CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, randomized, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines in healthy adults 50 to 75 years of age
Protocol Number:	mRNA-1011-P101
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Numbers:	Not yet available
Date of Original Protocol:	03 Jan 2023

CONFIDENTIAL

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

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	A Phase 1/2, randomized, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines in healthy adults 50 to 75 years of age
Protocol Number:	mRNA-1011-P101
Approval Date:	03 Jan 2023

Protocol accepted and approved by:

See eSignature and date signed on last page of the document.

Date

PPD
ModernaTX, Inc
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Cambridge, MA 02139
Telephone: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 1/2, randomized, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines in healthy adults 50 to 75 years of age" dated 03 Jan 2023 and the most recent version of the Investigator's Brochure.

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

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

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

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Products: mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1, and mRNA-1010 products (mRNA-1010, mRNA-1010.2 and mRNA-1010.3)

Protocol Number: mRNA-1011-P101

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

Brief Title: A Phase 1/2 study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 influenza vaccines in healthy adults 50 to 75 years of age

Regulatory Agency Identifier Number: Not yet available

Background and Rationale:

Currently licensed seasonal influenza virus vaccines have suboptimal efficacy, rarely exceed 50% overall effectiveness, and are poorly effective during years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2020). Influenza vaccines based on mRNA technology could provide several benefits compared to current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, potential for stronger immune responses, as well as improved protection in older adults (Rockman et al 2020).

Current quadrivalent seasonal influenza vaccines are manufactured to prevent influenza illness caused by 4 influenza strains that include 2 influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria). However, influenza A/H3N2 remains the major driver of influenza-related hospitalizations and deaths, particularly in older adults. Lower vaccine effectiveness against the influenza A/H3N2 viruses may be in part caused by vaccine mismatches that can occur due to co-circulation of multiple different A/H3N2 clades, whereas only one of those clades is generally covered by the vaccine. The inclusion of additional strains could allow for expanded coverage against multiple co-circulating A/H3N2 strains of distinct antigenic clades in influenza vaccination programs; and furthermore, enable public health authorities to recommend a higher number of strains for inclusion into the vaccine.

The Sponsor is conducting this Phase 1/2 study to evaluate safety and immunogenicity of 3 next-generation seasonal influenza mRNA vaccines with coverage for more than one A/H3N2 strain (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1) compared to the quadrivalent mRNA-1010 vaccine with coverage for 1 A/H3N2 strain. mRNA-1011.1 contains 5 mRNAs encoding hemagglutinin antigens (HAs) for A/H1N1, B/Victoria, B/Yamagata, and two A/H3N2 strains, while mRNA-1011.2 contains 4 mRNAs encoding HAs similar to mRNA-1011.1 (including coverage for two A/H3N2 strains) but with B/Yamagata excluded. The rationale for excluding B/Yamagata is due to the lack of circulation of B/Yamagata-lineage viruses in recent years and thus, allowing for a higher proportion of other strains to be represented in the vaccine

within the same total mRNA dose. mRNA-1012.1 contains 5 mRNAs encoding HAs similar to 1011.2 but with 1 additional HA from the A/H3N2 lineages (coverage for three A/H3N2 strains).

The comparator mRNA-1010 vaccine is the Sponsor's first-generation quadrivalent vaccine containing HAs from A/H1N1, B/Yamagata, B/Victoria, and 1 of three A/H3N2 lineages that matches those in the next-generation vaccines (mRNA-1010, mRNA-1010.2, and mRNA-1010.3). The mRNA-1010 vaccine is currently under investigation in an ongoing Phase 3 immunogenicity study in adults ≥18 years of age (NCT05415462) and Phase 3 efficacy study in adults ≥50 years of age (NCT05566639).

The objective of the study (mRNA-1011-P101) is to establish preliminary safety and immunogenicity data to support selection of a lead candidate for initiation of pivotal studies. The mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) development candidates are administered as a single dose and are aimed to elicit protection from all seasonal influenza viruses covered by the candidate vaccines.

The study design has safety and reactogenicity evaluation as the primary objective, with a secondary objective of evaluating immunogenicity for each HA component using the HAI assay, because HAI titers have been established as a correlate of protection against influenza illness. 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; EMA Guidance 2016; Dunning et al 2016).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3)	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • MAAEs from Day 1 to Day 181/EoS • AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1 in comparison with mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3) against vaccine-matched	• GMT and GMFR, comparing Day 29 with Day 1 (baseline), and percentage of participants with seroconversion, defined as a postbaseline titer ≥1:40 if baseline is <1:10 or a 4-fold or greater rise if baseline is ≥1:10 in

Objectives	Endpoints
influenza A and B strains at Day 29	anti-HA antibodies measured by HAI assay

Abbreviations: AE = adverse event; AESI = adverse event of special interest; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; HAI = hemagglutination inhibition; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; SAE = serious adverse event.

Overall Study Design

This prospective, open-label Phase 1/2 study will enroll approximately 700 healthy adults ≥50 to ≤75 years of age. Participants will be stratified by prior season influenza vaccination status; those who received a licensed or investigational influenza vaccine within 180 days prior to enrollment will be excluded. Different dose levels will be assessed in parallel across 7 treatment arms. Each participant will receive a single injection administered intramuscularly in the deltoid muscle and will be followed for 6 months post vaccination.

Brief Summary

The purpose of this study is to measure the safety and the immune response to 3 next-generation influenza vaccine candidates (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1) compared with influenza vaccine candidate mRNA-1010 controls in healthy adult participants. The study duration will be up to 7 months including screening. The treatment will be administered as a single dose on Day 1.

Key study details include:

- Screening Visit (up to 28 days before the Day 1 visit).
- Randomization Visit at Day 1 (Baseline).
- Subsequent study visits will occur on Day 8, Day 29 (Month 1), and Day 181 (Month 6)/EoS.
- Five safety telephone call visits at Days 15, 57, 91, 121, and 151 will be conducted.
- Unscheduled visits for protocol-defined influenza-like illness (ILI) symptoms. Symptom assessment and collection of NP sample should be performed ≤7 days from onset of ILI symptoms.
- All participants will be asked to complete an eDiary for solicited ARs from Day 1 to Day 7.

Number of Participants: Approximately 700 participants will be enrolled into 7 treatment arms.

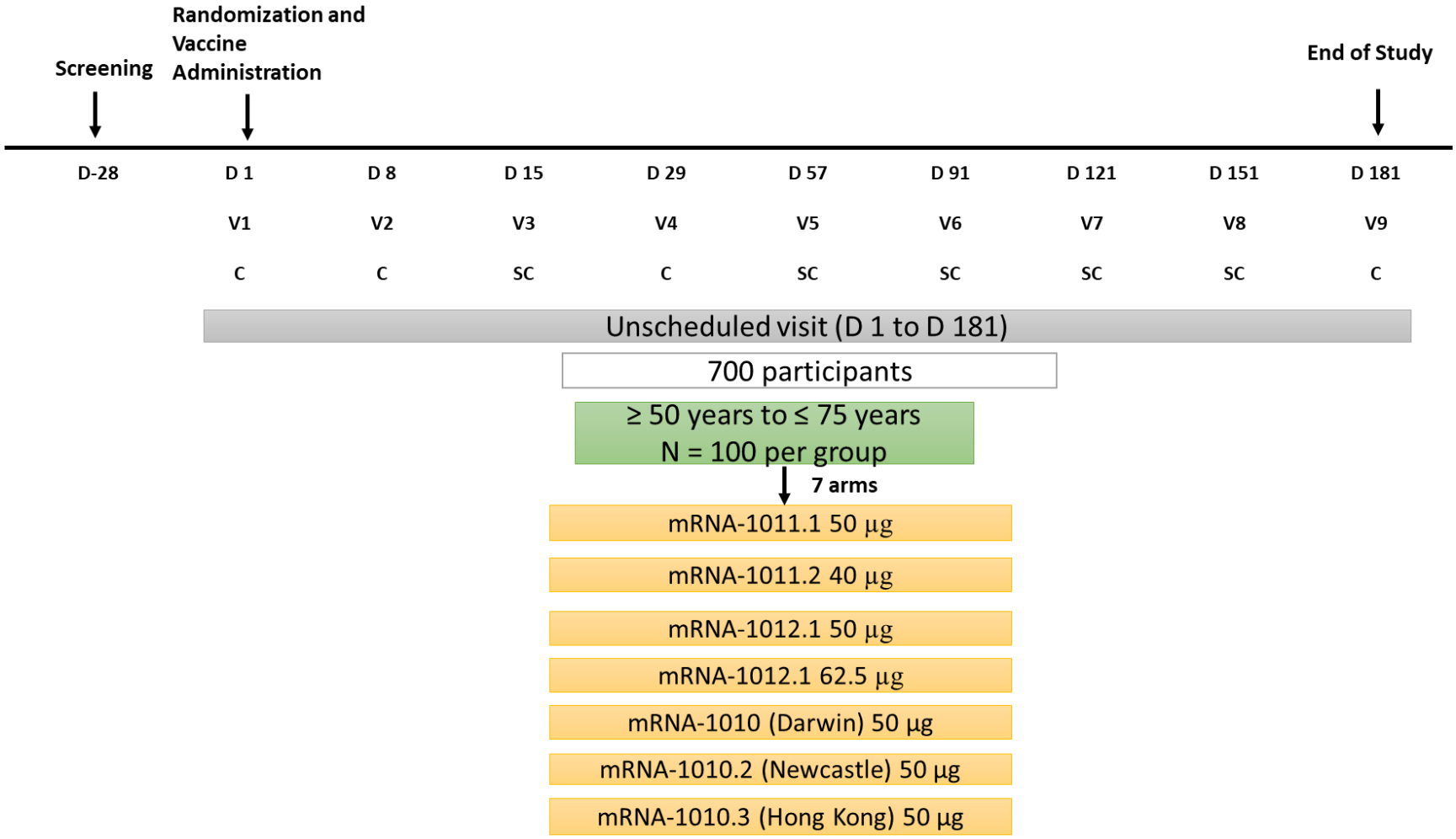
Note: Enrolled means participants agree to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol.

Study Arms and Duration:

- The study comprises 7 treatment arms of different dose levels of drug products with 6-month follow-up post vaccination.
- The total duration (including screening) for each participant is up to 7 months.

1.2. Schema

Figure 1: Study Schema



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

1.3. Schedule of Events

Table 1: Schedule of Events

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5, 6, 7, 8**	**9**	**USV**
Type of Visit	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint					**M1**	**M2, M3, M4, M5**	**M6**	**Up to M6**
Visit Day	**Screening[a]**	**D1 (Baseline)[a]**	**D8**	**D15**	**D29**	**D57, D91, D121, D151**	**D181/ EoS**	**N/A**
Window Allowance (Days)	**-28**	**-**	**-1/+3**	**±3**	**-7/+3**	**±5**	**±14**	**N/A**
Informed consent form, demographics, concomitant medications, medical history	X							
Inclusion/exclusion criteria	X	X						
Blood collection for safety laboratory samples[b]	X		X					
Physical examination[c]	X	X	X		X		X	X
Injection site and corresponding draining lymph nodes assessment[d]		X						
Vital sign measurements[e]	X	X						
Pregnancy testing[f]	X	X						
Randomization		X						
Study vaccination (including 60-minute, postdose observation period)		X[g]						
Blood collection for humoral immunogenicity[h]		X			X		X	
Blood collection for cellular immunogenicity[h]		X			X			
Optional blood collection for genomics[i]		X						
Optional blood collection for transcriptomics[i]		X	X		X			

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5, 6, 7, 8**	**9**	**USV**
Type of Visit	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint					**M1**	**M2, M3, M4, M5**	**M6**	**Up to M6**
Visit Day	**Screening[a]**	**D1 (Baseline)[a]**	**D8**	**D15**	**D29**	**D57, D91, D121, D151**	**D181/ EoS**	**N/A**
Window Allowance (Days)	**-28**	**-**	**-1/+3**	**±3**	**-7/+3**	**±5**	**±14**	**N/A**
Nasopharyngeal swab for virus detection[j]		X						X
eDiary activation for recording solicited ARs (7 days)[k]		X						
Review of solicited AR eDiary			X					
Follow-up safety call[l]				X		X		
Recording of unsolicited AEs through Day 29 and concomitant medications		X	X	X	X			X
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications relevant to or for their treatment		X	X	X	X	X	X	X
Recording of nonstudy vaccinations	X	X	X	X	X	X	X	
Study completion							X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; C = clinic visit; D = day; eDiary = electronic diary; EoS = end of study; FSH = follicle-stimulating hormone; HCP = health care practitioner; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SC = safety (telephone) call; SCRN = Screening; USV = unscheduled visit.

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

b Safety laboratory tests include total white blood cell count, hemoglobin, platelets, ALT, AST, creatinine, alkaline phosphatase, and total bilirubin.

c A full physical examination, including height and weight, will be performed at Screening; symptom-directed physical examinations will be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by an HCP during clinic visits should be reported as a MAAE.

d Prior to injection on the day of vaccination (Day 1), the injection site and associated draining lymph nodes (ipsilateral axillary lymph nodes) should be examined, and any abnormalities should be documented.

e Systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be recorded as vital signs. The preferred route of temperature assessment is oral. Vital signs will only be collected at Screening and on the day of vaccination (Day 1), once before and at least 60 minutes after vaccination. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.

f A point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injection on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The FSH level may be measured at the Screening Visit, if necessary and at the discretion of the Investigator, to confirm menopausal status.

g All participants will be randomized to receive a single IM injection in the deltoid muscle.

h Samples for humoral immunogenicity and cellular immunogenicity must be collected prior to receipt of vaccination on Day 1. Cellular immunogenicity will be sampled and assessed in a subset of approximately 15 to 20 participants per arm.

i Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by participants. Blood draws on Day 1 must occur prior to participants being vaccinated.

j An NP swab specimen for viral respiratory pathogens will be collected prior to the study intervention administration on Day 1. An NP swab should be collected through study completion for protocol-defined ILI ≤7 days of symptom onset.

k The eDiary entries will be recorded by the participant starting approximately 60 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after vaccination, on the day of vaccination and for subsequent 6 days following vaccination.

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

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LIST OF ABBREVIATIONS

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

Abbreviation or Specialist Term	Definition
AE	Adverse event
AESI	Adverse events of special interest
AR	Adverse reactions
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
DHHS	Department of Health and Human Services
DP	Drug product
ECG or EKG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EDC	Electronic data capture
EMA	European Medicines Agency
EoS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	Geometric mean fold rise
GMP	Good manufacturing practices
GMT	Geometric mean titer
GMTR	Geometric mean titer ratios

Abbreviation or Specialist Term	Definition
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HCP	Healthcare practitioner
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
ILI	Influenza-like illness
IM	Intramuscular(ly)
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
IST	Internal safety team
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibody
NH	Northern hemisphere
NP	Nasopharyngeal
PCR	Polymerase chain reaction
PP	Per-protocol

Abbreviation or Specialist Term	Definition
QA	Quality assurance
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SH	Southern hemisphere
SM	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6 (undecyloxy)hexyl)amino)octanoate
SoE	Schedule of Events
ULOQ	Upper limit of quantification
US	United States
WHO	World Health Organization
WOCBP	Woman of childbearing potential

2. INTRODUCTION

2.1. Study Rationale

Influenza A/H3N2 is a major driver of influenza-related hospitalizations and deaths, particularly in older adults. Lower vaccine efficacy against A/H3N2 viruses may contribute to the higher medical burden of influenza A. The inclusion of additional strains could allow for expanded coverage against multiple co-circulating A/H3N2 strains of distinct antigenic clades in influenza vaccination programs; and furthermore, enable public health authorities to recommend a higher number of strains for inclusion into the vaccine. Therefore, the Sponsor intends to evaluate mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 vaccine candidates which include additional HAs from influenza A/H3N2 strains. mRNA-1010 vaccine, a quadrivalent HA investigational product, is currently under investigation in an ongoing Phase 3 immunogenicity study in adults ≥18 years of age (NCT05415462) and a Phase 3 efficacy study in adults ≥50 years of age (NCT05566639). Three mRNA-1010 products (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) contain HA from different H3N2 strains to match the A/H3N2 strains in the experimental products and will serve as comparison controls for this study of next-generation influenza mRNA candidates.

The Sponsor is conducting this Phase 1/2 study to evaluate safety and immunogenicity of 3 next-generation seasonal influenza mRNA vaccines with coverage for more than one A/H3N2 strain (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1) compared to the quadrivalent mRNA-1010 vaccine with coverage for one A/H3N2 strain. mRNA-1011.1 contains 5 mRNAs encoding HAs for A/H1N1, B/Victoria, B/Yamagata, and two A/H3N2 strains, while mRNA-1011.2 contains 4 mRNAs encoding HAs similar to mRNA-1011.1 (including coverage for two A/H3N2 strains) but with B/Yamagata excluded. The rationale for excluding B/Yamagata is due to the lack of circulation of B/Yamagata-lineage viruses in recent years and thus, allowing for a higher proportion of other strains to be represented in the vaccine within the same total mRNA dose. mRNA-1012.1 contains 5 mRNAs encoding HAs similar to 1011.2 but with 1 additional HA from the A/H3N2 lineages (coverage for three A/H3N2 strains).

The comparator mRNA-1010 vaccine is the Sponsor's first-generation quadrivalent vaccine containing HAs from A/H1N1, B/Yamagata, B/Victoria, and 1 of three A/H3N2 lineages that matches those in the next-generation vaccines (mRNA-1010, mRNA-1010.2, and mRNA-1010.3). The mRNA-1010 vaccine is currently under investigation in an ongoing Phase 3 immunogenicity study in adults ≥18 years of age (NCT05415462) and Phase 3 efficacy study in adults ≥50 years of age (NCT05566639).

The objective of this study (mRNA-1011-P101) is to establish preliminary safety and immunogenicity data to support selection of a lead candidate for initiation of pivotal studies. The rationale for excluding B/Yamagata from mRNA-1011.2 and mRNA-1012.1 is due to limited circulation of B/Yamagata-lineage viruses in recent years and thus, allowing for a lower total mRNA dose or other strains to be represented in the vaccine within the same total mRNA dose.

The mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 and mRNA-1010 (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) development candidates are administered as a single dose and are aimed to elicit protection from all seasonal influenza viruses covered by the candidate vaccines.

The study design has safety and reactogenicity evaluation as the primary objective, and with secondary objective of evaluating immunogenicity of each HA component using the HAI assay because HAI titers have been established as a correlate of protection against influenza illness. 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; EMA 2016; Dunning et al 2016).

2.2. Background and Overview

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 resulting in a severe challenge to public health (WHO 2018). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the NH and SH (Riedel et al 2019). Since influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto 2018). Based on the observed circulation patterns and antigenic changes, the WHO expert panel recommends influenza virus strains to be used for vaccine manufacturing twice a year (once for the NH and SH independently). Influenza A and influenza B virus strains 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).

The candidate vaccines to be evaluated are included in Section 4.1.

Currently licensed seasonal influenza virus vaccines have suboptimal efficacy; rarely exceed 50% overall effectiveness and are poorly effective during years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2020). Influenza vaccines based on mRNA technology could provide several benefits compared to current vaccines, including the ability to respond to strain changes within a season more quickly, avoidance of mutations that may be acquired during traditional vaccine production in eggs or cell culture, potential for stronger immune responses, as well as improved protection in older adults (Rockman et al 2020).

Current quadrivalent seasonal influenza vaccines are manufactured to prevent influenza illness caused by 4 influenza strains that include 2 influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria). However, influenza A/H3N2 remains the major driver of influenza-related hospitalizations and deaths, particularly in older adults. Lower vaccine effectiveness against the influenza A/H3N2 viruses may be in part caused by vaccine mismatches that can occur due to co-circulation of multiple different A/H3N2 clades, whereas only one of those clades is generally covered by the vaccine. The inclusion of additional strains could allow for expanded coverage against multiple co-circulating A/H3N2 strains of distinct antigenic clades in influenza vaccination programs; and furthermore, enable public health authorities to recommend a higher number of strains for inclusion into the vaccine.

The Sponsor is planning to test 3 next-generation influenza development candidates (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1) containing additional influenza A/HA strains in a Phase 1/2 study to identify the optimal candidate to advance into pivotal studies. The Sponsor's first-generation quadrivalent development candidate, mRNA-1010, which is based on WHO recommended influenza strains with different H3N2 HA in each, will be included as controls. The vaccines will be administered as a single dose with primary endpoints of safety and

reactogenicity with up to 6 months follow-up. Secondary endpoints will include assessing humoral protective immunity from influenza viruses covered by the vaccine.

Lipid Nanoparticle-Encapsulated mRNA Development Program

The Sponsor has developed a rapid-response, custom-manufactured vaccine platform based on a mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. This platform is the basis of the Sponsor's product, mRNA-1273 (SPIKEVAX®), that was granted approval for full licensure for active immunization to prevent COVID-19 infection in individuals 18 years of age and older. This same platform will be used for these proposed influenza mRNA vaccine candidates.

2.2.1. Nonclinical Studies

In support of the proposed Phase 1 clinical study of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1, nonclinical pharmacology, pharmacokinetic, and toxicology studies have been completed with the candidate vaccines or other similar mRNA-based vaccines formulated in the same LNPs containing SM-102. This includes mRNA-1010 and/or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs.

Data from the following nonclinical testing programs support the clinical development of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1:

- In BALB/c mice, mRNA-1011s and mRNA-1012 induced robust IgG-binding antibodies against each HA encoded by the vaccine, as well as robust HAI antibody titers.
- In ferrets, mRNA-1011s and mRNA-1012 induced robust HAI antibody titers against each strain encoded by the vaccine.
- The safety and tolerability of similar mRNA-based vaccines formulated in an SM-102-containing LNP matrix encapsulating mRNA constructs that encode for various antigens have been evaluated in multiple GLP-compliant, repeat-dose toxicity studies in Sprague Dawley rats, followed by a 2-week recovery period. The Sponsor proposes that the toxicity associated with mRNA vaccines formulated in LNP formulations is driven primarily by the LNP composition and, to a lesser extent, the biological activity of the expressed antigens of the mRNA vaccine. This is supported by the consistency of the aggregate rat repeat-dose toxicity profile observed in these GLP studies at IM doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and thus, is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix regardless of the encapsulated mRNA sequence(s). Thus, the aggregate toxicity results from these studies support the development of mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1.
- In mouse and ferret pharmacology studies, the absence of synergistic or additive immune responses to the individual antigens in the mRNA-1011s and mRNA-1012 immunogenicity studies suggests no synergistic or additive toxicities of various

antigens compared to mRNA-1010. mRNA-1010 has already been tested independently in nonclinical immunogenicity studies with safety endpoints, as well as human studies. Thus, additional repeat-dose toxicity studies with mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 were not conducted because they were not expected to contribute to the nonclinical risk assessment or identify new target organs of toxicities for mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1.

- The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of other IM vaccines and distribution via the lymphatic system. mRNA does not persist past 1 to 3 days in tissues other than the muscle of the injection site, proximal popliteal and distal axillary lymph nodes, and spleen. The average half-life values range from 14.9 to 63.0 hours.
- In vitro and in vivo studies have demonstrated that SM-102 is efficiently and extensively metabolized through ubiquitous and high capacity hydrolytic and oxidative pathways with no human-specific metabolites. Additionally, SM-102 and its metabolites are eliminated through both renal and hepatic routes (unpublished data).

Details of mRNA-1010 are provided in the mRNA-1010 IB.

2.2.2. Clinical Studies

The Sponsor's mRNA-1010-P101 study (NCT04956575) was a Phase 1/2, randomized, observer-blind, dose ranging study to evaluate the safety, reactogenicity, and immunogenicity of the mRNA-1010 vaccine in adult participants ≥18 years of age. The study comprised 3 parts: Phase 1/2 (placebo-controlled), Phase 2 NH (active-controlled), and Phase 2 Extension (active-controlled). All participants completed their 6-month follow-up.

In the Phase 1/2 part, approximately 180 participants were randomly assigned in a 1:1:1:1 ratio to receive a single dose of mRNA-1010 at different dose levels (50, 100, or 200 µg of total mRNA) or placebo. The Phase 2 NH part randomized approximately 500 participants in a 3:3:3:1 ratio to 1 of 4 vaccination groups to receive a single dose of mRNA-1010 at different dose levels (25, 50, or 100 µg of total mRNA) or a single dose of a licensed quadrivalent seasonal influenza vaccine (active comparator, Afluria®). The Phase 2 Extension part had randomized 200 participants in a 1:1:1:1 ratio to 1 of 4 vaccination groups to receive a single dose of mRNA-1010 at different dose levels (6.25, 12.5, or 25 µg of total mRNA) or a single dose of a licensed quadrivalent seasonal influenza vaccine (active comparator, Afluria).

The mRNA-1010 vaccine included mRNAs that encoded for the HAs of the influenza virus strains recommended by the WHO for 2021 SH (Phase 1/2 part) and 2021-2022 NH (Phase 2 NH part and Phase 2 Extension part) cell- or recombinant-based vaccines.

The Day 29 safety and immunogenicity interim analysis data are available from all 3 parts. Overall, no significant safety concerns have been observed across all doses from 6.25 to 200 µg. The local and systemic ARs were mostly mild to moderate in severity. The frequency and severity of solicited ARs in the mRNA-1010 groups increased in a dose-dependent manner. The younger age group (18 to <50 years old) had higher solicited ARs than the older adults (≥50 years old). The solicited ARs were higher in the mRNA-1010 groups than in the Afluria group. There were no Grade 4 ARs. There were no SAEs assessed by the Investigator as related

to the study intervention. There were no study discontinuations due to AEs, and no AEs that led to a study pause.

Vaccination with mRNA-1010 elicited HAI antibodies in both younger and older adults against all strains at all dose levels. The HAI antibodies on Day 29 substantially exceeded the 1:40 threshold associated with a 50% reduction in risk of infection. Antibody responses induced by mRNA-1010 against the influenza A strains H1N1 and H3N2 were higher compared to Afluria and similar for the influenza B strains.

The 50-µg dose level of mRNA-1010 has been selected for further evaluation in the Phase 3 studies based on this dose eliciting strong HAI antibody responses and demonstrating an acceptable reactogenicity and safety profile. The mRNA-1010 vaccine is currently being further evaluated in 2 additional clinical studies in adults: a Phase 3 safety and immunogenicity study in adults ≥18 years of age (Study mRNA-1010-P301, NCT05415462), and a Phase 3 safety and efficacy study in adults ≥50 years of age (mRNA-1010-P302, NCT05566639).

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

2.3. Benefit/Risk Assessment

2.3.1. Known Potential Benefits

Participants will have a baseline (Day 1) evaluation for viral respiratory pathogens for protocol-defined ILI throughout the study.

The study will contribute to the development of a potentially efficacious vaccine against seasonal influenza.

2.3.2. Risks from Study Participation and Their Mitigation

Immediate systemic allergic reactions, ranging from mild (eg, urticaria) to severe (eg, anaphylaxis) may occur very rarely following any vaccination. Systemic allergic reactions are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). Since the authorization of the Sponsor's mRNA-1273 vaccine for COVID-19, the US CDC estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precaution, all participants will remain under observation at the study site for at least 60 minutes after injection.

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

IM injection with other mRNA vaccines manufactured by the Sponsor containing the custom-manufactured SM-102 ionizable lipid formulation have commonly resulted in transient and self-limiting local inflammatory reactions. These typically included pain, erythema (redness), or swelling (hardness) at the injection site, which were mostly mild to moderate in severity and usually occurred within 24 hours of injection.

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection have been observed in early phase clinical studies with similar mRNA-based

vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown.

The most commonly reported local solicited ARs at the time of interim safety analysis in the ongoing Phase 1/2 mRNA-1010-P101 study were injection site pain and axillary swelling or tenderness. The most common systemic solicited ARs were headache, fatigue, myalgia, and chills. Most of these reactions were Grade 1 or 2 in severity and resolved within a few days.

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

2.3.3. Overall Benefit/Risk Conclusion

These vaccines may or may not offer protection against seasonal influenza.

Considering the nonclinical data for mRNA-1011.1, mRNA 1011.2, and mRNA-1012.1, as well as the safety data for mRNA-1010 and other mRNA vaccines containing the custom-manufactured SM-102 ionizable lipid formulation (eg, mRNA-1273) to date, the Sponsor considers the potential benefits of participation to exceed the risks. Refer to Section 2.2 for more details.

3. OBJECTIVES AND ENDPOINTS

The study objectives and associated endpoints are provided in Table 2.

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3)	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • MAAEs from Day 1 to Day 181/EoS • AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1 in comparison with mRNA-1010 controls (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) against vaccine-matched influenza A and B strains at Day 29	• GMT and GMFR, comparing Day 29 with Day 1 (baseline), and percentage of participants with seroconversion, defined as a postbaseline titer ≥1:40 if baseline is <1:10 or a 4-fold or greater rise if baseline is ≥1:10 in anti-HA antibodies measured by HAI assay
Exploratory (may be performed)	
• To evaluate the humoral immunogenicity of mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls against vaccine-matched influenza A and B strains at all evaluable humoral immunogenicity timepoints	• GMT, GMTR (mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 against mRNA-1010), and GMFR (compared with Day 1) of anti-HA as measured by HAI assay
• To evaluate the humoral immunogenicity against vaccine-matched influenza A and B strains by alternative methods at all evaluable timepoints	• GMT and GMFR (compared with Day 1) of anti-HA antibodies as measured by MN assays or other alternative methods against vaccine matched strains
• To evaluate the humoral immunogenicity against vaccine-mismatched influenza A and B strains at all evaluable timepoints	• GMT and GMFR (compared with Day 1) of anti-HA antibodies as measured by HAI or MN assays against vaccine-mismatched strains
• To evaluate cellular immunogenicity in a subset of participants at all evaluable timepoints	• Frequency, magnitude, and phenotype of virus-specific B-cell responses measured by flow cytometry or other methods, and to perform

Objectives	Endpoints
	targeted repertoire analysis of B-cells after vaccination
• 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 event of special interest; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutinin; ILI = Influenza-like illness; GMTR = geometric mean titer ratios; HAI = hemagglutination inhibition; MAAE = medically attended adverse event; MN = microneutralization; mRNA = messenger ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event.

4. STUDY DESIGN

4.1. General Design

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

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

The candidate vaccines to be evaluated include:

- mRNA-1011.1 vaccine consisting of 5 mRNAs encoding the HA surface glycoproteins of 4 influenza strains (A/H1N1, A/H3N2, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 additional A/H3N2 influenza strain (A/Newcastle/1/2021).
- mRNA-1011.2 vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, A/H3N2, and B/Victoria lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Newcastle/1/2021) to replace B/Yamagata.
- mRNA-1012.1 vaccine consisting of 5 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, A/H3N2, and B/Victoria lineage) recommended by the WHO for the 2022/2023 NH season, and 2 additional A/H3N2 influenza strains (A/Newcastle/1/2021 and A/Hong Kong/45/2019) to replace B/Yamagata.
- mRNA-1010: mRNA-1010 (Darwin) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 4 influenza strains (A/H1N1, A/H3N2, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season.
- mRNA-1010.2: mRNA-1010 (Newcastle) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Newcastle/1/2021).
- mRNA-1010.3: mRNA-1010 (Hong Kong) vaccine consisting of 4 mRNAs encoding the HA surface glycoproteins of 3 influenza strains (A/H1N1, B/Victoria lineage, and B/Yamagata lineage) recommended by the WHO for the 2022/2023 NH season, and 1 alternative A/H3N2 influenza strain (A/Hong Kong/45/2019).

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

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

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

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

Table 3: Study Arms and Dose Levels

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

Abbreviations: mRNA = messenger ribonucleic acid.

4.2. Scientific Rationale for Study Design

This study will enroll healthy adults aged ≥50 to ≤75 years to evaluate next-generation influenza mRNA vaccine candidates. This broad age range allows inclusion of older adults who often have higher risk of comorbidities and conditions that could lead to more negative health outcomes due to influenza. mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 could provide a public health benefit through increasing protection against circulating influenza A/H3N2 strains.

The additional H3N2 strains evaluated in this study were selected by the Sponsor for their antigenic distance compared to the Darwin strain contained in the 2022/2023 NH vaccine composition and greater antigenic breadth across the H3N2 virus family. Due to WHO reporting

limited circulation of the B/Yamagata virus in recent years, the mRNA-1011.1 and mRNA-1012.1 candidates were designed to not contain the B/Yamagata HA, allowing for higher proportion of other strains/additional strains to be represented in the vaccine. Data from this study will help distinguish the immune responses against the respective vaccine strains, using the HAI assay, and evaluate the added benefit of mRNAs encoding additional influenza A/H3N2 strains from the WHO recommended strains. The Sponsor expects to follow public health recommendations for inclusion of multiple H3N2 strains once such recommendations are available.

The study will be conducted in an open-label manner. Since all study arms will receive DP in a relatively narrow dosage range that have the same clinical indication, developed with the same technology platform (mRNA platform) and there is no placebo arm, the preference or bias for particular study products would be perceived to be minimum from either investigators' or participants' perspective.

4.3. Justification for Dose

The selection of the 50-µg dose level of the Sponsor's mRNA-1010 candidate is supported by the data from the Phase 1/2 and the Phase 2 NH interim analyses (see mRNA-1010 IB).

The safety and immunogenicity profile observed from the mRNA-1010-P101 study supports the use of 50 µg total mRNA dose level as the dose to base a dose-ranging study of these next-generation influenza mRNA candidates and in the selection of dosage of control comparisons. mRNA-1010 is a quadrivalent vaccine and contains 12.5 µg of mRNA encoding for each HA strain for a total of 50 µg mRNA, the dose of all the mRNA-1010 controls.

The mRNA-1011.1 and mRNA 1011.2 each contain 10 µg of each HA strain, resulting in a 50 µg and 40 µg dosage in the pentavalent and quadrivalent vaccine, respectively. mRNA-1012.1 is also a pentavalent vaccine and has a total dose of 50 µg with 10 µg of each HA. Lastly, mRNA-1012.1 will also be tested at a 62.5 µg dose, with 12.5 µg of each HA strain similar to the mRNA-1010 controls, thereby allowing evaluation of reactogenicity of each HA strain at the same dosage.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all periods of the study (Table 1). The end of study is defined as completion of the last visit of the last participant in the study or last scheduled procedure(s) as shown in the SoE (Table 1).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adults ≥50 to ≤75 years of age at the time of consent (Screening Visit) who, in the opinion of the Investigator, are in good health based on review of medical history and physical examination performed at the Screening Visit.
2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up and procedures.
3. Able to provide written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.
4. Body mass index of 18 kg/m^2 to 35 kg/m^2 (inclusive) at the Screening Visit.
5. Women of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized. FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. Women of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at the Screening Visit and on the day of vaccination (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1. Adequate female contraception is defined as consistent and correct use of a locally authorized or approved contraceptive method in accordance with the product label.
    - Has agreed to continue adequate contraception through 3 months following vaccine administration.
    - Is not currently breastfeeding.

5.2. Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Acutely ill or febrile (temperature ≥38.0°C/100.4°F) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day screening window and will retain their initially assigned participant number.
2. Clinical screening laboratory values for total white blood cell count, hemoglobin, alanine aminotransferase, aspartate aminotransferase, creatinine, alkaline phosphatase, and total bilirubin are >Grade 1 or platelets ≥Grade 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.
    - Asymptomatic conditions and conditions with no clinically significant end-organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that the participant is 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, immunosuppressive treatments), at the discretion of the Investigator.
    - Participants who have undergone surgical procedures within 28 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention administration are excluded. Minor surgical procedures under local anesthesia (eg, excision of skin lesion) or screening and diagnostic procedures (eg, colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency, immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Certain immune-mediated conditions that are stable and well controlled (eg, Hashimoto thyroiditis), as well as those that do not require systemic immunosuppressants (eg, asthma, psoriasis, or vitiligo) may be permitted at the discretion of the Investigator.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriatic patches or vitiligo affecting skin over the deltoid injection site area).
6. History of anaphylaxis or severe hypersensitivity reaction requiring medical intervention after receipt of a vaccine or any of the components contained in mRNA vaccines.
7. Coagulopathy or a bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
8. Diagnosis of malignancy within previous 5 years (excluding non-melanoma skin cancer).
9. Any medical, psychiatric, or occupational condition, including reported history of substance 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.
10. Has received systemic immunosuppressants for >14 days in total within 180 days prior to the Randomization Visit (for glucocorticosteroids ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study (including intra-articular steroid injections). Inhaled, nasal, and topical steroids are allowed.
11. Has received or plans to receive any licensed or authorized vaccine, including COVID-19 vaccines, ≤28 days prior to the study injection (Day 1) or plans to receive a licensed or authorized vaccine within 28 days after the study injection.
12. Has received a seasonal influenza vaccine or any other investigational influenza vaccine within 180 days prior to the Randomization Visit.

13. Has tested positive for influenza by local health authority-approved testing methods within 180 days prior to the Randomization Visit.
14. Has been treated with antiviral therapies for influenza (eg, Tamiflu®) within 180 days prior to the Randomization Visit.
15. Has had close contact with someone with laboratory-confirmed influenza infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu) within the past 5 days prior to the Randomization Visit.
16. Has had close contact to someone or been diagnosed themselves with respiratory syncytial virus or SARS-CoV-2 infection as defined by the CDC in the past 10 days prior to the Randomization Visit.
17. Has received systemic immunoglobulins, long-acting biological therapies that affect immune responses (eg, infliximab), or blood products within 90 days prior to the Randomization Visit or plans to receive them during the study.
18. History of myocarditis, pericarditis, or myopericarditis.
19. History of Guillain-Barre syndrome.
20. Has donated ≥450 mL of blood products within 28 days prior to the Randomization Visit or plans to donate blood products during the study.
21. Has participated in an interventional clinical study within 28 days prior to the Randomization Visit 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 described in this protocol. (Note: Interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary).
22. Is working or has worked as a study personnel or is an immediate family member or house member of study personnel, study site staff, or Sponsor personnel.

5.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken. Participants should defer vaccination with licensed or authorized vaccines, including COVID-19 vaccines, until after completion of their Day 29 Visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, and eligibility criteria.

6. STUDY INTERVENTIONS

6.1. Study Interventions Administered

The term "study intervention" refers to mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1, and mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3) that will be administered in this study. The vaccines to be evaluated are described in Section 4.1.

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.

6.2. Randomization

Randomization will be performed using an IRT system.

The Sponsor's Biostatistics Department or designee will generate the randomized allocation schedule(s) for vaccination group assignment. Overall, approximately 700 healthy adults will be randomized in parallel into 7 treatment arms to receive either mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 candidate seasonal influenza vaccines or mRNA-1010 control (mRNA-1010, mRNA-1010.2, and mRNA-1010.3) vaccines, with approximately 100 healthy adult participants randomly assigned to each of vaccination groups 1 to 7. Different dose levels will be assessed in parallel (Table 3). Randomization will be stratified by influenza vaccination status in the previous influenza season (received or not received).

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Preparation of Study Intervention

The study intervention will be prepared for each participant based on the vaccination group. The study intervention (mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls) preparation instructions are detailed in the Pharmacy Manual.

6.3.2. Study Intervention Administration

The study intervention (mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls) will have a dose volume of 0.5 mL and will be administered as a single IM injection into the deltoid muscle on Day 1, with preference in the non-dominant arm.

Participants will be monitored for a minimum of 60 minutes after administration of the study intervention. Assessments will include vital sign measurements and monitoring for local or systemic reactions as shown in the SoE (Table 1).

The study site 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-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls are described in the Pharmacy Manual.

6.3.3. Study Intervention Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the study interventions; mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, and mRNA-1010 controls.
- Confirming the appropriate labeling of the study intervention for clinical study use so that it complies with the US legal requirements.

The Investigator is responsible for acknowledging receipt of the study intervention by a designated staff member at the site, which includes the following:

- Confirming that the study intervention was received in good condition.
- Confirming that the temperature during shipment from the Sponsor to the Investigator's designated storage location was appropriate.
- Confirming that the Sponsor has authorized the study intervention for use.
- Ensuring the appropriate dose level of the study intervention is properly prepared using aseptic technique.

Further description of the study intervention and corresponding instructions for the receipt, storage, preparation, administration, accountability, and destruction are described in the Pharmacy Manual.

6.3.4. Study Intervention Packaging and Labeling

The study intervention will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

All study interventions used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, CFR Title 21 GMP guidelines, ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.3.5. Study Intervention Storage

All study interventions must be stored in a secure area with limited access and must be protected from moisture and light until it is prepared for administration in accordance with the instructions in the Pharmacy Manual.

6.3.6. Study Intervention Accountability

The Investigator is responsible for ensuring the study intervention accountability staff maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study intervention, and the return to the Sponsor or alternative disposition of used/unused product(s) in a drug accountability log. Drug accountability will be noted by the site monitor during site visits and at the completion of the study. For further direction, refer to the Pharmacy Manual.

6.3.7. Study Intervention 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 a Sponsor selected third party, as appropriate.

Study intervention may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A document for destruction (ie, Certificate of Destruction) must be obtained and sent to the Sponsor or designee. Refer to Pharmacy Manual for further directions.

6.4. Study Intervention Compliance

All study interventions will be administered at the study site under direct observation of medically qualified study staff, and study intervention administration will be appropriately recorded (date and time) in the eCRF. Qualified staff will confirm that the participant has received the entire dose of the study intervention. If a participant does not receive the study intervention, the reason for the missed dose will be recorded. Data will be reconciled with site accountability records to assess compliance.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window specified in the SoE (Table 1). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

6.5. Dose Modification

No dose modifications are allowed.

6.6. Continued Access to Study Intervention after the End of the Study

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

6.7. Prior and Concomitant Therapy

At each visit, the study site staff should question the participant regarding any medications taken and vaccinations received and record the information as specified in Section 6.7.1 and Section 6.7.2.

6.7.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the eCRF.

6.7.2. Concomitant Medications and Vaccinations

The following information regarding concomitant medication and vaccinations will be recorded in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the study intervention and through Day 181 (Month 6)/EoS.
- Any authorized or investigational COVID-19 vaccine at any time before the study intervention and through Day 181 (Month 6)/EoS.
- All concomitant medications taken through 28 days after the study intervention. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Systemic steroids (≥10 mg/day of prednisone or equivalent), immunosuppressants, immunoglobulins, or long-acting biological therapies that affect immune responses (eg, infliximab), 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 a 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 medication to treat or prevent fever or pain within 7 days after the study intervention, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the study visits after vaccination or via other participant interactions (eg, telephone calls).

Concomitant medications (including vaccinations) will be coded using the WHODrug Global Dictionary.

It is the Investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

6.7.3. 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 9.4.):

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

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

7.1. Pause Rules

Study pause rules will be continuously monitored during the study by the Investigators and IST, as warranted. If the Investigator and/or IST request that the study be paused due to a safety concern, further study intervention will be suspended while all other planned procedures relating to safety, reactogenicity, and immunogenicity assessments will continue as described in the protocol. The Sponsor will notify the Center for Biologics Evaluation and Research within 48 hours in the event of a study pause.

7.1.1. Pause Rules Based on the Occurrence of a Single Event and Adjudicated by the Data Safety Monitoring Board

The occurrence of any of the events listed in Table 4, regardless of the treatment arm, will result in immediate pause of enrollment. An unscheduled safety review will be convened to assess specific data concerns and make recommendations.

Table 4: Pause Rule Criteria, Events, and Thresholds - Single Event

Pause Rule	Event	Number of Participants
1	Any SAE that cannot be reasonably attributed to a cause other than study vaccination	≥1
2	Any Grade 4 local or systemic solicited AR or any Grade 4 laboratory abnormality that cannot be reasonably attributed to a cause other than study vaccination[a]	≥1
3	Any case of myocarditis and/or pericarditis that cannot be reasonably attributed to a cause other than study vaccination	≥1

Abbreviations: AE = adverse event; AR = adverse reaction; FDA = Food and Drug Administration; SAE = serious adverse event; US = United States.

[a] Grading of laboratory parameters will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." (DHHS 2007b).

7.1.1.1. Pause Rules Based on the Occurrence of Events in a Proportion of Participants

The occurrence of safety events that will pause study dosing based on defined threshold levels, which are aggregate incidences relative to the number of exposed participants within a vaccination group, are summarized in Table 5.

Table 5: Pause Rule Criteria, Events, and Thresholds – Proportion of Participants

Pause Rule	Event	Number or Percentage of Participants[a]
4	Any severe unsolicited nonserious AE that cannot be reasonably attributed to a cause other than the study vaccination (independent of within or not within the same system organ class)	≥2 participants per group or ≥20% of total participants[b]
5	Any Grade 3 local solicited AR lasting more than 48 hours that cannot be reasonably attributed to a cause other than the study vaccination, starting within the 7-day postdosing period[c]	≥2 participants per group or ≥20% of total participants[b]
6	Any Grade 3 systemic solicited AR lasting more than 48 hours (24 hours for fever) that cannot be reasonably attributed to a cause other than the study vaccination, starting within the 7-day postdosing period[c]	≥2 participants per group or ≥20% of total participants[b]

Abbreviations: AE = adverse event; AR = adverse reaction; MedDRA = Medical Dictionary for Regulatory Activities.

a The rate of AEs/ARs will be computed based on the number of exposed participants in each treatment group. For solicited ARs, participants need to experience the same solicited AR. Unsolicited events will be counted independent of within or not within the same system organ class.

b For the first 7 participants in each dosing group, the pause rule will be considered met if two of the first 7 participants experience AEs/ARs per footnote a. The calculation for ≥20% of participants includes the total number of participants within a dosing group who have completed a postdosing visit in the denominator. Reactogenicity e-diary data confirmed by the Investigator as being entered by the participant in error will not contribute toward a stopping rule.

c Grading of parameters will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." (DHHS 2007b).

If a pause is triggered in the study, each participant's study site visits will continue until EoS. If a pause affects a participant's vaccination visit, the window for that participant's vaccination visit will be suspended until the pause is lifted and vaccination can resume. Once the pause is lifted, vaccination should be reinstated as soon as possible.

If a participant is in the screening period for more than 28 days as a result of a pause, the participant may be rescreened for study eligibility (and will receive a new screening number) as long as the participant continues to provide consent to participate in the study.

7.2. Criteria for Delay or Withholding of Study Intervention

Body temperature must be measured at the dosing visit before administration of study intervention. The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may be injected at a later date within the time window specified in the SoE (Table 1):

- Acute moderate or severe infection with or without fever at the time of dosing.
- Fever, defined as body temperature ≥38.0°C (100.4°F) at the time of dosing.
- Receipt of all other vaccinations within 28 days of planned Day 1.

Participants with a minor illness in the absence of fever, as assessed by the Investigator, can be administered the study intervention. Participants with a fever ≥38.0°C (100.4°F) will be contacted within the time window acceptable for participation and reevaluated for eligibility. If the Investigator determines that the participant's health on the day of administration temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

The Investigator, in consultation with the Sponsor's medical monitor, should withhold the study intervention if the participant meets any of the following criteria:

- Becomes pregnant.
- Develops symptoms or conditions listed in the exclusion criteria.
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements or general condition that, in the judgment of the Investigator, requires withholding of study intervention.

The reason(s) for withholding the study intervention will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the Investigator could delay the study intervention within the visit window or withhold the study intervention based on a joint decision of the Investigator and the CRO's medical monitor.

7.3. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced unless otherwise stated in the protocol.

A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

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

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

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

Information related to the withdrawal will be documented in the eCRF. The Investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the Investigator, as well as the reason for withdrawal.

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

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

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

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

7.4. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the 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 registered letters) should be documented in the participant's medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence, as described above, has been completed.

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an informed consent form (Section 11.1.6). Participants will undergo study procedures at the timepoints specified in the SoE (Table 1).

A participant can also be seen for an unscheduled visit at any time during the study. Reasons for an unscheduled visit may include, but are not limited to, reactogenicity issues, symptoms of potential ILI, and new or ongoing AEs. The site also has discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoE (Table 1). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. 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.
- The Screening Visit and Day 1 Visit will not be performed on the same day. The Screening Visit may be performed over multiple visits if within the 28-day screening window.

8.1. Study Vaccine Administration

A single dose vaccination (mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, or mRNA-1010 controls) will be administered to all participants.

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

8.2. Safety Assessments and Procedures

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

- Solicited local and systemic ARs (Section 8.4.4) that occur during the 7 days following the study intervention (ie, the day of study vaccination [Day 1] and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported within 28 days following the study intervention, with the day of study vaccination as Day 1 (Section 8.4.2).

- AEs leading to discontinuation from study participation from Day 1 through Day 181 (Month 6)/EoS or withdrawal from the study.
- MAAEs from Day 1 through Day 181 (Month 6)/EoS or withdrawal from the study (Section 8.4.5).
- AESIs from Day 1 through Day 181 (Month 6)/EoS or withdrawal from the study (Section 8.4.6).
- SAEs from Day 1 through Day 181 (Month 6)/EoS or withdrawal from the study (Section 8.4.3).
- Results of abnormal safety laboratory tests (Section 8.2.12).
- Abnormal vital sign measurements (Section 8.2.1).
- Abnormal physical examination findings (Section 8.2.1).
- Details of all pregnancies in female participants will be collected from Day 1 through Day 181 (Month 6)/EoS (Section 8.2.2).

8.2.1. Physical Examination and Vital Signs

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

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

On the day of Vaccination (Day 1), injection site and associated draining lymph nodes should be examined prior to administration of study intervention and results documented for any abnormalities.

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

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

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

8.2.2. Pregnancy Testing

A point-of-care urine pregnancy test will be performed for all female participants of childbearing potential at the Screening visit and before study intervention administration on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. Additional pregnancy testing during the study may also be performed if required by local regulatory requirements. The participant's FSH level may be measured at the

Screening visit, at the discretion of the Investigator, when necessary, to confirm postmenopausal status (Contraceptive Guidance, Section 11.2).

Further details on reporting and follow-up of pregnancy are provided in Section 8.2.6.

8.2.3. Assessments for Respiratory Viral Infections

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

8.2.4. Safety Telephone Calls

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

8.2.5. Use of Electronic Diaries

At the time of consent, the participants must confirm they are 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 7.

Solicited local and systemic reactogenicity ARs will be collected on the day of study intervention and during the 7 days after study intervention (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.4.4.

At the dosing visit, participants will record data into the eDiary starting approximately 60 minutes after dosing under supervision of the study site staff to ensure successful entry of assessments. The 60-minute observation period is an opportunity for the study site staff to train the participant on eDiary completion requirements. The site staff will perform any retraining as necessary.

At the dosing visit, participants will also 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) during the 7 days after study vaccination. Daily measurements should be performed at approximately the same time each day using the thermometer and ruler provided by the study site staff.

The participant will be trained on how to complete the eDiary questions according to the SoE (Table 1) and also reminded to call the site immediately if they experience any signs or symptoms of ILI. If eDiary questions result in identification of relevant safety events according

to the study period, 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 SoE, study site staff will follow-up with the participant.

8.2.6. Recording and Follow-up of Pregnancy

The effects of the study interventions on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant and do not become pregnant during the course of the study. Female individuals who have a positive pregnancy test at the Screening visit should not be enrolled; participants who have a positive pregnancy test at Day 1 must not receive the study intervention and should be withdrawn from the study. Female participants who become pregnant at any time during the study after receiving the study intervention should be asked to remain in the study and be followed up for safety. Pregnancy testing is scheduled to occur at the Screening visit and Day 1 (Table 1). Additional pregnancy testing during the study may also be performed if required by local regulatory requirements.

Pregnancies reported in female participants will be collected after the start of study intervention and until Day 181 (Month 6)/EoS.

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

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

8.2.7. Recording and Follow-up of an AE and/or SAE

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

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

MAAEs, SAEs, and AESIs will be collected from participants as specified in the SoE (Table 1) from Day 1 until the end of their participation in the study. Any AEs occurring before receipt of the study intervention will be analyzed separately from TEAEs.

At every study site visit or telephone contact, participants will be asked a standard set of questions to elicit any medically related changes in their well-being (including surveillance for respiratory viral infection symptoms) according to a provided script. 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 nonstudy vaccinations.

In addition to participant observations, physical examination findings and other documents relevant to participant safety classified as an AE will be documented in EDC.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.4).

8.2.8. Reporting Adverse Events

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

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

Refer to Section 8.2.10 for reporting of medical occurrences that begin before study intervention administration but after obtaining informed consent.

8.2.9. Reporting Serious Adverse Events

Any AE considered serious by the Investigator or that meets SAE criteria (Section 8.4.3) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The Investigator will assess whether there is a reasonable possibility that the study intervention caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as required per applicable regulations. The Investigator is responsible for notifying the IRB or IEC directly.

If the eCRF is unavailable at the time of the SAE, the paper SAE/AESI Report Form distributed to the study sites should be completed and sent via e-mail or fax as provided on the form.

Regulatory reporting requirements for SAEs are described in Section 8.4.9.

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

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

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

Adverse events may be collected as follows:

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

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of becoming aware of the event, as indicated in Section 8.4.3. 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 AEs or SAEs after conclusion of the study participation (EoS). However, if an Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.2.11. Method of Detecting AEs and SAEs

The eDiary has specifically been designed for this study by the Sponsor to collect solicited ARs. Refer to Section 8.2.5 for further details on the use of eDiary. Details on recording of solicited ARs in an eDiary are included in Section 8.4.4.

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

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

8.2.12. Safety Laboratory Assessments

Planned blood sampling for safety laboratory assessments will occur as indicated in the SoE (Table 1). Tests will include white blood cell count, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and creatinine. Laboratory tests will be performed by the central laboratory, unless otherwise specified.

8.2.13. Blood Sampling Volumes

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

8.2.14. Ancillary Supplies for Participant Use

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

8.3. Immunogenicity Assessments

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

- Serum antibody level as measured by HAI assay.
- Serum nAb level as measured by MN assay or similar method, if necessary.

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

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

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

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

8.4. Safety Definitions and Related Procedures

8.4.1. 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:

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

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

CDC-defined ILI:

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

RT-PCR-confirmed Protocol-defined Influenza Infection:

An RT-PCR-confirmed 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.

RT-PCR–confirmed CDC-defined Influenza Infection

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

Through Day 28, any illness assessed for protocol-defined ILI should be captured as an AE in EDC. Starting on Day 29, illnesses assessed for protocol-defined ILI should only be captured as AEs if they otherwise meet the criteria for reporting as an SAE (Section 8.4.3), MAAE (Section 8.4.5) or event leading to discontinuation from the study. An event should not be recorded as a MAAE based on visits to the clinical study site for protocol-required assessment of ILI symptoms and NP swab collection.

8.4.2. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a pharmaceutical product, whether or not considered related to the product.

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

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE in EDC. The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Events Meeting the Adverse Event Definition

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

Events NOT Meeting the Adverse Event Definition

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

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR (Section 8.4.4) in the protocol; or is specified as a solicited AR in the protocol, but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after study intervention).

8.4.3. Serious Adverse Events

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

- **Death**

  A death that occurs during the study or that comes to the attention of the Investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the study intervention.

- **Is life-threatening**

  An AE is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- **Inpatient hospitalization or prolongation of existing hospitalization**

  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least 1 overnight stay as an inpatient for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.

- **Persistent or significant disability or substantial disruption of the ability to conduct normal life functions**

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and

accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Congenital anomaly or birth defect**
- **Medically important event**

An AE is medically important if, per the medical judgment of the Investigator or the Sponsor, it is determined that SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

8.4.4. Solicited Adverse Reactions

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

Severity grading of reactogenicity events will be automatically assigned upon participant entry into the eDiary based on the grading scales presented in Table 7, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b). All solicited ARs (local and systemic) will be considered causally related to dosing.

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

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

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

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

Table 7: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[a] (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

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

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

[a] Grading of Grade 4 events will be determined per Investigator and assessment is recorded in EDC.

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

8.4.5. Medically Attended Adverse Events

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

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.

8.4.6. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the

Investigator to the Sponsor are required. Such events may require further investigation to characterize and understand them.

In addition to anaphylaxis and myocarditis/pericarditis, AESIs for this protocol (thrombocytopenia and new onset of or worsening of neurologic diseases) are described in Section 11.3.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via EDC. If a site receives a report of a new AESI from a participant or receives updated information on a previously reported AESI at a time after the eCRF has been taken offline, then the site should report this information on the paper SAE/AESI Report Form provided to the study site via e-mail or fax as provided on the form (Section 8.2.9).

8.4.6.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as AESIs, reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an AESI and/or SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, per Section 8.2.9. The Investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

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

Anaphylaxis is a clinical syndrome characterized by the following:

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

8.4.6.2. Myocarditis/Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC Working Case Definitions. The event should also be reported as an SAE if it meets seriousness criteria (see Section 8.2.9).

An independent CEAC will review reported cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Section 8.5.2).

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

8.4.7. Assessment of Intensity/Severity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.4.3), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007b) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.4.4.

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

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

Study site staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

8.4.8. Assessment of Causality

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

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

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

8.4.9. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities 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, IRB/IEC, and Investigators.

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

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

8.5. Safety Oversight

8.5.1. Internal Safety Team

Safety monitoring for this study will include the study team members, inclusive of, at a minimum, the Sponsor medical monitor and a CRO medical monitor and an IST. The study team will conduct safety reviews during the study and will be responsible for notifying the IST of potential safety signal events. The IST will conduct a scheduled review of safety data after approximately 49 participants (approximately 7 per study arm) have completed the Day 8 visit, as well as ad hoc safety data reviews, if requested by the study monitor or study team. Enrollment will be ongoing while this review is conducted and if the study team has not identified any safety concerns.

8.5.2. Independent Cardiac Event Adjudication Committee

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

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

8.6. Treatment of Overdose

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

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

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

8.7. Pharmacokinetics

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

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9. Biomarkers

Immunogenicity assessments are described in Section 8.3. Biomarker assessments (to be determined) will be evaluated in this study, which may include genomic and transcriptomic studies.

8.10. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Blinding and Responsibility for Analyses

This is an open-label study.

9.2. Statistical Hypotheses

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

9.3. Sample Size Determination

Approximately 700 participants will be randomized in this study, with approximately 100 participants each in Vaccination Groups 1-7 (≥50 to ≤75 years of age). Details regarding the number of participants in each vaccination group are presented in Table 3. The probability of AEs based on sample size is presented in Table 8. With 100 participants in each group receiving the study intervention, there is an approximately 87% probability to observe at least 1 participant with an AE if the true incidence of the AE is 2%; if the true incidence rate is 3%, then the probability to observe an AE is approximately 95%.

Table 8: Probability of AEs Based on Sample Size

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

AE = adverse event

9.4. Analysis Populations

Table 9 describes the analysis populations.

Table 9: Analysis Sets

Set	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.
FAS[a]	The FAS consists of all randomly assigned participants who receive the study vaccination.
PP Set[b]	The PP Set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least the Day 29 post-injection assessment, have no RT-PCR–confirmed influenza infection prior to Day 29 visit and have no major protocol deviations that impact the immune response.
Safety Set[c]	The safety set consists of all randomly assigned participants who receive the study vaccination.
Solicited Safety Set[d]	The solicited safety set consists of all participants in the safety set who contribute any solicited AR data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; PP = per-protocol; RT-PCR = reverse transcriptase polymerase chain reaction.

a For the FAS, participants will be analyzed according to the group to which they were randomized.
b The PP Set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.
c The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the vaccination group corresponding to what they actually received.
d The solicited safety set will be used for the analyses of solicited ARs, and participants will be included in the vaccination group corresponding to what they actually received.

9.5. Statistical Methods

General Considerations: All analyses will be performed by treatment arm, unless otherwise specified. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

9.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, sex, race, ethnicity, height, weight, and body mass index) and baseline characteristics will be summarized by vaccination group and overall. Summary statistics (mean and standard deviation for continuous variables and number and percentage for categorical variables) will be provided.

9.5.2. Safety Analyses

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

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

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and any solicited AR during the 7 day follow-up period after study intervention will be summarized.

Number and percentage of participants with unsolicited AEs, SAEs, MAAEs, severe AEs, AESIs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized.

Number of events of unsolicited AE, SAEs, AESIs, and MAAEs will be reported in summary tables accordingly.

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

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by treatment arm and visit at each timepoint.

The number and percentage of participants who have chemistry, hematology, and vital signs results below or above the normal laboratory ranges will be tabulated by timepoint.

9.5.3. Immunogenicity Analyses

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

For the immunogenicity endpoints, GM of specific antibody titers with corresponding 95% CI at each timepoint and GMFR of specific antibody titers with corresponding 95% CI at each postbaseline timepoint over preinjection baseline at Day 1 will be provided by treatment arm. Descriptive summary statistics including median, minimum, and maximum will also be provided.

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

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

GMTRs with corresponding 95% CI will be calculated for each candidate vaccine group against matched mRNA-1010 controls (mRNA-1010, mRNA-1010.2 and mRNA-1010.3) after adjustment of baseline titers, at each available timepoint.

Further details will be described in the SAP.

9.5.4. Exploratory Analyses

Exploratory analyses will be described in the SAP.

9.5.5. Subgroup Analyses

The protocol does not define any formal subgroup analyses. However, future subgroups may be defined in the SAP.

9.6. Planned Analyses

9.6.1. Interim Analyses

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

The final clinical study report will include full analyses of safety and immunogenicity data available through Day 181(Month 6)/EoS.

The SAP will describe the planned interim and final analyses in greater detail.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. APPENDIX 1: Study Governance Considerations

11.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB 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.
- 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 GCP guidelines, the IRB, and all other applicable local regulations.

11.1.2. Study Monitoring

Before an investigational study site can enter a participant into the study, the Sponsor or its representatives will visit the study site for the following:

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

According to ICH GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the Investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the Investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data

and/or documents. In addition, the study monitor will explain to and interpret for the Investigator all regulations applicable to the clinical evaluation of IP as documented in ICH guidelines.

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

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

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

11.1.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The Investigator agrees to allow the Sponsor Inc., their designee(s), the IRB, or regulatory authorities to inspect the study intervention storage area, study intervention stocks, study intervention records, participant charts, and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and the IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and whether data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 [R2], and any applicable regulatory requirements. The Investigator should contact the Sponsor. immediately if contacted by a regulatory agency about an inspection.

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

11.1.4. Financial Disclosure

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

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

11.1.5. Recruitment Strategy

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

Participant recruitment and retention initiatives will be incorporated into the 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/IEC.

11.1.6. Informed Consent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study site. All consent documents will be approved by the appropriate IRB. The actual ICF used at each study site may differ, depending on local regulations and IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the form being used.

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

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

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

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The

information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

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

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

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

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

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

11.1.7. 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 that would make the participant identifiable will not be transferred.

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

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

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

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

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

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

11.1.8. Sample Retention and Future Biomedical Research

Samples may be used for purposes related to this research. The Sponsor may store samples for the time frame specified in the ICF to achieve study objectives. In addition, identifiable samples can be destroyed at any time at the request of the participant.

These samples could be used to address further scientific questions related to mRNA-1011.1, mRNA-1011.2, mRNA-1012.1, or anti-respiratory virus immune response, to research the complications associated with influenza and other conditions for which individuals with influenza are at increased risk, and to improve treatment. During the study or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity to seasonal influenza to include humoral and cellular immune assay methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. A decision to perform such exploratory research may arise from new scientific findings related to the drug/vaccine class or disease, as well as reagent and assay availability.

11.1.9. Dissemination of Clinical Study Data

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

11.1.10. Data Quality Assurance and Quality Control

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

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be transferred to another location or party without written notification to the Sponsor.

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

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

11.1.11. Source Documents

Source documents are original documents or certified copies and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

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

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

11.1.12. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

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

11.1.13. Study and Site Closure

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

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

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to the following:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or ICH GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further mRNA-1011.1, mRNA-1011.2, and mRNA-1012.1 development.

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

11.1.14. Publication Policy

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

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

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

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

11.2. APPENDIX 2: Contraceptive Guidance

Definitions:

Woman of Childbearing Potential (WOCBP):

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

a. Following menarche

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 women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Documented tubal ligation
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the study site 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 first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

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

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device

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

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. The above applies to females of child-bearing potential who are sexually active with male partners and not to females with same sex partners or those who are not sexually active as their usual lifestyle.

11.3. APPENDIX 3: Adverse Events of Special Interest Terms

Investigators should report all events that fall into the categories presented in Table 10 as an AESI per the reporting processes in Section 8.2.9. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines.

Table 10: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $<125\times10^9$ • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome • Acute disseminated encephalomyelitis (ADEM) • 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 IP administration as defined per protocol (Section 8.4.6.1) • Follow reporting procedures in protocol (Section 8.2.9)
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

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

11.4. APPENDIX 4: CDC Working Case Definition 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 11 as guidance.

Table 11: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms:* Chest pain, pressure, or discomfort. Dyspnea, shortness of breath, or pain with breathing. Palpitations. Syncope.	Presence of ≥1 new or worsening of the following clinical symptoms:* Chest pain, pressure, or discomfort. Dyspnea, shortness of breath, or pain with breathing. Palpitations. Syncope.
	AND ≥1 new finding of Troponin level above upper limit of normal (any type of troponin). Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§. Abnormal cardiac function or wall motion abnormalities on echocardiogram. cMRI findings consistent with myocarditis.	**AND** ≥1 new finding of Histopathologic confirmation of myocarditis†. cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin).
	AND No other identifiable cause of the symptoms and findings.	**AND** No other identifiable cause of the symptoms and findings.
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: Acute chest pain††. Pericardial rub on exam. New ST-elevation or PR-depression on EKG. New or worsening pericardial effusion on echocardiogram or MRI.	

Condition	Definition
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

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

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

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

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

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

Using either the original or the revised Lake Louise criteria.

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** 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).

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