reactions (see Section 2.8.3.6). At the time of consent, the participants must confirm they will be willing to complete the eDiary via an application downloaded to their smartphone or via a device that is provided at the time of enrollment. Prior to enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days). The diary will include prelisted ARs (solicited ARs) and intensity scales.

At every clinic/in-person 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) for detection of unsolicited AEs, 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.

Detection of all AEs will be through 28 days after study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Detecting MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Day 181 (Month 6)/EoS (Table 1).

The Investigator is responsible for the documentation of AEs regardless of treatment 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.

2.8.3.8.3. Follow-up of AEs and SAEs

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

All SAEs and AESIs (as defined in Section 2.8.3.11) 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 2.7.1.2). Further information on the follow-up procedures is provided in Section 5.3.

2.8.3.8.4. Regulatory Reporting Requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

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

For expedited reporting purposes, the expectedness of SAEs will be assessed against the investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB/package insert for investigational product(s) and comparator(s) will be considered unexpected.

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

2.8.3.8.5. Pregnancy

The effects of mRNA-1010 on the unborn child and on the newborn baby are not known. Because of this, it is important that research study participants are not pregnant and do not become pregnant during the course of the research study. Pregnancy testing is scheduled to occur at the Screening Visit and Day 1 (Table 1). Individuals who have a positive pregnancy test at the Screening Visit must not be enrolled. Additional pregnancy testing may also be performed at any time during the study if required by local regulatory requirements, or at the discretion of the Investigator.

The occurrence of pregnancy in participants will be collected after the start of study intervention and until Day 181 (Month 6)/EoS. If a pregnancy is reported, the Investigator will record pregnancy information on the form provided and submit it to the Sponsor within 24 hours of learning of the pregnancy. Participants who have a positive pregnancy test after receiving study intervention should remain in the study and be followed-up for safety.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (refer to Section 5.3). Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 5.3).

If pregnancy extends s beyond the participant's EoS visit, follow-up with the participant by phone approximately one month after the estimated due date is expected. The Investigator will collect follow-up information on the pregnancy and its outcome on the form provided, and the information will be forwarded to the Sponsor.

2.8.3.9. Solicited Adverse Reactions

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

checklist. Participants will record such occurrences in the eDiary on the day of study intervention dosing and 6 subsequent days.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented Section 5.3, which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b). All solicited ARs (local and systemic) will be considered causally related to dosing.

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 in EDC.

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 in EDC, where reactogenicity is collected.

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

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

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

2.8.3.10. Medically Attended Adverse Events

The definition of MAAE is provided in Section 5.3.3.

2.8.3.11. Adverse Events of Special Interest

The definition of AESI is provided in Section 5.3.4. AESIs for this protocol are listed in Section 5.3.

2.8.3.11.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention dosing should be recorded as AESIs and reported as an SAE (Section 5.3 [Reporting of SAEs]), based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown 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
- Involving 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.

2.8.3.11.2. Myocarditis and/or 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 case definition. The event should also be reported as an SAE if it meets seriousness criteria (see Section 5.3.2).

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical trials per the CEAC charter, to determine if they meet CDC criteria for “probable” or “confirmed” events (Section 5.1.6.2).

The CDC Working Case Definitions are provided in Section 5.5 as guidance.

2.8.3.11.3. Influenza-like Illness Case Definitions

Protocol-defined ILI

A protocol-defined ILI is determined by the occurrence of at least 1 respiratory illness symptom concurrently with at least 1 systemic symptom, or the occurrence of any 2 or more respiratory symptoms, as shown in Table 5.

Table 5: Respiratory and Systemic Symptoms for Protocol-defined Influenza-like Illness

Respiratory symptoms	Systemic symptoms
1. Sore throat 2. Cough/rhinorrhea/nasal congestion (≥1 of the 3 symptoms count as 1 respiratory symptom) 3. Sputum production 4. Wheezing 5. Difficulty breathing	1. Body temperature ≥37.5°C (≥99.5°F) 2. Chills 3. Tiredness 4. Headache 5. Myalgia 6. Nausea/vomiting 7. Diarrhea

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-defined ILI performed at any setting during the study period.

2.8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

2.8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

2.8.6. Genetics

A prospective research sample(s), to be used for future genomic research, will be collected from participants who have consented to participate in the genomic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genomic research may still participate in the study.

2.8.7. Biomarkers

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

2.8.8. Immunogenicity Assessments

Antibodies to the study intervention will be evaluated in serum samples collected from all participants according to the SoA (Table 1). These samples will be tested by the Sponsor or Sponsor's designee.

The detection and characterization of antibodies to the study intervention will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to the study intervention will also be evaluated for study intervention serum concentration to enable interpretation of the antibody data. Antibodies may be further

characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for the time period specified in the ICF (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to the study intervention.

2.8.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

2.9. Statistical Considerations (Part A)

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of the statistical analyses will be provided in the SAP, which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

2.9.1. Blinding and Responsibility for Analyses

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

- Unblinded personnel (of limited numbers) will be assigned to study intervention accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participants or the blinded clinic staff involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded clinic staff will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned primary analysis (see Section 2.9.6). Sponsor team members will be prespecified to be unblinded to the primary analysis and will not communicate the results to the blinded investigators, clinic staff, clinical monitors, or participants.

- The IST may review data, as appropriate, to safeguard the interests of participants and to help ensure the integrity of the study.

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

Procedures for breaking the blind in the case of a medical emergency are provided in Section 2.5.2.7.

2.9.2. Statistical Hypotheses

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

Each of the 8 coprimary immunogenicity endpoints will be evaluated for noninferiority of mRNA-1010 versus the active comparator at a 2-sided alpha of 0.05 level. The study is considered as a success if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria.

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

2.9.3. Sample Size Determination

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

The study has at least 95% power to demonstrate noninferiority of the immune response in all 4 strains, as measured by seroconversion rate in the mRNA-1010 group compared with that in the active comparator group, at a 2-sided alpha of 0.05 level, assuming a seroconversion rate of 69% in influenza A strains and 59% in influenza B strains, respectively, in the mRNA-1010 group (a true rate difference is -1% compared to the active comparator group), and a noninferiority margin of 10%.

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

2.9.4. Analysis Sets

The analysis sets are defined in Table 6.

Table 6: Populations for Analysis

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

Abbreviations: AR = adverse reaction; FAS = Full Analysis Set; HAI = hemagglutination inhibition; PP = per-protocol; RT-PCR = reverse transcription polymerase chain reaction.

2.9.5. Statistical Analyses

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

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

2.9.5.1. Immunogenicity Analyses

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

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

Rate of seroconversion is defined as the proportion of participants with either a 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.

An ANCOVA model will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, treatment group as the fixed variable, log-transformed baseline HAI titers as a fixed covariate, adjusting for the stratification factors. The GLSM and its corresponding 95% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale, as an estimate of the GMT. 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 to the active comparator group at Day 29. For each strain, the noninferiority of GMT will be considered demonstrated if the lower bound of the 95% CI of the GMR is >0.667 based on a noninferiority margin of 1.5.

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

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

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

In addition, 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.

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

2.9.5.2. Adverse Events

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 treatment group, unless otherwise specified.

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

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

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

Solicited ARs will be coded according to the MedDRA for AR terminology. The Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used in this study (DHHS 2007b).

The number of events of unsolicited AEs/SAEs, AESIs, MAAEs, and AEs leading to discontinuation from study participation will be reported in summary tables accordingly. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

2.9.5.3. Exploratory Analyses

Number and percentage of participants with RT-PCR confirmed influenza infection within the period of 14 days postinjection up to EoS and within the period of Day 1 up to EoS will be summarized for the Safety Set. A 2-sided 95% CI using the Clopper-Pearson method will be provided for the percentage of participants with the RT-PCR confirmed influenza infection.

Exploratory analyses not addressed in Section 2.9.5.3 will be described in the SAP before database lock.

2.9.6. Planned Analyses

2.9.6.1. Primary Analyses

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

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

2.9.6.2. Final Analysis

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

2.9.7. Multiplicity

No multiplicity adjustment will be applied because the study is considered as a success only if all the 8 coprimary immunogenicity endpoints meet the noninferiority criterion. Each of the coprimary immunogenicity endpoints will be tested at 2-sided alpha of 0.05 level.

3. PART B

3.1. Protocol Summary

3.1.1. Synopsis (Part B)

Rationale:

The Sponsor is conducting Part B of this Phase 3 study, mRNA-1010-P303, to further evaluate its candidate seasonal influenza mRNA vaccine (mRNA-1010) compared to a SD seasonal influenza vaccine in adults 18 to <65 years old, to establish immunogenicity and obtain additional safety data in support of licensure. The design of this study will include immunogenicity objectives for HAI, a surrogate endpoint of prevention of influenza illness and its complications. The rationale for this approach is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults 18 to <65 years old.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the safety, including reactogenicity, of mRNA-1010.	• Frequency and severity of solicited local and systemic ARs during a 7-day follow-up period postinjection. • Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection. • Frequency of any SAEs, MAAEs, AESIs, and AEs leading to discontinuation from Day 1 to Day 181/EoS.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 (for superiority) relative to a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.

Objectives	Endpoints
• To evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched or vaccine-mismatched A and B strains.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; MAAE = medically attended adverse event; MN = microneutralization; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; SAE = serious adverse event; SD = standard dose

Overall Design Synopsis:

mRNA-1010-P303 Part B is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults 18 to <65 years old.

Approximately 3000 medically stable adults 18 to <65 years of age, at the time of signing the ICF, will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) at Day 1. Randomization will be stratified by the previous flu season (since September 2022) vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study [yes/no]).

Brief Summary:

The study aims to demonstrate noninferiority of mRNA-1010 versus a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) in the immune response, as measured by GMT and seroconversion rate at Day 29, using HAI assay, for each of the 4 vaccine-matched influenza virus A and B strains.

Study details include:

- There will be 3 to 4 clinic/in-person visits (Screening Visit and at Days 1, 29, and Day 181 [Month 6]/EoS [in a subset of ~ 1000 participants]) and 2 to 3 safety phone

call at Days 8, 91, and 181 (non-subset participants) as specified in the SoA. The Screening Visit and Day 1 may be performed on the same day or a different day.

- All participants will be asked to complete an eDiary for solicited ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days).
- Detection of all AEs will be through 28 days after study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Detecting MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Day 181 (Month 6)/EoS.

Number of Participants: Approximately 3000 participants will be enrolled in Part B.

Study Arms and Duration:

- The study will comprise 2 study arms: investigational vaccine (mRNA-1010) group and licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) group.
- The total study duration (including screening) for each participant is up to 7 months.

3.1.2. SoA (Part B)

Table 7: Schedule of Activities (Part B)

Visit Number		**1**	**2**	**3**	**4**	**5**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	
Month Timepoint				**M1**	**M3**	**M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	
Informed consent form, demographics, concomitant medications, medical history[b]	X						
Inclusion/exclusion criteria	X	X					Refer to Section 3.4.1 and Section 3.4.2
Physical examination[b]	X						Refer to Section 3.8.3.1
Vital signs measurements	X	X					Refer to Section 3.8.3.2
Pregnancy testing	X	X					Prior to study intervention dosing on Day 1 Refer to Section 3.8.3.3
Randomization		X					Refer to Section 3.6
Blood collection for humoral immunogenicity		X		X		X[i]	Prior to study intervention dosing on Day 1
Study intervention dosing (including 30-minute, postdose observation period)[c]		X					One IM injection in the deltoid muscle Refer to Section 3.5.2.2

Visit Number		**1**	**2**	**3**	**4**	**5**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	
Month Timepoint				**M1**	**M3**	**M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	
eDiary activation for recording solicited ARs/medication recording (7 days)[d]		X					Refer to Section 3.8.3.5
Follow up safety call[e]			X		X	X[i]	Refer to Section 3.8.3.4
Review of solicited ARs eDiary		X	X				
Recording of unsolicited AEs		X	X	X			Refer to Section 3.8.3.7 and Section 5.3
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[f]		X	X	X	X	X	
Recording of concomitant medications[g]		X	X	X			Refer to Section 3.6.6.2
Recording of nonstudy vaccinations[h]		X	X	X	X	X	Refer to Section 3.6.6.2
Recording of concomitant procedures/surgeries		X	X	X	X	X	Refer to Section 3.6.6.2
Study completion						X	

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

a. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window.
b. Verbal medical history is acceptable. Clinically significant findings during the Screening Visit physical examination should also be recorded in the participant's medical history.
c. See Section 3.5.1, Table 9 for dose levels and treatment groups.
d. The eDiary entries will be recorded at approximately 30 minutes after study intervention dosing while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, on the day of study intervention dosing and the subsequent 6 days following study intervention dosing.
e. An unscheduled follow-up safety call may be triggered by the identification of a relevant safety event from an eDiary record, or other participant contact. A safety phone call may trigger an unscheduled visit.
f. Trained clinic staff will call (or contact by electronic means) all participants to collect information relating to any MAAEs, AEs leading to discontinuation from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.
g. All concomitant medications will be recorded from Day 1 through Day 29; thereafter, only concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded through Day 181 (Month 6)/EoS.
h. All nonstudy vaccinations will be recorded through 181 days after the dose of study intervention.
i. Samples for humoral immunogenicity on Day 181 (Month 6)/EoS will be collected for first 1000 participants and analyzed in a subset. Participants in the subset require a clinic visit on Day 181 (Month 6)/EoS for sample collection. All other participants will require a safety call.

3.2. Objectives and Endpoints (Part B)

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 8.

Table 8: Objectives and Endpoints (Part B)

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults 18 to <65 years old.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the safety, including reactogenicity, of mRNA-1010.	• Frequency and severity of solicited local and systemic ARs during a 7-day follow-up period postinjection. • Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection. • Frequency of any SAEs, MAAEs, AESIs, and AEs leading to discontinuation from Day 1 to Day 181/EoS.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 (for superiority) relative to a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29.	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.

Objectives	Endpoints
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) against vaccine-matched or vaccine-mismatched A and B strains.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; MAAE = medically attended adverse event; MN = microneutralization; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; SAE = serious adverse event; SD = standard dose.

3.3. Study Design (Part B)

3.3.1. Overall Design (Part B)

mRNA-1010-P303 Part B is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults 18 to <65 years old.

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

Medically stable adults (see Part B Exclusion Criterion # 3), aged 18 to <65 years, will be screened and enrolled. A complete list of inclusion and exclusion criteria is provided in Section 3.4.

Approximately 3000 participants will be randomly assigned (see Section 3.6) to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent, Table 9).

Table 9: Treatment Groups and Dose Levels (Part B)

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

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid

Table 7 displays the study SoA. Clinic/in-person visits will consist of a Screening Visit (up to 28 days before the Day 1 Visit and may be performed over multiple visits if within the 28-day screening window), a dosing visit on Day 1 (Baseline; may be on the same day as the Screening

Visit), a visit on Day 29 (Month 1), and a subsequent visit on Day 181 (Month 6)/EoS [in a subset of ~ 1000 participants]), with up to 7 months of study participation for each participant. There will also be contacts by electronic means or telephone calls on Day 8, Day 91 (Month 3), and Day 181 (Month 6 [non-subset participants]).

Table 7 displays the time periods for collecting solicited ARs via eDiary (Section 3.8.3.5) and unsolicited AEs. MAAEs, SAEs, AESIs and AEs leading to discontinuation will be collected from Day 1 to Day 181 (Month 6)/EoS. All participants will provide blood samples that may be used for assessment of GMT, GMFR, and seroconversion, as measured by HAI (Table 7 and Section 3.8.8).

There may be situations in which the Investigator asks a participant to report for an unscheduled visit following the report of an AE. The eCRF should be completed for each unscheduled visit.

This is an observer-blind study (refer to Section 3.6.1 for details). The Investigator may unblind in the event of an emergency (refer to Section 3.5.2.7 for details).

An IST and CEAC will be involved (refer to Section 5.1.6 for details).

3.3.2. Scientific Rationale for Study Design

Part B of this study aims to demonstrate noninferiority of mRNA-1010 versus a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) in the immune response for all 4 strains, as measured by GMT and by seroconversion rate, in adults between the ages of 18 to <65 years.

The rationale for using HAI as a surrogate endpoint of prevention of influenza illness and its complications is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016).

3.3.3. Justification for Dose

The Sponsor has completed a Phase 1/2 study of mRNA-1010 (mRNA-1010-P101, NCT04956575) at dose levels up to 200 µg and is now conducting three Phase 3 studies at a 50 µg dose level: mRNA-1010-P301, a safety and immunogenicity study (NCT05415462), mRNA-1010-P302, a safety and efficacy study (NCT05566639), and mRNA-1010-P303 Part A (NCT05827978). No safety concerns were identified with dose levels up to 200 µg. The 50-µg dose was chosen for the Phase 3 studies based on the observed reactogenicity and immunogenicity profile (refer to Section 1.2 for details).

3.3.4. End of Study Definition

See Section 2.3.4 for details.

3.4. Study Population (Part B)

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

3.4.1. Inclusion Criteria (Part B)

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

Age

1. At least 18 and <65 years of age, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Investigator has assessed that the participant understands and is willing and physically able to comply with protocol mandated follow-up, including all procedures.

Sex and Contraceptive/Barrier Requirements

3. Participants AFAB are eligible to participate if they are not pregnant or breastfeeding/chestfeeding/bodyfeeding, and one of the following conditions applies:
   - Is a PONCBP as defined in Section 5.6.
   - Is a POCBP and using an acceptable contraceptive method as described in Section 5.6 from at least 28 days before the dose of study intervention and during the study intervention period (at a minimum until 90 days after the dose of study intervention).
   - A POCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at the Screening Visit and before the dose of study intervention, if Day 1 is not on the same day as the Screening Visit (see Section 3.8.3.3).
     - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
   - Additional requirements for pregnancy testing during and after study intervention are located in Section 3.8.3.3.
   - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a person with an early undetected pregnancy.

Informed Consent

4. Capable of giving signed informed consent as described in Section 5.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

3.4.2. Exclusion Criteria (Part B)

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

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window.
2. 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 Day 1.

3. 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 Day 1 and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
    - Asymptomatic conditions and conditions with no clinically significant end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, if they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the Investigator.
    - Participants who have undergone surgical procedures within 7 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention dosing are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Participants who are HIV positive and on antiviral therapy with cluster of differentiation 4 count ≥350 cells/mm^3 and HIV RNA ≤500 copies/mL within the past 12 months.
    - Participants with immune-mediated diseases which are stable (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or auto-immune ovarian failure, which do not require systemic immunosuppressants per Part B Exclusion Criterion # 13.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos; psoriasis patches affecting skin over the deltoid areas).
6. Participant has tested positive for influenza by local health authority-approved testing methods within 180 days prior to Day 1.
7. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of mRNA vaccines or any components of the mRNA-1010 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. Malignancy within the previous 2 years (excluding nonmelanoma skin cancer).
10. History of myocarditis, pericarditis, or myopericarditis within 180 days prior to Day 1 or have not returned to Baseline clinical status. Participants who have not returned to Baseline after their convalescent period will also be excluded.
11. History of Guillain-Barre syndrome after any influenza vaccine.

12. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.

Prior/Concomitant Therapy

13. Participant has received systemic immunosuppressants or immune-modifying drugs that may impact the immune response for >14 days in total within 180 days prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study intervention dosing.
14. Participant has received any vaccine authorized or approved by local health agency ≤28 days prior to study intervention dosing (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after study intervention dosing.
15. Participant has received a licensed seasonal influenza vaccine within 6 months (180 days) prior to Day 1.
16. Participant has participated in any investigational seasonal influenza vaccine study where the study vaccine was administered within 12 months prior to Day 1. Participants who were previously enrolled in mRNA-1010-P303 Part A are not eligible to participate in Part B.
17. Participant is not aware whether they have received an influenza vaccine since September 2022.
18. Participant has been treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to Day 1.
19. Participant has received systemic immunoglobulins or blood products within 90 days prior to Day 1 or plans to receive systemic immunoglobulins or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to Day 1, or plan to receive them, are also excluded.
20. Participant has donated ≥450 mL of blood products within 28 days prior to Day 1 or plans to donate blood products during the study.

Other Exclusion Criteria

21. Participant has participated in an interventional clinical study within 28 days prior to Day 1, based on the medical history interview or plans to do so while participating in this study. Participants may continue in prior interventional study follow-up activities, as long as it does not involve further investigational treatment other than the study intervention described in this protocol (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.

3.4.3. Screen Failures

See Section 2.4.3 for details.

3.4.4. Criteria for Temporarily Delaying the Day 1 Visit

See Section 2.4.4 and Section 3.7 for details, and refer to SoA for Part B (Table 7).

3.5. Study Intervention(s) and Concomitant Therapy (Part B)

Study intervention(s) refers to the mRNA-1010 vaccine and to the licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) intended to be administered to the study participants during the study conduct.

3.5.1. Study Intervention(s) Administered

The study intervention(s) to be administered and the treatment groups in the study are provided in Table 10.

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

The active comparator administered in this study is a licensed SD seasonal influenza vaccine, Fluarix Quadrivalent administered as a single 0.5 mL IM injection.

Table 10: Study Intervention(s) Administered

Intervention Label	**mRNA-1010.4**	**Fluarix**
Treatment Group Type	Experimental	Active comparator
Intervention Name	mRNA-1010	Fluarix SD Quadrivalent
Intervention Description	mRNA-1010 contains LNP dispersion encoding the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2023 to 2024 NH cell or recombinant-based vaccines. All mRNAs are formulated in LNPs composed of 4 lipids and provided as a sterile liquid for injection, white-to-off white dispersion in appearance, at a concentration of 0.10 mg/mL in 20 mM Tris buffer with 87 g/L sucrose, and 2.2 mM sodium acetate at pH 7.5.	Licensed quadrivalent seasonal vaccine Fluarix Quadrivalent contains the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2023 to 2024 NH egg-based vaccines.
Type	Vaccine	Vaccine
Dosage Level(s)	50 µg of mRNA Single dose	60 µg of proteins Single dose

Intervention Label	mRNA-1010.4	Fluarix
Route of Administration	IM	IM
Use	Experimental	Active control
IMP and AxMP	IMP	IMP
Sourcing	By Sponsor	By Sponsor
Packaging and Labeling	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

Abbreviations: AxMP = auxiliary medicinal product; CFR = Code of Federal Regulations; GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; HA = hemagglutinin; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IM = intramuscular(ly); IMP = investigational medicinal product; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; NH = Northern Hemisphere; SD = standard dose; WHO = World health Organization.

3.5.2. Preparation, Handling, Storage, and Accountability

See Section 2.5.2 for details.

3.5.2.1. Study Intervention(s) Preparation

The study intervention will be prepared for each participant based on their treatment group assignment. The mRNA-1010 vaccine will be administered as a single 0.5 mL IM injection and will contain mRNA-1010 at a dose of 50 µg. The licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) will be administered at a volume of 0.5 mL. The mRNA-1010 and the licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) preparation instructions are detailed in the Pharmacy Manual.

3.5.2.2. Study Intervention(s) Administration

The study intervention (mRNA-1010) or the licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) will be administered as a single IM injection into the deltoid muscle on Day 1. Preferably, the study intervention should be administered into the nondominant arm.

Participants will be monitored for a minimum of 30 minutes after administration of the study intervention. Assessments will include vital sign measurements and monitoring for solicited ARs as shown in the SoA for Part B (Table 7)

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 licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) are described in the Pharmacy Manual.

3.5.2.3. Study Intervention(s) Packaging and Labeling

See Section 2.5.2.3 for details.

3.5.2.4. Study Intervention(s) Storage

mRNA-1010 must be stored at the clinical site at 2°C to 8°C in a secure area with limited access and must be protected from moisture and light until it is prepared for administration (Section 3.5.2.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. The refrigerator should be connected to a backup generator. In addition, for study intervention accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The clinic is responsible for reporting any 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. Please note that mRNA-1010 will be stored at -25°C to - 15°C at the depots and during shipments to the clinical sites.

The licensed SD seasonal influenza vaccine (Fluarix Quadrivalent) should be stored in its original container and in accordance with the instructions in the Pharmacy Manual.

3.5.2.5. Study Intervention(s) Accountability

See Section 2.5.2.5 for details.

3.5.2.6. Study Intervention(s) Handling and Disposal

See Section 2.5.2.6 for details.

3.5.2.7. Unblinding

See Section 2.5.2.7 for details.

3.6. Assignment to Study Intervention (Part B)

Randomization will be performed using an IRT. Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed SD seasonal influenza vaccine (Fluarix Quadrivalent, Table 10). Randomization will be stratified by previous flu season (since September 2022) vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study [yes/no]).

3.6.1. Blinding

See Section 2.6.1 for details.

3.6.2. Study Intervention Compliance

See Section 2.6.2 for details.

3.6.3. Dose Modification

Not applicable.

3.6.4. Continued Access to Study Intervention After the End of the Study

See Section 2.6.4 for details.

3.6.5. Treatment of Overdose

See Section 2.6.5 for details.

3.6.6. Prior and Concomitant Therapy

See Section 2.6.6 for details.

3.6.6.1. Prohibited Therapy

See Section 2.6.6.1 for details.

3.6.6.2. Recording of Concomitant Medications, Concomitant Vaccinations and Concomitant Procedures

See Section 2.6.6.2 for details.

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

See Section 2.6.6.3 for details.

3.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal (Part B)

Discontinuation of specific sites or of the study as a whole are detailed in Section 5.1.10.

3.7.1. Discontinuation of Study Intervention

Not applicable.

3.7.2. Participant Discontinuation/Withdrawal from the Study

See Section 2.7.1.1 for details and refer to SoA for Part B (Table 7).

3.7.3. Lost to Follow-up

See Section 2.7.1.2 for details.

3.7.4. Pause Rules

Not applicable.

3.8. Study Assessments and Procedures (Part B)

See Section 2.8 for details and refer to SoA for Part B (Table 7).

3.8.1. Demography

See Section 2.8.1 for details.

3.8.2. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA for Part B (Table 7).

The following analytes will be measured:

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

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

Serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to influenza vaccines, additional assay development, and the immune response across influenza viruses.

3.8.3. Safety Assessments

See Section 2.8.3 for details and refer to SoA for Part B (Table 7).

3.8.3.1. Physical Examinations

See Section 2.8.3.1 for details and refer to SoA for Part B (Table 7).

3.8.3.2. Vital Signs

See Section 2.8.3.2 for details and refer to SoA for Part B (Table 7).

3.8.3.3. Pregnancy Testing

See Section 2.8.3.3 for details and refer to SoA for Part B (Table 7).

3.8.3.4. Safety Phone Calls

See Section 2.8.3.5 for details and refer to SoA for Part B Table 7).

3.8.3.5. Use of Electronic Diaries

See Section 2.8.3.6 for details and refer to SoA for Part B (Table 7).

3.8.3.6. Ancillary Supplies for Participant Use

See Section 2.8.3.7 for details and refer to SoA for Part B Table 7.

3.8.3.7. AEs, SAEs, and Other Safety Reporting

The definitions of AEs, SAEs, solicited ARs, and unsolicited AEs can be found in Section 5.3.

See Section 2.8.3.8 for details.

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

See Section 2.8.3.8.1 for details.

3.8.3.7.2. Method of Detecting AEs and SAEs

See Section 2.8.3.8.2 for details and refer to SoA for Part B Table 7).

3.8.3.7.3. Follow-up of AEs and SAEs

See Section 2.8.3.8.3 and refer to SoA for Part B (Table 7).

3.8.3.7.4. Regulatory Reporting Requirements for SAEs

See Section 2.8.3.8.4 for details.

3.8.3.7.5. Pregnancy

Refer to Section 2.8.3.8.5 for details and refer to SoA for Part B (Table 7).

3.8.3.8. Solicited Adverse Reactions

See Section 2.8.3.9 for details and refer to SoA for Part B (Table 7).

3.8.3.9. Medically Attended Adverse Events

The definition of MAAE is provided in Section 5.3.3.

3.8.3.10. Adverse Events of Special Interest

The definition of AESI is provided in Section 5.3.4. AESIs for this protocol are listed in Section 5.3.

3.8.3.10.1. Anaphylaxis

See Section 2.8.3.11.1 for details.

3.8.3.10.2. Myocarditis and/or Pericarditis

See Section 2.8.3.11.2 for details.

3.8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

3.8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

3.8.6. Genetics

N/A.

3.8.7. Biomarkers

N/A.

3.8.8. Immunogenicity Assessments

See Section 2.8.8 for details and refer to SoA for Part B (Table 7).

3.8.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

3.9. Statistical Considerations (Part B)

See Section 2.9 for details.

3.9.1. Blinding and Responsibility for Analyses

See Section 2.9.1 and Section 3.9.6 for details.

3.9.2. Statistical Hypotheses

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

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

  Null hypothesis: H_0^1: GMR $\leq$0.667 (inferior) vs.

  Alternative hypothesis: H_a^1: GMR >0.667 (noninferior),

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

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

  Null hypothesis: H_0^2: SCR difference $\leq$-10% (inferior) vs.

  Alternative hypothesis: H_a^2: SCR difference >-10% (noninferior)

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

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

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

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

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

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

  Null hypothesis: H_0^3: GMR = 1 vs.

  Alternative hypothesis: H_a^3: GMR >1 (superior)

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

  Null hypothesis: H_0^4: SCR difference = 0 vs.

  Alternative hypothesis: H_a^4: SCR difference >0 (superior)

The multiplicity adjustment procedures for the superiority tests of the 8 immunogenicity endpoints are specified in Section 4.9.7 (also see Figure 1).

3.9.3. Sample Size Determination

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

- The study has at least 99% power to meet the noninferiority success criteria in GMT for all 4 strains at a 1-sided alpha of 0.025 level with a noninferiority margin of 1.5. An underlying GMR (mRNA-1010 vs. the licensed SD Fluarix Quadrivalent vaccine) of 0.95 is assumed for each of the 4 strains and the standard deviation of the natural log-transformed levels is assumed to be 1.5.
- The study has at least 98% power to meet the noninferiority success criteria in SCR for all 4 strains, at a 1-sided alpha of 0.025 level with a noninferiority margin of 10%. The SCRs of 58% for influenza A strains and 48% for influenza B strains are assumed in the mRNA-1010 group, whereas the SCRs for influenza A and B strains in the licensed SD Fluarix Quadrivalent group are assumed to be 59% and 49%, respectively.

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

3.9.4. Analysis Sets

See Section 2.9.4 for details.

3.9.5. Statistical Analyses

See Section 2.9.5 for details.

3.9.5.1. Immunogenicity Analyses

The immunogenicity analyses for Part B will be conducted separately. See Section 2.9.5.1 for details.

3.9.5.2. Adverse Events

See Section 2.9.5.2 for details.

3.9.5.3. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

3.9.6. Planned Analyses

3.9.6.1. Primary Analyses

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

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

3.9.6.2. Final Analysis

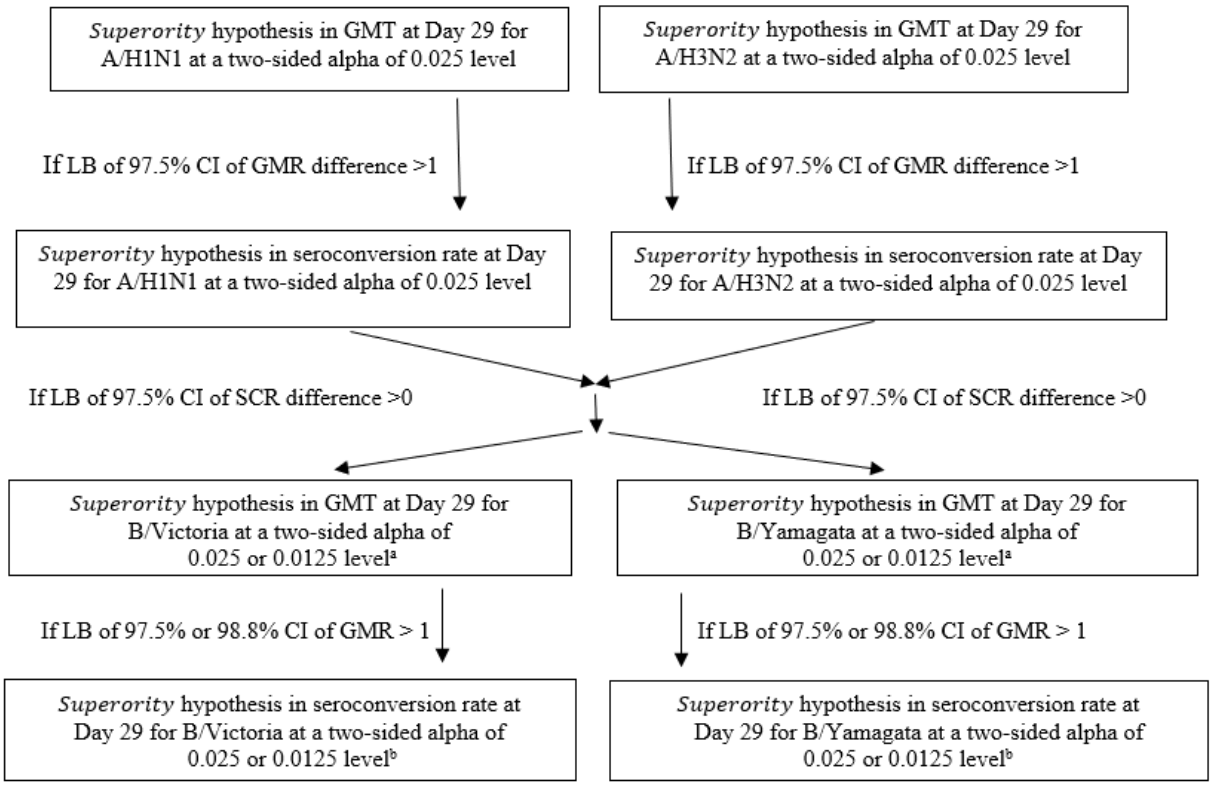
Final analysis of all safety and immunogenicity data in Part B will be performed once all participants complete the Day 181 (Month 6)/EoS Visit.

3.9.7. Multiplicity

No multiplicity adjustment will be applied for the primary noninferiority objective because Part B is successful only if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level.

Upon successful demonstration of the noninferiority, the superiority hypotheses specified in Section 3.9.2 will be tested following the prespecified order as illustrated in Figure 1.

Figure 1: Prespecified Order for Superiority Hypothesis Testing



Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; LB = lower bound.

a. If both hypotheses at the previous step are successful, the hypothesis at the current step will be tested at two-sided alpha of 0.025; if only one hypothesis at the previous step is successful, the current hypothesis will be tested at two-sided alpha of 0.0125.

b. The hypothesis will be tested at the same alpha level from the previous step (if success achieved at previous steps).

4. PART C

4.1. Protocol Summary

4.1.1. Synopsis (Part C)

Rationale:

The Sponsor is conducting this Part C of its Phase 3 study, mRNA-1010-P303, to further evaluate its candidate seasonal influenza mRNA vaccine (mRNA-1010) to establish immunogenicity and safety in support of licensure. Part C will evaluate the immune response of mRNA-1010 compared to a high dose seasonal influenza vaccine (Fluzone® HD) in adults ≥65 years old. Because of increased morbidity and mortality associated with influenza infections in older adults, Fluzone HD Quadrivalent vaccine is one of 3 influenza vaccines (along with Flublok® Quadrivalent and Fluad® Quadrivalent) that is preferentially recommended for people 65 years and older. This preferential recommendation was new for the 2022 to 2023 season. Interim analysis results from a Phase 1/2 study suggested immune responses of mRNA-1010 were on par with immune responses to Fluzone HD. The design of this study will include immunogenicity objectives for HAI, a surrogate endpoint of prevention of influenza illness and its complications. The rationale for this approach is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007 a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults ≥65 years old.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the reactogenicity and safety of mRNA-1010.	• Frequency and severity of solicited local and systemic reactogenicity ARs during a 7-day follow-up period postinjection. • Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection. • Frequency of any SAEs, MAAEs, AESIs, and AEs leading to discontinuation from Day 1 to Day 181/EoS.

Objectives	Endpoints
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 (for superiority) relative to a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched influenza A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29.	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched or vaccine-mismatched A and B strains.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; HD = high dose; MAAE = medically attended adverse event; MN = microneutralization; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody.

Overall Design Synopsis:

mRNA-1010-P303 Part C is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults ≥65 years old.

Approximately 3000 medically stable adults ≥65 years of age, at the time of signing the ICF, will be randomly assigned to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed HD seasonal influenza vaccine (Fluzone HD) at Day 1. Randomization will be stratified by the previous flu season (since September 2022) vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study [yes/no]).

Brief Summary:

The study aims to demonstrate noninferiority of mRNA-1010 versus the licensed HD seasonal influenza vaccine (Fluzone HD) in the immune response, as measured by GMT and by seroconversion rate at Day 29, using HAI assay, for each of the 4 vaccine-matched influenza virus A and B strains.

Study details include:

- There will be 3 or 4 clinic/in-person visits (Screening Visit and at Days 1, 29, and Day 181 [Month 6]/EoS [in a subset of ~ 1000 participants]) and 2 to 3 safety phone call at Days 8, 91, and 181 (non-subset participants) as specified in the SoA. The Screening Visit and Day 1 may be performed on the same day or a different day.
- All participants will be asked to complete an eDiary for solicited ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days).
- Detection of all AEs will be through 28 days after study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Detecting MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through Day 181 (Month 6)/EoS.

Number of Participants: Approximately 3000 participants will be enrolled.

Study Arms and Duration:

- Part C will comprise 2 study arms: investigational vaccine (mRNA-1010) group and licensed HD seasonal influenza vaccine (Fluzone HD) group.
- The total study duration (including screening) for each participant is up to 7 months.

4.1.2. SoA (Part C)

Table 11: Schedule of Activities (Part C)

Visit Number		**1**	**2**	**3**	**4**	**5**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	
Month Timepoint				**M1**	**M3**	**M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	
Informed consent form, demographics, concomitant medications, medical history[b]	X						
Inclusion/exclusion criteria	X	X					Refer to Section 4.4.1 and Section 4.4.2
Physical examination[b]	X						Refer to Section 4.8.3.1
Vital signs measurements	X	X					Refer to Section 4.8.3.2
Randomization		X					Refer to Section 4.6
Blood collection for humoral immunogenicity		X		X		X[i]	Prior to study intervention dosing on Day 1
Study intervention dosing (including 30-minute, postdose observation period)[c]		X					One IM injection in the deltoid muscle Refer to Section 4.5.2.2
eDiary activation for recording solicited ARs/medication recording (7 days)[d]		X					Refer to Section 4.8.3.6
Follow up safety call[e]			X		X	X[i]	Refer to Section 4.8.3.3

Visit Number		**1**	**2**	**3**	**4**	**5**	**Notes**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	
Month Timepoint				**M1**	**M3**	**M6**	
Visit Day	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**D91**	**D181/ EoS**	
Window Allowance (Days)	**-28**	**N/A**	**+3**	**-7 to +3**	**±5**	**±14**	
Review of solicited ARs eDiary		X	X				
Recording of unsolicited AEs		X	X	X			Refer to Section 4.8.3.6 and Section 5.3
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation from study participation, and concomitant medications/procedures relevant to or for their treatment[f]		X	X	X	X	X	
Recording of concomitant medications[g]		X	X	X			Refer to Section 4.6.6.2
Recording of nonstudy vaccinations[h]		X	X	X	X	X	Refer to Section 4.6.6.2
Recording of concomitant procedures/surgeries		X	X	X	X	X	Refer to Section 4.6.6.2
Study completion						X	

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

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

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

c. See Section 4.5.1, Table 13 for dose levels and treatment groups.

d. The eDiary entries will be recorded at approximately 30 minutes after study intervention dosing while at the clinic with instruction provided by the clinic staff. Study participants will continue to record in the eDiary for solicited ARs each day after they leave the clinic, on the day of study intervention dosing and the subsequent 6 days following study intervention dosing.
e. An unscheduled follow-up safety call may be triggered by the identification of a relevant safety event from an eDiary record, or other participant contact. A safety phone call may trigger an unscheduled visit.
f. Trained clinic staff will call (or contact by electronic means) all participants to collect information relating to any MAAEs, AEs leading to discontinuation from study participation, SAEs, AESIs, information on concomitant medications associated with those events, and any nonstudy vaccinations.
g. All concomitant medications will be recorded from Day 1 through Day 29; thereafter, only concomitant medications relevant to or for the treatment of an SAE, AESI, or MAAE will be recorded through Day 181 (Month 6)/EoS.
h. All nonstudy vaccinations will be recorded through 181 days after the dose of study intervention.
i. Samples for humoral immunogenicity on Day 181 (Month 6)/EoS will be collected for approximately the first 1000 participants and analyzed in a subset. Participants in the subset require a clinic visit on Day 181 (Month 6)/EoS for sample collection. All other participants will require a safety call.

4.2. Objectives and Endpoints (Part C)

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 12.

Table 12: Objectives and Endpoints (Part C)

Objectives	Endpoints
Primary	
• To evaluate the humoral immunogenicity (for noninferiority) of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against 4 vaccine-matched influenza virus A and B strains at Day 29 in adults ≥65 years old.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To evaluate the reactogenicity and safety of mRNA-1010.	• Frequency and severity of solicited local and systemic reactogenicity ARs during a 7-day follow-up period postinjection. • Frequency and severity of any unsolicited AEs during the 28-day follow-up period postinjection. • Frequency of any SAEs, MAAEs, AESIs, and AEs leading to discontinuation from Day 1 to Day 181/EoS.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 (for superiority) relative to a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched influenza A and B strains at Day 29.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI.
• To further evaluate the humoral immunogenicity of each study arm against vaccine-matched influenza A and B strains at Day 29.	• The proportion of participants with HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
Exploratory (May be Performed)	
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched influenza virus A and B strains at Day 181/EoS in a subset of participants.	• GMT at Day 181 as measured by HAI. • Proportion of participants reaching seroconversion at Day 181 as measured by HAI.

Objectives	Endpoints
• To evaluate the humoral immunogenicity of mRNA-1010 relative to that of a licensed HD seasonal influenza vaccine (Fluzone HD) against vaccine-matched or vaccine-mismatched A and B strains.	• GMT and GMFR of nAbs by assays such as MN assays or alternative methods against vaccine-matched/mismatched strains on Day 29 compared with Day 1 (Baseline). • GMT and GMFR of anti-HA antibodies as measured by HAI against vaccine-mismatched strains on Day 29 compared with Day 1 (Baseline).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; HD = high dose; MAAE = medically attended adverse event; MN = microneutralization; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; SAE = serious adverse event

4.3. Study Design (Part C)

4.3.1. Overall Design (Part C)

mRNA-1010-P303 Part C is a Phase 3, randomized, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 seasonal influenza vaccine in adults ≥65 years old.

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

Medically stable adults (see Part C Exclusion Criterion # 3), ≥65 years old, will be screened and enrolled. A complete list of inclusion and exclusion criteria is provided in Section 4.4.

Approximately 3000 participants will be randomly assigned (see Section 4.6) to treatment in this study in a 1:1: ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent, Table 13).

Table 13: Treatment Groups and Dose Levels (Part C)

Treatment Group	Study Intervention Received	mRNA/Antigen HA (each) (µg)	Total Dose (µg)	Number of Participants
5	mRNA-1010	12.5 (of mRNA)	50 (of mRNA)	1500
6	Active Comparator (Fluzone HD Quadrivalent)	60 (of protein)	240 (of protein)	1500

Abbreviations: HA = hemagglutinin; HD = high dose; mRNA = messenger ribonucleic acid

Table 11 displays the study SoA. Clinic/in-person visits will consist of a Screening Visit (up to 28 days before the Day 1 Visit and may be performed over multiple visits if within the 28-day screening window), a dosing visit on Day 1 (Baseline; may be on the same day as the Screening Visit), a visit on Day 29 (Month 1), and a subsequent visit on Day 181 (Month 6)/EoS (in a

subset of ~1000 participants) with up to 7 months of study participation for each participant. There will also be contacts by electronic means or telephone calls on Day 8, Day 91 (Month 3) and Day 181 (Month 6 [non-subset participants]).

All participants will provide blood samples for assessment of GMT, GMFR, and seroconversion, as measured by HAI (Table 11 and Section 4.8.2). Table 11 displays the time periods for collecting solicited ARs via eDiary (Section 4.8.3.4) and unsolicited AEs. MAAEs, SAEs, AESIs, and AEs leading to discontinuation will be collected from Day 1 to Day 181 (Month 6)/EoS.

There may be situations in which the Investigator asks a participant to report for an unscheduled visit following the report of an AE. The eCRF should be completed for each unscheduled visit.

This is an observer-blind study (refer to Section 4.6.1 for details). The Investigator may unblind in the event of an emergency (refer to Section 4.5.2.7 for details).

An IST and CEAC will be involved (refer to Section 5.1.6 for details).

4.3.2. Scientific Rationale for Study Design

Part C of this study aims to demonstrate noninferiority of mRNA-1010 versus a licensed high dose seasonal influenza vaccine (Fluzone HD) in the immune response for all 4 strains, as measured by GMT and by seroconversion rate, in adults ≥65 years.

Because of increased morbidity and mortality associated with influenza infections in older adults, Fluzone HD Quadrivalent vaccine is one of 3 influenza vaccines (along with Flublok Quadrivalent and Fluad Quadrivalent) that is preferentially recommended for people 65 years and older. The Sponsor conducted a Phase 1/2 study which suggested immune responses were on par with immune responses to Fluzone HD.

The rationale for using HAI as a surrogate endpoint of prevention of influenza illness and its complications is based on the established precedent of using HA-based immunologic correlates for clinical assessment and licensure of influenza vaccines (DHHS 2007a, DHHS 2007b, Dunning et al 2016, European Medicines Agency 2016).

4.3.3. Justification for Dose

The Sponsor has completed a Phase 1/2 study of mRNA-1010 (mRNA-1010-P101, NCT04956575) at dose levels up to 200 µg and is now conducting three Phase 3 studies at a 50 µg dose level: mRNA-1010-P301, a safety and immunogenicity study (NCT05415462), mRNA-1010-P302, a safety and efficacy study (NCT05566639), and mRNA-1010-P303 Part A (NCT05827978). No safety concerns were identified with dose levels up to 200 µg. The 50-µg dose was chosen for the Phase 3 studies based on the observed reactogenicity and immunogenicity profile (refer to Section 1.2 for details).

4.3.4. End of Study Definition

See Section 2.3.4 for details.

4.4. Study Population (Part C)

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

4.4.1. Inclusion Criteria (Part C)

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

Age

1. At least 65 years of age or older, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Investigator has assessed that the participant understands and is willing and physically able to comply with protocol mandated follow-up, including all procedures.

Sex and Contraceptive/Barrier Requirements

3. A participant AFAB is eligible to participate if they are postmenopausal or a person of nonchildbearing potential.

Informed Consent

4. Capable of giving signed informed consent as described in Section 5.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

4.4.2. Exclusion Criteria (Part C)

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

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window.
2. 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 Day 1.
3. 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 Day 1 and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
    - Asymptomatic conditions and conditions with no clinically significant end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, if they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may

be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the Investigator.

- Participants who have undergone surgical procedures within 7 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention dosing are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.

4. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition or immune-mediated disease, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
   - Participants who are HIV positive and on antiviral therapy with cluster of differentiation 4 count ≥350 cells/mm^3 and HIV RNA ≤500 copies/mL within the past 12 months.
   - Participants with immune-mediated diseases which are stable (eg, Hashimoto's thyroiditis and type 1 diabetes) or conditions such as asthma, psoriasis, vitiligo, gout, alopecia areata, or auto-immune ovarian failure, which do not require systemic immunosuppressants per Part C Exclusion Criterion # 13.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos; psoriasis patches affecting skin over the deltoid areas).
6. Participant has tested positive for influenza by local health authority-approved testing methods within 180 days prior to Day 1.
7. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of mRNA vaccines or any components of the mRNA-1010 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. Malignancy within the previous 2 years (excluding nonmelanoma skin cancer).
10. History of myocarditis, pericarditis, or myopericarditis within 180 days prior to Day 1 or have not returned to Baseline clinical status. Participants who have not returned to Baseline after their convalescent period will also be excluded.
11. History of Guillain-Barre syndrome after any influenza vaccine.
12. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.

Prior/Concomitant Therapy

13. Participant has received systemic immunosuppressants or immune modifying drugs that may impact the immune response for >14 days in total within 180 days prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study intervention dosing.

14. Participant has received any vaccine authorized or approved by local health agency ≤28 days prior to study intervention dosing (Day 1) or plans to receive a vaccine authorized or approved by local health agency within 28 days before or after study intervention dosing.
15. Participant has received a licensed seasonal influenza vaccine within 6 months (180 days) prior to Day 1.
16. Participant has participated in any investigational seasonal influenza vaccine study where the study vaccine was administered within 12 months prior to Day 1. Participants who were previously enrolled in mRNA-1010-P303 Part A are not eligible to participate in Part C.
17. Participant is not aware whether they have received an influenza vaccine since September 2022.
18. Participant has been treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to Day 1.
19. Participant has received systemic immunoglobulins or blood products within 90 days prior to Day 1 or plans to receive systemic immunoglobulins or blood products during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to Day 1, or plan to receive them, are also excluded.
20. Participant has donated ≥450 mL of blood products within 28 days prior to Day 1 or plans to donate blood products during the study.

Other Exclusion Criteria

21. Participant has participated in an interventional clinical study within 28 days prior to Day 1, based on the medical history interview or plans to do so while participating in this study. Participants may continue in prior interventional study follow-up activities, as long as it does not involve further investigational treatment other than the study intervention described in this protocol (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.

4.4.3. Screen Failures

See Section 2.4.3 for details.

4.4.4. Criteria for Temporarily Delaying the Day 1 Visit

See Section 2.4.4 and Section 4.7 for details and refer to SoA for Part C (Table 11).

4.5. Study Intervention(s) and Concomitant Therapy (Part C)

Study intervention(s) refers to the mRNA-1010 vaccine and to the licensed HD seasonal influenza vaccine (Fluzone HD) intended to be administered to the study participants during the study conduct.

4.5.1. Study Intervention(s) Administered

The study intervention(s) to be administered and the treatment groups in the study are provided in Table 14.

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

The active comparator administered in this study is a licensed HD seasonal influenza vaccine, Fluzone HD Quadrivalent administered as a single 0.7 mL IM injection.

Table 14: Study Intervention(s) Administered

Intervention Label	**mRNA-1010.4**	**Fluzone HD**
Treatment Group Type	Experimental	Active comparator
Intervention Name	mRNA-1010	Fluzone HD Quadrivalent
Intervention Description	mRNA-1010 contains LNP dispersion encoding the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2023 to 2024 NH cell or recombinant-based vaccines. All mRNAs are formulated in LNPs composed of 4 lipids and provided as a sterile liquid for injection, white-to-off white dispersion in appearance, at a concentration of 0.10 mg/mL in 20 mM Tris buffer with 87 g/L sucrose, and 2.2 mM sodium acetate at pH 7.5.	Licensed high dose quadrivalent seasonal vaccine. Fluzone HD Quadrivalent contains the seasonal influenza vaccine antigens, HAs, from the strains recommended by the WHO for 2023 to 2024 NH egg-based vaccines.
Type	Vaccine	Vaccine
Dosage Level(s)	50 µg of mRNA Single dose	240 µg of proteins Single dose
Route of Administration	IM	IM
Use	Experimental	Active control
IMP and AxMP	IMP	IMP
Sourcing	By Sponsor	By Sponsor
Packaging and Labeling	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.	The study intervention will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

Abbreviations: AxMP = auxiliary medicinal product; CFR = Code of Federal Regulations; GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; HA = hemagglutinin; HD = high dose; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IM = intramuscular(ly); IMP = investigational medicinal product; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; NH = Northern Hemisphere; WHO = World health Organization.

4.5.2. Preparation, Handling, Storage, and Accountability

See Section 2.5.2 for details.

4.5.2.1. Study Intervention(s) Preparation

The study intervention will be prepared for each participant based on their treatment group assignment. The mRNA-1010 vaccine will be administered as a single 0.5 mL IM injection and will contain mRNA-1010 at a dose of 50 µg. The licensed HD seasonal influenza vaccine (Fluzone HD) will be administered at a volume of 0.7 mL. The mRNA-1010 and the licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent) preparation instructions are detailed in the Pharmacy Manual.

4.5.2.2. Study Intervention(s) Administration

The study intervention (mRNA-1010) or the licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent) will be administered as a single IM injection into the deltoid muscle on Day 1. Preferably, the study intervention should be administered into the nondominant arm.

Participants will be monitored for a minimum of 30 minutes after administration of the study intervention. Assessments will include vital sign measurements and monitoring for solicited ARs as shown in the SoA (Table 11).

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 licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent) are described in the Pharmacy Manual.

4.5.2.3. Study Intervention(s) Packaging and Labeling

See Section 2.5.2.3 for details.

4.5.2.4. Study Intervention(s) Storage

mRNA-1010 must be stored at the clinical site at 2°C to 8°C in a secure area with limited access and must be protected from moisture and light until it is prepared for administration (Section 4.5.2.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. The refrigerator should be connected to a backup generator. In addition, for study intervention accountability, staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The clinic is responsible for reporting any 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. Please

note that mRNA-1010 will be stored at -25°C to - 15°C at the depots and during shipments to the clinical sites.

The licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent) should be stored in its original container and in accordance with the instructions in the Pharmacy Manual.

4.5.2.5. Study Intervention(s) Accountability

See Section 2.5.2.5 for details.

4.5.2.6. Study Intervention(s) Handling and Disposal

See Section 2.5.2.6 for details.

4.5.2.7. Unblinding

See Section 2.5.2.7 for details.

4.6. Assignment to Study Intervention (Part C)

Randomization will be performed using an IRT. Approximately 3000 participants will be randomly assigned to treatment in this study in a 1:1 ratio to 1 of 2 treatment groups to receive either a single dose of mRNA-1010 or a single dose of a licensed HD seasonal influenza vaccine (Fluzone HD Quadrivalent, Table 14). Randomization will be stratified by the previous flu season (since September 2022) vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study [yes/no]).

4.6.1. Blinding

See Section 2.6.1 for details.

4.6.2. Study Intervention Compliance

See Section 2.6.2 for details.

4.6.3. Dose Modification

Not applicable.

4.6.4. Continued Access to Study Intervention After the End of the Study

See Section 2.6.4 for details.

4.6.5. Treatment of Overdose

See Section 2.6.5 for overdose.

4.6.6. Prior and Concomitant Therapy

See Section 2.6.6 for details.

4.6.6.1. Prohibited Therapy

See Section 2.6.6.1 for details.

4.6.6.2. Recording of Concomitant Medications, Concomitant Vaccinations and Concomitant Procedures

See Section 2.6.6.2 for details.

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

See Section 2.6.6.3 for details.

4.7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal (Part C)

Discontinuation of specific sites or of the study as a whole are detailed in Section 5.1.10.

4.7.1. Discontinuation of Study Intervention

Not applicable.

4.7.2. Participant Discontinuation/Withdrawal from the Study

See Section 2.7.1.1 for details and refer to SoA for Part C (Table 11).

4.7.3. Lost to Follow-up

See Section 2.7.1.2 for details.

4.7.4. Pause Rules

Not applicable.

4.8. Study Assessments and Procedures (Part C)

See Section 2.8 for details and refer to SoA for Part C (Table 11).

4.8.1. Demography

See Section 2.8.1 for details.

4.8.2. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA for Part C (Table 11).

The following analytes will be measured:

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

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

Serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to influenza vaccines, additional assay development, and the immune response across influenza viruses.

4.8.3. Safety Assessments

See Section 2.8.3 for details and refer to SoA for Part C (Table 11).

4.8.3.1. Physical Examinations

See Section 2.8.3.1 for details and refer to SoA for Part C (Table 11).

4.8.3.2. Vital Signs

See Section 2.8.3.2 for details and refer to SoA for Part C (Table 11).

4.8.3.3. Safety Phone Calls

See Section 2.8.3.5 and refer to SoA for Part C (Table 11).

4.8.3.4. Use of Electronic Diaries

See Section 2.8.3.6 for details and refer to SoA for Part C (Table 11).

4.8.3.5. Ancillary Supplies for Participant Use

See Section 2.8.3.7 for details and refer to SoA for Part C (Table 11).

4.8.3.6. AEs, SAEs, and Other Safety Reporting

The definitions of AEs, SAEs, solicited ARs, and unsolicited AEs can be found in Section 5.3.

See Section 2.8.3.8 for details.

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

See Section 2.8.3.8.1 for details.

4.8.3.6.2. Method of Detecting AEs and SAEs

See Section 2.8.3.8.2 for details and refer to SoA for Part C (Table 11).

4.8.3.6.3. Follow-up of AEs and SAEs

See Section 2.8.3.8.3 for details and refer to SoA for Part C (Table 11).

4.8.3.6.4. Regulatory Reporting Requirements for SAEs

See Section 2.8.3.8.4 for details.

4.8.3.6.5. Pregnancy

Not applicable.

4.8.3.7. Solicited Adverse Reactions

See Section 2.8.3.9 for details and refer to SoA for Part C (Table 11).

4.8.3.8. Medically Attended Adverse Events

The definition of MAAE is provided in Section 5.3.3.

4.8.3.9. Adverse Events of Special Interest

The definition of AESI is provided in Section 5.3.4. AESIs for this protocol are listed in Section 5.3.

4.8.3.9.1. Anaphylaxis

See Section 2.8.3.11.1 for details.

4.8.3.9.2. Myocarditis and/or Pericarditis

See Section 2.8.3.11.2 for details.

4.8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

4.8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

4.8.6. Genetics

N/A.

4.8.7. Biomarkers

N/A.

4.8.8. Immunogenicity Assessments

See Section 2.8.8 for details and refer to SoA for Part C (Table 11).

4.8.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

4.9. Statistical Considerations (Part C)

See Section 2.9 for details.

4.9.1. Blinding and Responsibility for Analyses

See Section 2.9.1 and Section 4.9.6 for details.

4.9.2. Statistical Hypotheses

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

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

  Null hypothesis: H_0^1: GMR $\leq$0.667 (inferior) vs.

  Alternative hypothesis: H_a^1: GMR >0.667 (noninferior)

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

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

  Null hypothesis: H_0^2: SCR difference $\leq$ -10% (inferior) vs.

  Alternative hypothesis: H_a^2: SCR difference > -10% (noninferior)

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

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

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

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

- For each of the 4 vaccine-matched strains, the superiority hypothesis in terms of the GMT at Day 29 is:

  Null hypothesis: H_0^3: GMR = 1 vs.

  Alternative hypothesis: H_a^3: GMR >1 (superior)

- For each of the 4 vaccine-matched strains, the superiority hypothesis in seroconversion rate at Day 29 is:

  Null hypothesis: H_0^4: SCR difference = 0 vs.

  Alternative hypothesis: H_a^4: SCR difference >0 (superior)

The multiplicity adjustment procedures for the superiority tests of the 8 immunogenicity endpoints are specified in Section 4.9.7 (also see Figure 1 in Section 3.9.7).

4.9.3. Sample Size Determination

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

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

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

4.9.4. Analysis Sets

See Section 2.9.4 for details.

4.9.5. Statistical Analyses

See Section 2.9.5 for details.

4.9.5.1. Immunogenicity Analyses

The immunogenicity analyses will be conducted for Part C separately. See Section 2.9.5.1 for details.

4.9.5.2. Adverse Events

See Section 2.9.5.2 for details.

4.9.5.3. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

4.9.6. Planned Analyses

4.9.6.1. Primary Analyses

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

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

4.9.6.2. Final Analysis

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

4.9.7. Multiplicity

No multiplicity adjustment will be applied for the primary noninferiority objective because Part C is successful only if all the 8 coprimary immunogenicity endpoints meet the noninferiority criteria. Each of the coprimary immunogenicity endpoints will be tested at 1-sided alpha of 0.025 level.

Upon successful demonstration of the noninferiority, the superiority hypotheses specified in Section 4.9.2 will be tested following the prespecified order of the superiority tests (see Section 3.9.7 and Figure 1 for details).

5. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

5.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

5.1.1. Regulatory and Ethical Considerations

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

5.1.2. Financial Disclosure

Investigators and Subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

5.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- 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.

There will be separate consents that address the samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

5.1.4. 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 study. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical study sites, participant support services such as concierge, and study 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.

5.1.5. 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 who will be required to give consent for their data to be used as described in the informed consent.

- 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 members, and by inspectors from regulatory authorities.
- 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.

5.1.6. Committee Structure

5.1.6.1. Internal Safety Team

An IST will be formed to review primary and cumulative blinded and unblinded safety data on a regular basis.

5.1.6.2. Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review all reported cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis, pericarditis, or myopericarditis will be referred to the Sponsor, who will then determine if additional action is needed. The CEAC operates under the rules of an approved charter, details regarding the CEAC composition, responsibilities, procedures, and frequency of data review are defined in the charter.

5.1.7. Dissemination of Clinical Study Data

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

5.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded in eCRFs. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.

- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 onsite monitoring) are provided in the 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).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation 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.

5.1.9. Source Documents

- 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 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.
- Definition of what constitutes source data and its origin can be found in Data Agreements and Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized clinic staff 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.

5.1.10. Study and Site Start Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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. 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.

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:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRB, 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.

5.1.11. 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.

5.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 15 will be performed by a laboratory by local and the central laboratories.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 2.4 for Part A, Section 3.4 for Part B, and Section 4.4 for Part C of the protocol.

Investigators must document their review of each laboratory safety report.

Table 15: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)[a]
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed for PONCBP)

Abbreviations: hCG = human chorionic gonadotropin; POCBP = person of childbearing potential; PONCBP: person of nonchildbearing potential

a. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

5.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

5.3.1. Definition of AE

AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory (hematology, clinical chemistry, or urinalysis) or diagnostic (eg, electrocardiogram, radiological scans, vital signs measurements) test results or physical examination finding, including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Unsolicited and Solicited AE

An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

5.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

NOTE: Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions not resulting in hospitalization.

5.3.3. Definition of MAAE

A MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to a study site for unscheduled assessments not required per protocol (eg, rash assessment, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (eg, emergency room, urgent care, primary care physician).

An unscheduled visit for assessment of protocol-defined ILI (symptoms assessment and NP swab) is not considered a MAAE unless additional medical evaluation, including examinations/testing not required per protocol, and/or treatment is provided during the visit.

5.3.4. Definition of AESI

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.

The AESIs defined for this protocol can be found in Section 5.3.4.

5.3.5. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event and then record all relevant AE/SAE information in EDC.
- There may be instances when copies of medical records are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee. It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the eCRF/required form.
- The Investigator will attempt to establish at least a provisional diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with activities of daily living.
- Moderate:
  Usually alleviated with additional specific therapeutic intervention. The event interferes with activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  Interrupts activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. The intensity grading scale used in this study is presented in Table 16.

Table 16: Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or >2 episodes/2 4 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	<38.0°C <100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	>40.0°C >104.0°F

Note: Events listed above but starting >7 days poststudy intervention dosing will be recorded in the eCRF. Causality for each event will be determined per assessment by the Investigator.
Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b).

Assessment of Causality

- The Investigator must assess the relationship between study intervention and each occurrence of each AE/SAE, based on clinical judgment, and document this in the source document and EDC.
- **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.
- There may be situations in which the Investigator has minimal information concerning an AE; however, an assessment of causality must be provided by the Investigator at the time of reporting to the Sponsor or designee based on their clinical understanding of the event, knowledge of the study intervention, and current information available.

Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or

designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded as revisions to the original report.

The Investigator will report any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

5.3.6. Reporting of SAEs/AESI

Note: AESI will be reported in the same way as SAEs.

The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic EDC.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool provided by the Sponsor to report the event within 24 hours.

- SAE reports should be emailed to drugsafety@modernatx.com.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

NOTE: Initial notification via email or fax does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.

After the study is completed at a given site, the EDC tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

5.4. Appendix 4: Adverse Event of Special Interest

Investigators should report all events that fall into the categories presented in Table 17 as an AESI per the reporting processes in Section 5.3.6. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines or the vaccine platform.

Table 17: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $<125 \times 10^9$. • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or Hemolysis, elevated liver enzymes, low platelet count 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 associated with study intervention dosing as defined per protocol (Section 2.8.3.11.1). • Follow reporting procedures in Section 5.3.6.
Myocarditis/Pericarditis	• Myocarditis. • Pericarditis. • Myopericarditis.

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

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 18 as guidance.

Table 18: Case Definitions of Probably 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 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).

Condition	Definition	
	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 participants who meet criteria for both myocarditis and pericarditis.	

Abbreviations: cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

* 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).

5.6. Appendix 6: Contraceptive and Barrier Guidance

5.6.1. Definitions

Person of Childbearing Potential

Persons AFAB in the following categories are considered POCBP (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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in persons not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - Persons on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.
     - 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 clinic staff'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 study intervention dosing, additional evaluation should be considered.

Person of Nonchildbearing Potential

Participants in the following categories are considered PONCBP:

1. Premenopausal participant with permanent infertility due to one of the following:
   a. Documented hysterectomy.
   b. Documented bilateral salpingectomy.
   c. Documented bilateral oophorectomy.

d. 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.

2. Postmenopausal participant

a. 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 participants 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.

– Participants on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

5.6.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation.[c]
• Intrauterine device.
• Intrauterine hormone-releasing system.[c]
• Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a medical cause). *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the person of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the clinic staff's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• External or internal condom with or without spermicide.
• Cervical cap, diaphragm, or sponge with spermicide.
• A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).[c]
a. Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Use of external condoms in addition to hormonal contraception is recommended. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Considered effective, but not highly effective - failure rate of ≥1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure from friction).

5.7. Appendix 7: Protocol Amendment History

5.7.1. Global Amendment 1, 10 Oct 2023:

This amendment is considered to be substantial.

Main Rationale for the Amendment:

The primary analysis results from Part A of this study demonstrated noninferior immunogenicity of mRNA-1010 compared to a standard dose (SD) Quadrivalent seasonal influenza vaccine (Fluarix Quadrivalent) based on the prespecified success criteria for noninferiority: the lower bounds of 95% confidence intervals (CIs) for the geometric mean ratio (GMR) >0.667, and the lower bounds of the CIs for seroconversion rate (SCR) difference >-10% for all 4 strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). The purpose of adding Part B to this study is to further characterize the safety of mRNA-1010 candidate seasonal influenza vaccine in adults in the age group of 18 to <65 years old. The purpose of adding Part C to the study is to evaluate safety and immunogenicity of mRNA-1010 compared to a licensed high dose (HD) Quadrivalent seasonal influenza vaccine (Fluzone HD) in adults ≥65 years old.

Summary of Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature Page, Protocol Amendment Summary of Changes, Header	Updated the brief title, and protocol version and date, as applicable.	To align with all parts of the study (Part A, B, and C) and to reflect the current version.
Section 1 (Protocol Summary) and Section 2 (Introduction)	Section 2 (Introduction) was moved to the beginning as Section 1. Section 1 (Protocol Summary) was changed to Section 2.1 under Part A (Section 2).	To align the Introduction with all parts of the study (Part A, B, and C).
Section 1.1 (Protocol Synopsis), Section 1.2 (Schema), and Section 1.3 (Schedule of Activities	Section 1.1 was changed to Section 2.1.1. Section 1.2 was deleted. Section 1.3 was changed to Section 2.1.2) under Part A.	To reorganize as protocol summary for Part A.
Section 2.3.2, Benefit Assessment	New Section 1.3.2, Removed NP swab testing from statement, “Participant will obtain information about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination, vital signs measurement, NP swab testing).”	NP swab testing is no longer required in newly added Part B and Part C.

Section # and Name	Description of Change	Brief Rationale
Section 5.3 (Screen Failures)	New Section 2.4.3, Removed statement regarding retaining initially assigned participant numbers: Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time and will retain their initially assigned participant number.	To correct an error in the original protocol.
Sections 3 to 9	Changed: Section 3 (Objectives and Endpoints) to Section 2.2; Section 4 (Study Design) to Section 2.3; Section 5 (Study Population) to Section 2.4; Section 6 (Study Intervention and Concomitant Therapy) to Section 2.5; Section 6.3 (Assignment to Study Intervention) to Section 2.6; Section 7 (Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal) to Section 2.7; Section 8 (Study Assessments and Procedures) to Section 2.8; Section 9 (Statistical Considerations) to Section 2.9 under Part A.	To reorganize the study procedures under Part A.
Section 10 and Section 11	Section 10 (Supporting Documentation and Operational Considerations) was changed to Section 5, and Section 11 (References) was changed to Section 6.	To align these sections with all 3 parts of the study (Part A, B, and C).
Section 2.8.3 (Safety Assessment)	Added pregnancy testing to Part A.	To correct an omission in the original protocol.
Section 2.9.6.1 (Primary Analysis)	Added Part A to the sentence.	To align the primary analysis with Part A of the study.
Section 2.9.6.2 (Final Analysis)	Added Part A to the sentence.	To align the final analysis with Part A of the study.

Section # and Name	Description of Change	Brief Rationale
New Section 3 (Part B)	Added a new section (Part B) to further evaluate the safety and reactogenicity of mRNA-1010 against the licensed standard dose influenza vaccine, Fluarix SD, in adults 18 to <65 years old.	To further evaluate the safety of mRNA-1010 against the licensed standard dose influenza vaccine, Fluarix SD, in adults 18 to <65 years old.
New Section 4 (Part C)	Added a new section (Part C) to evaluate the immunogenicity, reactogenicity, and safety of mRNA-1010 against the licensed high dose influenza vaccine, Fluzone HD, in adults ≥65 years old.	To evaluate the immunogenicity and safety of mRNA-1010 against the licensed high dose influenza vaccine, Fluzone HD, in adults ≥65 years old.
Section 5.6.1 (Definitions)	Added definition for Person of Nonchildbearing Potential (PONCBP)	To align with inclusion criteria # 3 of Part C.

6. REFERENCES

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr., et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3 14.

Centers for Disease Control and Prevention (CDC) [internet]. Atlanta, GA: CDC seasonal flu vaccine effectiveness studies. 2023 Aug 24 [cited 2023 Sep 14]. Available from: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm.

Centers for Disease Control and Prevention (CDC) [internet]. Atlanta, GA: Influenza virus testing methods. 2020b Aug 10 [cited 2023 Sep 14]. Available from: https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Clinical data needed to support the licensure of pandemic influenza vaccines. May 2007a [cited 2023 Sep 14]. Available from: https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--Clinical-Data-Needed-to-Support-the-Licensure-of-Pandemic-Influenza-Vaccines.pdf

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007b [cited 2023 Sep 14]. Available from: https://www.fda.gov/media/73679/download.

Dunning AJ, DiazGranados CA, Voloshen T, Hu B, Landolfi VA, Talbot HK. Correlates of protection against influenza in the elderly: results from an influenza vaccine efficacy trial. Clin Vaccine Immunol. 2016;23(3):228 35.

European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guidance on Influenza Vaccines: Non-clinical and Clinical Module. London, 21 July 2016. EMA/CHMP/VWP/457259/2014 [cited 2023 Sep 14]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf.

Food and Drug Administration. Conduct of clinical trials of medical products during the COVID 19 public health emergency: guidance for industry, investigators, and institutional review boards. 2020 Mar [updated: 2021 Aug 30; cited: 2023 Sep 14]. Available from: https://www.fda.gov/media/136238/download.

Food and Drug Administration. E9(R1) Statistical principals for clinical trials: addendum: Estimands and sensitivity analysis in clinical trials [May 2021]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID 19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977 82.

Monto AS. Reflections on the Global Influenza Surveillance and Response System (GISRS) at 65 years: an expanding framework for influenza detection, prevention, and control. Influenza Other Respir Viruses. 2018;12(1):10 12.

Riedel S, Hobden JA, Miller S, Morse SA, Mietzner TA, Detrick B, et al. Orthomyxoviruses (Influenza Viruses). In: Riedel S, Morse SA, Mietzner TA, Miller S, eds. Jawetz, Melnick & Adelberg's Medical Microbiology. 28th ed. New York, New York: McGraw Hill Education; 2019. p. 565 78.

Rockman S, Laurie KL, Parkes S, Wheatley A, Barr IG. New technologies for influenza vaccines. Microorganisms. 2020;8(11):1745.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

World Health Organization (WHO) [internet]. Geneva, Switzerland: Influenza (seasonal): Ask the expert: influenza Q&A. 2023 Jan 23 [cited 2023 Sep 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

World Health Organization (WHO) [internet]. Recommended composition of influenza virus vaccines for use in the 2023- 2024 northern hemisphere influenza season. Feb 2023 [cited 2023 Sep 14]. Available from: https://cdn.who.int/media/docs/default-source/influenza/who-influenza-recommendations/vcm-northern-hemisphere-recommendation-2023-2024/202302_seasonal_recommendation_a.pdf?sfvrsn=42612ae5_3&download=true

World Health Organization (WHO) [internet]. Recommended composition of influenza virus vaccines for use in the 2023 southern hemisphere influenza season. Sep 2022b [cited 2023 Sep 14]. Available from: https://cdn.who.int/media/docs/default-source/influenza/who-influenza-recommendations/vcm-southern-hemisphere-recommendation-2023/202209_recommendation.pdf?sfvrsn=83a26d50_3&download=true

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