CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized, Observer-blind, Active-controlled, Case-driven Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Seasonal Influenza Vaccine Compared with a Licensed Inactivated Seasonal Influenza Vaccine in Adults ≥50 Years of Age
Protocol Number:	mRNA-1010-P304
Amendment Number	1
Amendment Scope	Global
Compound:	mRNA-1010
Brief Title:	A Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Influenza Vaccine Compared with a Licensed Influenza Vaccine in Adults ≥50 Years of Age
Study Phase:	3
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	325 Binney Street Cambridge, MA 02142
Regulatory Agency Identifier Number(s):	**Registry** **ID** IND 27460 EU CT 2024-516240-26-00 NCT 06602024
Date:	12 Feb 2025

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

CONFIDENTIAL

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 3, Randomized, Observer-blind, Active-controlled, Case-driven Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Seasonal Influenza Vaccine Compared with a Licensed Inactivated Seasonal Influenza Vaccine in Adults ≥50 Years of Age" dated 12 Feb 2025 and the most recent version of the mRNA-1010 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 local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB/IEC approval except to eliminate an immediate risk to participants.

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

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

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

Signature of Principal Investigator	**Date**

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document	**Date**
Global Amendment 1	12 Feb 2025
Amendment KOR-1	11 Sep 2024
Original Protocol	14 Mar 2024

Amendment 1 (12 Feb 2025)

Overall Rationale for the Amendment:

The main purpose of this amendment is to include the IA decision rules for sample size reassessments and to update the projected information fraction for the IA.

The Summary of Changes table below describes the key changes made in global Protocol Amendment 1, including the sections modified and the corresponding rationale. These changes include those from the Administrative Change Letter (28 Aug 2024) and the country amendment KOR-1.

Section # and Name	Description of Change	Brief Rationale
Title Page	The Sponsor's legal registered address and the EU CT number was updated. NCT number obtained.	To provide accuracy as per Administrative Change Letter (28 Aug 2024).
1.1 Synopsis	Changes in other parts of the protocol were included in the synopsis, when applicable.	Consistency within the document.
2.2 Background	Added brief conclusions from 2 recently completed studies with mRNA-1010.	Communicate conclusions from the mRNA-1010 clinical program.
3. Objectives and Endpoints	More precise language was used for objectives/ endpoints. Revised the secondary efficacy endpoint for RT-PCR-confirmed ILI with antigenic match to the vaccine strains.	The secondary efficacy endpoint for RT-PCR-confirmed ILI with antigenic match to vaccine strains is based on culture test in breakthrough cases. Another endpoint incorporating similarity to vaccine strains through genetic assessment is treated as an exploratory endpoint.
4.3 Justification for Dose	Added information on the 2 recently completed Phase 3 studies. Added justification of dose from [redacted] µg to 37.5 µg.	To provide further details of the dose justification.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria No. 20, No. 23, and No. 25	Added to No. 20: "Note: participants from mRNA-1010-P304 Season 1 are NOT eligible to re-enroll into Season 2." Added a cross-reference to Appendix 6 for the KOR-specific requirements to No. 23 and No. 25.	No. 20: To provide clarification on participant enrollment for Season 2. Request from the South Korean Ministry of Food and Drug Safety.
6.1 Study Interventions(s) Administered	Added all trade names for the active comparator used in the study to Table 3.	For completeness.
6.3 Assignment of Study Intervention.	The number of participants randomized in the first season was updated to approximately [redacted] The number of planned participants to be randomized will stay the same. Added text indicating a sample size reassessment may be performed at the IA.	To ensure the maximum number of cases obtained in the first year. Additionally, as the case accrual in the 2024-2025 season has been rapid, the case target for the IA is expected to be achieved earlier than planned.
6.9.1 Recording of Prior Medications, Vaccines, and Procedures	Added the recording of medical procedures applicable to females of childbearing potential and prior medical history or a diagnostic procedure.	To clarify and ensure data capture completeness for medical procedures.
6.9.3 Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses.	Changed the time a nonstudy vaccine administration would eliminate a participant from the PP analyses (from Day 28 to Day 14).	Consistency with Exclusion Criteria No. 18.
7.1 Discontinuation of Study Intervention	Added clarification that no early termination/suspension criteria are planned since the vaccine treatment is 1 day and no safety pause rules are prespecified.	Request from the South Korean Ministry of Food and Drug Safety.
7.2 Participant Discontinuation/Withdrawal from Study	Updated possible reasons for withdrawal from 'Withdrawal by participant' to 'Withdrawal of consent.' Added 'Randomization by mistake.'	To align with eCRF.
8.1.1 Assessment of Clinical Events	Clarified that results of RT-PCR and NP swab test results will not be available to Investigators and that confirmation of influenza by a diagnostic test performed outside of the study is acceptable. Updated Figure 1 accordingly.	Clarify the recording of efficacy and safety assessments.

Section # and Name	Description of Change	Brief Rationale
8.1.3.3 Unscheduled Illness Visits	Added that NP swab tests performed outside of the study center are allowed if the RT-PCR kits have a regulatory certification (eg, Clinical Laboratory Improvement Amendment).	Ensure all eligible NP swab results are collected.
8.3.1.5 Solicited Adverse Reactions	Updated text for participants who missed an eDiary entry for solicited ARs.	To align with eCRF.
8.6 Future Research	Added in consented participants and geographies.	To provide clarity.
9.2 Statistical Hypotheses	Added hypothesis for super-superiority testing.	To prespecify hypothesis testing for super-superiority at a CCI superiority margin.
9.3 Analysis Sets	Updated "major" protocol deviations to "important" protocol deviations	To provide clarity.
9.4.1.1 Analysis of Primary Efficacy Endpoint, 9.5 CCI 9.6 Sample Size Determination	Updated the nominal alpha levels (1-sided) from CCI to CCI Added super-superiority.	To update the information fraction at IA is projected to be CCI of the target total number.
9.4.5 Estimands	Added intercurrent event types in Table 8 that were protocol deviations. The primary objectives and estimands (Table 9) were updated accordingly.	Formal definition of the intercurrent events due to protocol deviations resulting in exclusions from PPS is added. Clarified the rationale and considerations for the primary estimand to avoid misinterpretation and to ensure the methods are aligned to the study objectives.
9.5 CCI	CCI	CCI
9.6 Sample Size Determination	1) Added sample size reassessments may be performed at the IA. 2) CCI	1) Predefine a strategy for potential sample size increases at the IA. 2) CCI

Section # and Name	Description of Change	Brief Rationale
9.7.1 Interim Analysis	Revised the criteria for conducting an IA (when approximately CCI are expected to have accrued). Added sample size reassessments for the IA.	The IA will be reviewed by the Data Safety Monitoring Board to recommend if the study met early success criteria and if the sample size increases were needed based on prespecified rules.
10.6. Appendix 6: Country-specific Requirements	Section 5.2 Exclusion Criteria No. 23: Added 'Participants in a clinical study with investigational treatment within 6 months (instead of 90 days) prior to Day 1 (Baseline) based on the medical history interview or plans to do so while participating in this study.' No. 25: Added 'Participants who reside in a collective facility (eg, elderly welfare facility).'	Request from the South Korean Ministry of Food and Drug Safety.
11 References	Updated references	For completeness.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CD4	clusters of differentiation 4
CDC	US Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CoP	correlate of protection
CoR	correlate of risk
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DSMB	Data and Safety Monitoring Board
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
H_0	null hypothesis
HA	hemagglutinin
HAI	hemagglutinin inhibition
hCG	human chorionic gonadotropin

Abbreviation	Definition
HCP	healthcare professional
HD	high dose
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
ILI	influenza-like illness
IM	intramuscular
IND	Investigational New Drug
IRB	institutional review board
IRT	interactive response technology
KOR	South Korea
LLOQ	lower limit of quantification
LSM	Least squares mean
LTFU	lost to follow up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
mRNA	messenger ribonucleic acid
NA	neuraminidase
NCT	National Clinical Trial
NI	noninferiority
NIM	noninferiority margin
NP	nasopharyngeal
POCBP	person of childbearing potential
PONCBP	person of nonchildbearing potential
PP	Per-Protocol
PPIS	Per-Protocol Immunogenicity Subset
QIV	quadrivalent influenza vaccine

Abbreviation	Definition
QTL	quality tolerance limit
RT-PCR	reverse transcription polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard dose
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TIV	trivalent influenza vaccine
CCI	CCI
ULOQ	upper limit of quantification
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 3, Randomized, Observer-blind, Active-controlled, Case-driven Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Seasonal Influenza Vaccine Compared with a Licensed Inactivated Seasonal Influenza Vaccine in Adults ≥50 Years of Age

Brief Title:

A Study to Investigate the Safety, Efficacy, and Immunogenicity of mRNA-1010 Candidate Influenza Vaccine Compared with a Licensed Influenza Vaccine in Adults ≥50 Years of Age

Regulatory Agency Identifier Number(s):

IND 27460 NCT 06602024

EU CT 2024-516240-26-00

Rationale:

mRNA-1010-P304 is a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with a licensed inactivated seasonal influenza vaccine in adults ≥50 years of age. This study is being conducted to support licensure of mRNA-1010 for the prevention of influenza disease caused by any influenza A or B strains in the target population (≥50 years of age).

Objectives and Endpoints:

Primary and secondary objectives that will be evaluated in this study and endpoints associated with each objective are provided below.

Objective	Endpoint
Primary Objectives and Endpoints	
To evaluate the safety and reactogenicity of mRNA-1010.	• Solicited local and systemic ARs from Day 1 (Baseline) to Day 7 in a subset of approximately 6000 participants. • All unsolicited AEs from Day 1 to Day 28. • MAAEs from Day 1 (Baseline) to Month 6 (Day 181). • AEs leading to discontinuation from Day 1 (Baseline) to Month 6 (Day 181). • SAEs from Day 1 to Month 6 (Day 181). • AESIs from Day 1 (Baseline) to Month 6 (Day 181).

Objective	Endpoint
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed protocol-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
Secondary Objectives and Endpoints	
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains.	First episode of RT-PCR-confirmed protocol-defined ILI[a] or modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by influenza A or B strains with antigenic match[b] to the vaccine strains.
To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 2400 participants.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI. • Frequency of participants with an HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
To evaluate HAI titers as a surrogate of risk and protection against RT-PCR-confirmed protocol-defined ILI (CoR and CoP) for mRNA-1010 and an active comparator.	• HAI titers at Day 29. • First episode of RT-PCR-confirmed protocol-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = US Centers for Disease Control and Prevention; CoP = correlates of protection; CoR = correlates of risk; GMFR = geometric mean fold rise; GMT = geometric mean titer; HAI = hemagglutination inhibition; ILI = influenza-like illness; MAAE = medically attended adverse event; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy; SAE = serious adverse event.

a. ILI case definitions provided in Table 4.

b. Vaccine strain matches will be based on cultured virus isolate and subsequent determination of antigenic testing by serology methods.

Overall Design Synopsis:

This will be a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 versus an active comparator in adults ≥50 years of age. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator. Randomization will be stratified by age

category (≥50 to <65 years or ≥65 years) at Screening and influenza vaccine status in the previous influenza season (received or not received). Approximately 50% of enrolled participants will be ≥65 years of age at Screening, including approximately 10% who are ≥75 years of age at Screening.

All safety findings will be closely monitored and reviewed by the study team and an independent DSMB to evaluate the safety of all participants.

Brief Summary:

The purpose of this study is to measure the number of influenza cases after receiving mRNA-1010 compared with a licensed influenza vaccine in healthy adults ≥50 years of age. Study details include:

- Study duration is expected to be approximately 6 to 8 months for each participant but could be longer if the influenza season is longer than expected.
- The treatment duration will be 1 day.
- The visit frequency will be as presented in the SoA (Table 1).

Number of Participants:

Approximately 56,000 participants are expected to be randomized across 2 seasons, with about CCI enrolled during the first season. A sample size reassessment may be performed at the IA, allowing for enrollment of up to 82,000 participants if needed.

Study Arms and Duration:

Study duration (including screening) is expected to be approximately 6 to 8 months for each participant but could be longer if the influenza season is longer than expected. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator.

1.2. Schedule of Activities

Table 1: Schedule of Activities

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
						EOS[c]		**Up to the End of the Influenza Season[d]**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**M6[b] (Day 181)**	**End of the Influenza Season[d]**	
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
ICF, demographics, and vaccination and medical history (including substance use history)[e]	X							
Inclusion/exclusion criteria	X	X						
Physical examination[f]	X	X						
Vital signs[g]	X	X						X
Pregnancy testing (for POCBP)[h]	X	X						
Record all prior/concomitant medications[i]	X	X	X	X				
Record all concomitant procedures/surgeries[i]	X	X	X	X	X	X	X	
Record MAAEs, AEs leading to discontinuation, SAEs, and AESIs, as well as relevant concomitant medications/procedures[j]	X[k]	X[k]	X	X	X	X	X[l]	
Randomization		X						
EFS[m]		X						
Blood collection for humoral immunogenicity		X[n]		X				
Blood collection for cellular immunogenicity[o]		X		X				

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**EOS[c]** **M6[b] (Day 181)**	**EOS[c]** **End of the Influenza Season[d]**	**Up to the End of the Influenza Season[d]**
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
Study intervention (including 30-minute postinjection observation period)		X						
Reactogenicity eDiary will be used to collect solicited ARs only in a subset of approximately 6000 participants								
Activation of Reactogenicity eDiary		X						
Solicited AR reporting in the Reactogenicity eDiary		D1 (Baseline) to D7						
Review Reactogenicity eDiary and contact participants[p]		D1 (Baseline) to D7	X					
Symptom eDiary will be used to screen for protocol-defined respiratory illness[q] in all participants								
Activation of Symptom eDiary		X						
Symptom reporting in Symptom eDiary[r]		Twice weekly from D1 (Baseline) to the end of the influenza season						
Review Symptom eDiary and contact participants[q,s]		D1 (Baseline) to the end of the influenza season						
Record unsolicited AEs			X[t]	X				
Follow ongoing AEs, SAEs, AESI, and MAAEs at least monthly[u]			D8 to EOS[c]					
Record all concomitant medications that may lead to the elimination of a participant from PP analyses and all nonstudy vaccinations[v]					X	X	X	X
Review symptom history (including dates of onset)								X

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**USV**
Type of Visit/Contact	**C**	**C**	**SC/T**	**C**	**SC/T**	**SC/T**	**T**	**C**
Timepoint	**Screening[a]**	**D1 (Baseline)**	**D8**	**D29**	**M3[b] (Day 91)**	**EOS[c]** **M6[b] (Day 181)**	**EOS[c]** **End of the Influenza Season[d]**	**Up to the End of the Influenza Season[d]**
Window Allowance (Days)	**-28**	**N/A**	**-1 to +2**	**±3**	**±5**	**±14**	**±14**	**N/A**
Record concomitant medications[w] and nonstudy HCP visits related to or for the treatment of protocol-defined respiratory illness[q]								X
NP swab for virus detection[x]								X
Contact to follow-up on protocol-defined respiratory illness[q,y]		D1 (Baseline) to the end of the influenza season						
Study completion						X[c]		

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic/in-person visit; D = day; eDiary = electronic diary; EFS = Edmonton Frail Scale; EOS = end of study; FSH = follicle-stimulating hormone; HCP = healthcare professional; ICF = informed consent form; ILI = influenza-like illness; M = month; MAAE = medically attended adverse event; N/A = not applicable; NP = nasopharyngeal; POCBP = person of childbearing potential; PP = Per-Protocol; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SC = safety contact; SoA = schedule of activities; T = telephone contact; USV = unscheduled visit.

a. The Screening and Day 1 (Baseline) activities may be performed on the same day or on different days. Additionally, Screening Visit activities may be performed over multiple visits if within the 28-day screening window.
b. One month is defined as 30 days.
c. Study completion (EOS) will occur at either the Month 6 (Day 181) Visit or at the End of the Influenza Season Visit, whichever is later. The Month 6 (Day 181) Visit and the End of the Influenza Season Visit may be combined if both visits are within the relevant window periods.
d. The end of the influenza season is defined in Section 4.4.1.
e. Verbal medical history is acceptable. Any sign, symptom, or disease identified or starting before study intervention should be recorded as medical history. If the full date is unknown, all known date information should be collected.
f. A full physical examination, including height and weight, will be performed at Screening. On Day 1 (Baseline), physical examination will be limited to examination of the arm receiving the injection and the associated lymph node before study intervention; any abnormalities should be documented.
g. Systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature (oral). On Day 1 (Baseline), vital signs will be collected before study intervention and again approximately 30 minutes after study intervention.
h. Point-of-care urine pregnancy test at the Screening Visit and before study intervention on Day 1 (Baseline) (if Day 1 [Baseline] is not on the same day as the Screening Visit). At the discretion of the Investigator, a pregnancy test can be performed at any time during the pregnancy-reporting period (through Month

3 [Day 91]). The participant's FSH level may be measured at the Screening Visit, as necessary and at the discretion of the Investigator, to confirm postmenopausal status.

i. Prior/concomitant medications and procedures should be recorded as described in Section 6.9.
j. Concomitant medications/procedures relevant to or for the treatment of an MAAE, AE leading to discontinuation, SAE, or AESI will be recorded from Day 1 (Baseline) through Month 6 (Day 181).
k. SAEs will be collected from signing of the ICF through Month 6 (Day 181).
l. SAEs considered related to study intervention by the Investigator will be collected through the end of the study. No other AEs or SAEs should be collected after Month 6 (Day 181).
m. Only for participants ≥65 years of age.
n. Day 1 (Baseline) collection must be before study intervention.
o. Blood collection for cellular immunogenicity is only in a subset of approximately 200 participants. Day 1 (Baseline) collection must be before study intervention.
p. If a participant does not respond to the eDiary questions according to the SoA, study staff will follow-up with the participant. The site should also contact the participant under the following circumstances: a Grade 4 solicited AR is reported (contact participant as soon as possible), a Grade 3 solicited AR is reported on 2 consecutive days, and at the Investigator's discretion.
q. The definition of protocol-defined respiratory illness is new onset or worsening (>24 hours) of at least 1 of the following symptoms: sneezing, nasal congestion, rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing (refer to Table 4).
r. Participants are encouraged to respond to the eDiary as soon as possible if they have any respiratory symptoms and, upon experiencing respiratory symptoms, contact study staff. For participants with protocol-defined respiratory illness, oral temperature measurements should be performed daily while symptoms are ongoing, preferably at approximately the same time each day. Any body temperature >37.2°C (>99.0°F) should be reported to study staff as a possible symptom of protocol-defined ILI.
s. If a participant does not respond to the eDiary questions according to the SoA, study staff will follow-up with the participant. If a participant reports experiencing respiratory symptoms, study staff should contact the participant as soon as possible (preferably within 24 hours) to confirm protocol-defined respiratory illness and to arrange an unscheduled visit to collect an NP swab sample for RT-PCR testing.
t. Signs and symptoms that are consistent with any of the solicited AR terms in Table 6 that start on or before Day 7 should not be recorded as unsolicited AEs, unless the event meets seriousness criteria and the investigator considers it related to study intervention, in which case the event will be reported as an SAE.
u. All ongoing AEs/SAEs/AESIs/MAAEs will be followed at least monthly until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
v. Refer to Section 6.9.3 for medications that may lead to the elimination of a participant from PP analyses.
w. Record any new concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) or altered doses/frequencies of existing concomitant medications resulting from protocol-defined respiratory illness.
x. An NP swab sample will be collected from any participant with protocol-defined respiratory illness, preferably within 72 hours after symptom onset. Samples collected within 5 days after symptom onset are acceptable.
y. For participants with protocol-defined respiratory illness, study staff will contact the participant twice weekly until resolution of symptoms (or until the end of the window period for the End of the Influenza Season Visit) to update and review symptoms and concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) related to the participant's respiratory illness. Study staff will also contact the participant upon resolution of symptoms or 30 days after the onset of symptoms (or at the end of the window period for the End of the Influenza Season Visit), whichever is earlier, to collect information about healthcare usage and concomitant medications related to the participant's respiratory illness.

2. INTRODUCTION

2.1. Study Rationale

mRNA-1010-P304 is a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with a licensed inactivated seasonal influenza vaccine in adults ≥50 years of age. This study is being conducted to support licensure of mRNA-1010 for the prevention of influenza disease caused by any influenza A or B strains in the target population (≥50 years of age).

2.2. Background

Seasonal influenza A and B virus strains are estimated by the WHO to cause 3 to 5 million cases of severe illness and up to 650,000 deaths per year resulting in a severe challenge to public health (WHO 2023a). Currently licensed seasonal influenza vaccines rarely exceed 60% overall effectiveness, with lower effectiveness during years when the circulating viruses do not match the strains selected for the vaccine antigens (CDC 2023). Improved vaccine efficacy in adults ≥50 years of age is needed, given the increased morbidity and mortality in this population due to declining immunocompetence and increased burden of comorbid medical conditions with age. Influenza vaccines based on mRNA technology could provide several benefits in older adults compared with current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, and improved protection (Rockman et al 2020).

Study mRNA-1010-P301, which compared the immunogenicity and safety of mRNA-1010 (QIV; 50 µg total mRNA) with Fluarix® quadrivalent against vaccine-matched influenza A and B strains in participants ≥18 years of age, demonstrated noninferior immune responses for the influenza A strains, but not for the influenza B strains. Conducted in parallel with Study mRNA-1010-P301 was Study mRNA-1010-P302, an efficacy and safety study that used the same study intervention as mRNA-1010-P301 in adults ≥50 years of age. Protocol-defined influenza cases during the season were lower than targeted (77%) and the noninferiority objective was not achieved for influenza A or B; however higher positive rVE were observed for influenza caused by the A strain. No significant safety concerns were observed.

These results led to optimization of mRNA-1010 CCI [redacted]

Optimized mRNA-1010 (QIV; 50 µg total mRNA) was evaluated in Study mRNA-1010-P303 (a 3-part study). Part A compared the immunogenicity, reactogenicity, and safety of mRNA-1010 with SD seasonal influenza vaccine, Fluarix quadrivalent, against vaccine-matched influenza A and B strains in participants ≥18 years of age. Noninferiority of optimized mRNA-1010 was demonstrated for both influenza A strains and both influenza B strains. Higher GMT and seroconversion rate at Day 29 as measured by HAI assay (the primary immunogenicity endpoints of the study) were observed for mRNA-1010 compared with active comparator. These findings are consistent with superiority against SD vaccine. mRNA 1010 demonstrated a consistently

robust immunogenicity profile across all age groups with a trend toward higher GMRs in the older age group (≥65 years old).

Part B evaluated mRNA-1010 compared to a SD QIV comparator in adults ≥18 to <65 years old and Part C evaluated mRNA-1010 compared to a HD seasonal influenza vaccine (Fluzone® High-Dose QIV) in adults ≥65 years old. In Part B, superiority was demonstrated compared with SD licensed QIV comparator (Fluarix) at Day 29 for the secondary endpoints of GMT and seroconversion for all 4 influenza strains. Durability of immune responses through EOS/Day 181 was demonstrated for all 4 influenza strains with numerically higher GMTs in the mRNA-1010 group than in the SD licensed QIV comparator group. In Part C superiority was demonstrated compared to high-dose licensed QIV comparator at Day 29 for the secondary endpoints of GMT and seroconversion for all 4 influenza strains. Durability of immune responses through EOS/Day 181 was demonstrated for all 4 influenza strains with numerically higher GMTs in the mRNA-1010 group than in the HD licensed QIV comparator group.

Higher reactogenicity was observed with mRNA-1010 compared to the licensed QIV comparators, however decreased in frequency and severity among older age groups. No significant safety concerns were identified.

Based on the recent WHO recommendation to no longer include B/Yamagata in influenza vaccines (WHO 2023b), a TIV of optimized mRNA-1010 (37.5 µg total mRNA), containing mRNAs that encode for the HAs of the 3 strains recommended by WHO for cell- or recombinant-based vaccines (A/H1N1, A/H3N2, and B/Victoria) will be used in this study.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mRNA-1010 may be found in the IB.

2.3.1. Risks from Study Participation and Risk Mitigation

Appropriate eligibility criteria, as well as specific criteria for delaying study intervention, are included in this protocol. The risk to participants in this study may be minimized through compliance with the eligibility criteria and study assessments/procedures.

As with all injectable vaccines, immediate systemic allergic reactions to study intervention, ranging from mild (eg, urticaria) to severe (eg, anaphylaxis), can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for a minimum of 30 minutes after study intervention.

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

As with other IM injections, study intervention should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as hemophilia) because bleeding or bruising may occur following an IM injection in these individuals.

Local and systemic ARs reflective of reactogenicity are expected to occur after IM administration of study intervention. Local ARs are mostly mild or moderate in severity, transient, and self-limited, and may include pain, erythema (redness), or swelling/induration (hardness) at the injection site and/or ipsilateral underarm swelling/tenderness. The majority of systemic ARs are mild or moderate in severity. Systemic ARs reported with other mRNA vaccines include fatigue, headache, myalgia, fever, chills, arthralgia, and nausea/vomiting.

There have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in adolescent and young adult males, within 7 to 14 days after the second or subsequent doses of the vaccine. These are typically mild cases, and individuals tend to recover within a short time following conservative treatment. HCPs and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Table 12). It is not known whether the risk of myocarditis or pericarditis is increased following administration of non-COVID-19 mRNA vaccines. Exposure to mRNA-1010 in >15,000 participants has not shown an increased risk of myocarditis or pericarditis to date. An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis observed in this study (refer to Section 10.1.6.2).

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following vaccination were observed in some clinical studies with mRNA-based vaccines similar to mRNA-1010. 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.

For other AEs known to be associated with the licensed seasonal influenza active comparator, please refer to the package insert.

All safety findings will be closely monitored and reviewed by the study team and an independent DSMB to evaluate the safety of all participants.

All participants will receive mRNA-1010 or an SD licensed seasonal influenza vaccine. Some countries recommend higher-dose or adjuvanted influenza vaccines in older adults. These vaccines may be more effective than SD influenza vaccine for people in this population. Potential participants will be made aware of this recommendation.

2.3.2. Benefit Assessment

Participants who receive study intervention may be less likely to contract influenza or be less likely to develop complications if they do contract influenza.

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

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

2.3.3. Overall Benefit/Risk Conclusion

Given the acceptable safety profile and noninferior immune responses observed for mRNA-1010 in >15,000 participants to date, the Sponsor considers that the potential benefits of participation in this study outweigh the risks.

3. OBJECTIVES AND ENDPOINTS

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

Estimands are provided in Section 9.4.5.

Table 2: Objectives and Endpoints

Objective	Endpoint
Primary Objectives and Endpoints	
To evaluate the safety and reactogenicity of mRNA-1010.	• Solicited local and systemic ARs from Day 1 (Baseline) to Day 7 in a subset of approximately 6000 participants. • All unsolicited AEs from Day 1 to Day 28. • MAAEs from Day 1 (Baseline) to Month 6 (Day 181). • AEs leading to discontinuation from Day 1 (Baseline) to Month 6 (Day 181). • SAEs from Day 1 to Month 6 (Day 181). • AESIs from Day 1 (Baseline) to Month 6 (Day 181).
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed protocol-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
Secondary Objectives and Endpoints	
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed modified CDC-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains.	First episode of RT-PCR-confirmed protocol-defined ILI[a] or modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by influenza A or B strains with antigenic match[b] to the vaccine strains.

Objective	Endpoint
To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 2400 participants.	• GMT at Day 29 as measured by HAI. • Proportion of participants reaching seroconversion at Day 29 as measured by HAI. • Frequency of participants with an HAI titer ≥1:40 at Day 29. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by HAI.
To evaluate HAI titers as a surrogate of risk and protection against RT-PCR-confirmed protocol-defined ILI (CoR and CoP) for mRNA-1010 and an active comparator.	• HAI titers at Day 29. • First episode of RT-PCR-confirmed protocol-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
Exploratory Objectives and Endpoints (May Be Performed)	
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed CDC-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed WHO-defined ILI caused by any influenza A or B strains.	First episode of RT-PCR-confirmed WHO-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) caused by any influenza A or B strains.	First episode of RT-PCR-confirmed ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302) that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed influenza infection regardless of whether clinical symptoms meet ILI case definitions.	First episode of RT-PCR-confirmed influenza infection that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains regardless of whether clinical symptoms meet ILI case definitions.
To evaluate rVE of mRNA-1010 versus an active comparator against culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI caused by any influenza A or B strains.	First episode of culture-confirmed protocol-defined ILI or culture-confirmed modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains.

Objective	Endpoint
To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI or RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains with similarity and/or antigenic match to the vaccine strains.	First episode of RT-PCR-confirmed protocol-defined or RT-PCR-confirmed modified CDC-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains with similarity and/or antigenic match to the vaccine strains.
To evaluate the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains measured by MN assay in a subset of participants.	• GMT at Day 29 as measured by MN assay. • GMFR comparing Day 29 to Day 1 (Baseline) as measured by MN assay.
To characterize the cellular immune response of mRNA-1010 versus an active comparator against vaccine-matched influenza A and B strains in a subset of approximately 200 participants.	• T-cell response after mRNA-1010 and active comparator
To characterize the effect of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains by baseline frailty status in participants ≥65 years of age.	First episode of RT-PCR-confirmed protocol-defined ILI[a] that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains regardless of vaccine match in participants ≥65 years of age by baseline EFS status.
To evaluate rVE of mRNA-1010 versus an active comparator to prevent health outcomes associated with protocol-defined ILI.	In cases of protocol-defined ILI[a] with RT-PCR confirmation and without RT-PCR confirmation that begin at least 14 days after study intervention through the end of the influenza season: • Pneumonia beginning within 30 days after respiratory symptom onset. • New onset or exacerbation of cardiorespiratory disease (eg, CHF, COPD, asthma) beginning within 30 days after respiratory symptom onset. • Healthcare encounters (eg, hospitalization, emergency room visit, outpatient visit) beginning within 30 days after respiratory symptom onset.
To evaluate the effect of mRNA-1010 versus an active comparator on the frequency of reported symptoms of RT-PCR-confirmed protocol-defined ILI.	Frequencies of symptoms in cases of protocol-defined ILI with RT-PCR confirmation and regardless of RT-PCR confirmation.
To further characterize pre-existing immune responses as well as the immune responses to mRNA-1010 and an active comparator.	Frequency, specificity, or other endpoints to be determined, for the further characterization of immune responses.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = US Centers for Disease Control and Prevention; CHF = congestive heart failure; CoP = correlates of

protection; COPD = chronic obstructive pulmonary disease; CoR = correlates of risk; EFS = Edmonton Frailty Scale; GMFR = geometric mean fold rise; GMT = geometric mean titer; HAI = hemagglutination inhibition; ILI = influenza-like illness; MAAE = medically attended adverse event; MN = microneutralization; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy; SAE = serious adverse event; WHO = World Health Organization.

Note: Similarity to vaccine strains based on HA and NA sequencing.

a. ILI case definitions provided in Table 4.

b. Vaccine strain matches will be based on cultured virus isolate and subsequent determination of antigenic testing by serology methods.

4. STUDY DESIGN

4.1. Overall Design

This will be a Phase 3, randomized, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 versus an active comparator in adults ≥50 years of age. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator. Randomization will be stratified by age category (≥50 to <65 years or ≥65 years) at Screening and influenza vaccine status in the previous influenza season (received or not received). Approximately 50% of enrolled participants will be ≥65 years of age at Screening, including approximately 10% who are ≥75 years of age at Screening.

- Study duration (including screening) is expected to be approximately 6 to 8 months for each participant but could be longer if the influenza season is longer than expected.
- Participants will have up to 3 in-person visits (Screening, Day 1 [Baseline], and Day 29) and up to 4 telephone contacts (Day 8, Month 3 [Day 91], Month 6 [Day 181], and the End of the Influenza Season Visit). Additionally, in-person unscheduled visits will be arranged for participants who meet criteria for protocol-defined respiratory illness (refer to Table 4).
  - The Screening and Day 1 (Baseline) activities may be performed on the same day or on different days. Additionally, Screening Visit activities may be performed over multiple visits if within the 28-day screening window.
  - Study completion (EOS) will occur at either the Month 6 (Day 181) Visit or at the End of the Influenza Season Visit, whichever is later. The Month 6 (Day 181) Visit and the End of the Influenza Season Visit may be combined if both visits are within the relevant window periods.
- A subset of approximately 6000 participants will be prompted to report solicited local and systemic ARs in the Reactogenicity eDiary from Day 1 (Baseline) and during the 6 subsequent days (through Day 7).
- All participants will be prompted to report experiencing respiratory symptoms in the Symptom eDiary. Participants are required to complete the eDiary twice weekly from Day 1 (Baseline) to the end of the influenza season. An NP swab sample will be collected from any participant with protocol-defined respiratory illness, preferably within 72 hours after symptom onset. Samples collected within 5 days after symptom onset are acceptable.
- Blood samples to support humoral and cellular immunogenicity objectives will be collected as follows:
  - All participants will provide a blood sample on Day 1 (Baseline) (prior to study intervention) and on Day 29 to support potential CoR/CoP analysis.

- Of these, samples from a subset of approximately 2400 participants will be analyzed for HAI titers at Day 1 (Baseline) and Day 29 to assess humoral immunogenicity endpoints.

– A subset of approximately 200 participants will provide an additional blood sample on Day 1 (Baseline) (prior to study intervention) and on Day 29 to support cellular immunogenicity objectives.

- Blinding procedures are described in Section 6.4.

4.2. Scientific Rationale for Study Design

Improved vaccine efficacy in adults ≥50 years of age is needed, given the increased morbidity and mortality in this population due to declining immunocompetence and increased burden of comorbid medical conditions with age. Influenza vaccines based on mRNA technology could provide several benefits in older adults compared with current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, and improved protection (Rockman et al 2020).

SD licensed inactivated seasonal influenza vaccine will be used as a comparator because it is globally licensed for the prevention of influenza disease in the target population (≥50 years of age). For countries that recommend higher-dose or adjuvanted influenza vaccines in older adults, potential participants will be made aware of this recommendation.

A TIV of mRNA-1010 will be used in this study in accordance with recent WHO recommendations (WHO 2023b). Licensed TIV is the preferred active comparator; however, because the change from QIV to TIV may take several seasons to implement in some regions, licensed QIV may be used as an active comparator in participating countries where licensed TIV is unavailable. Based on studies conducted when there was limited circulation of B/Yamagata, similar rVE is expected for TIV (without B/Yamagata) and QIV (with B/Yamagata) (Gaglani et al 2021, Young-Xu et al 2018).

4.2.1. Patient Input into Design

Moderna incorporates feedback from patients when designing study protocols. This approach aims to gather insights about the experiences of participants, which can lead to better-informed decisions about the execution of the study. To collect this feedback, Moderna may use a variety of methods such as surveys, one-on-one interviews, focus groups, and patient advisory boards. For mRNA-1010-P304, Moderna will ensure public participation in evaluating the patient information sheet and the ICF before these documents are submitted for ethical review and approval.

4.3. Justification for Dose

The Sponsor has completed a dose-finding Phase 1/2 study (mRNA-1010-P101, NCT04956575) evaluating mRNA-1010 at dose levels up to 200 µg, and no safety concerns were identified at these doses. The 50-µg dose was chosen for Phase 3 studies based on the observed reactogenicity and immunogenicity profiles (refer to the mRNA-1010 IB for details). The Sponsor completed 3 Phase 3 studies at a 50-µg dose level: mRNA-1010-P301 (NCT05415462) to evaluate

immunogenicity and safety; mRNA-1010-P302 (NCT05566639) to evaluate efficacy and safety and; mRNA-1010-P303 (NCT05827978) to evaluate immunogenicity, reactogenicity and safety. Across these studies, the safety profile of mRNA-1010 was acceptable and no safety concerns were identified.

In previous studies a quadrivalent mRNA-1010 was evaluated at a total dose of 50 µg because each strain (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) contained a 12.5 µg dose. In response to the latest WHO recommendations, which no longer include the B/Yamagata strain in influenza vaccines (WHO 2023b), Study mRNA-1010-P304 will evaluate a trivalent version of mRNA-1010. The per-strain dose remains consistent at 12.5 µg. However, since the vaccine now targets only 3 strains (A/H1N1, A/H3N2, and B/Victoria), the total mRNA dose is adjusted to 37.5 µg.

4.4. EOS Definition

The end of the study is defined as the date the last study sample is processed for humoral immunogenicity endpoints based on HAI titer and cellular immunogenicity endpoints.

A participant is considered to have completed the study if the participant has completed the last visit shown in the SoA (Table 1).

4.4.1. End of the Influenza Season Definition

The end of the influenza season is anticipated to be 30 April (for each season) based on historical epidemiological data. The Sponsor will use epidemiological information from public health authorities such as the CDC, ECDC, and the Public Health Agency of Canada to determine whether or not seasonal influenza activity has reached an interseasonal level, and whether to extend influenza testing and reporting of clinical efficacy endpoints beyond this date. Decision-making criteria are provided below. These criteria give independent and valuable information, providing an adequate picture of influenza activity in a particular geographic area at a particular point in time.

Across regions, the Sponsor will base the decision on the following criteria:

1. The geographic spread and intensity of influenza as reported for the region where the research site is located.
2. The percentage of specimens tested that are positive for influenza for the region where the site is located.
3. The most updated ILI and/or acute respiratory infection activity trends for the region/country where the site is located, based on data including (but not limited to) ILINet from the CDC, European Respiratory Virus Surveillance Summary Data, and FluWatch reports from Public Health Agency of Canada.

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

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

1. At least 50 years of age at the time of signing the ICF.
2. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
3. Participants who are assigned female at birth or can become pregnant are eligible to participate if:

   - The participant is a PONCBP, as defined in Section 10.5.1.

   OR

   - The participant is a POCBP, as defined in Section 10.5.1, who:
     - Is not breast/chestfeeding.
     - Is using an acceptable contraceptive method, as described in Section 10.5.2 from at least 28 days prior to Day 1 (Baseline) to at least 90 days after Day 1 (Baseline).
     - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulation or IRB/IEC) at the Screening Visit and before study intervention (Section 8.2.3) (if the Day 1 [Baseline] Visit is not on the same day as the Screening Visit).

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

5.2. Exclusion Criteria

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

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to Day 1 (Baseline). See Section 5.3 for guidance on rescreening.
2. Close contact with someone with laboratory-confirmed influenza infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu®/oseltamivir) within 5 days prior to Day 1 (Baseline).
3. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable or may affect participant safety, assessment of study endpoints, assessment of immune response, or adherence to study procedures.

   Clinically unstable is defined as a diagnosis or condition requiring changes in management or medication within 60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

4. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, asplenia, or recurrent severe infections disease.

   HIV positive participants on antiretroviral therapy with CD4 count ≥500 cells/mm^3 and HIV RNA ≤500 copies/mL within the past 365 days are allowed.

   Certain immune-mediated conditions that are stable and well-controlled (eg, Hashimoto's thyroiditis), as well as those that do not require systemic immunosuppressants per Exclusion Criterion 14 and Exclusion Criterion 15 (eg, asthma, psoriasis, or vitiligo) may be allowed at the discretion of the Investigator.

5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid injection site areas).
6. Tested positive for influenza by local health authority-approved testing methods within 180 days prior to Day 1 (Baseline).
7. History of anaphylaxis or severe hypersensitivity reaction requiring medical intervention after receipt of any of the following: mRNA vaccine or therapeutic; components of an mRNA vaccine or therapeutic; influenza vaccine; or components of an influenza vaccine, including egg protein.
8. History of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
9. Malignancy within 2 years prior to Day 1 (Baseline) (adequately treated basal cell carcinoma and squamous cell carcinoma are allowed).
10. History of Guillain-Barre syndrome after any influenza vaccine.
11. History of myocarditis, pericarditis, or myopericarditis, including treatment or any associated symptoms, within 180 days prior to Day 1 (Baseline).
12. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
13. Underwent a surgical procedure within 7 days prior to Day 1 (Baseline) or are scheduled to undergo a surgical procedure within 28 days after Day 1 (Baseline).

    Minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.

14. Received corticosteroids at ≥10 mg/day of prednisone or equivalent for >14 days in total within 90 days prior to Day 1 (Baseline) or is anticipating the need for corticosteroids at any time during the study.

    Epidural or major joint intra-articular injections (eg, knee, hip, shoulder) or other injections with long-acting corticosteroids within 28 days prior to or anticipated within 28 days after Day 1 (Baseline) are not allowed.

    Inhaled, nasal, and topical steroids are allowed.

15. Received systemic immunosuppressive treatment, including long-acting biological therapies that affect immune responses (eg, infliximab), within 180 days prior to Day 1 (Baseline) or plans to do so during the study.
16. Treated with antiviral therapies for influenza (eg, Tamiflu) within 180 days prior to Day 1 (Baseline).
17. Received systemic immunoglobulins or blood products within 90 days prior to Day 1 (Baseline) or plans to do so during the study.
18. Received any vaccine authorized or approved by local health agency within 28 days prior to Day 1 (Baseline) or plans to do so within 14 days after Day 1 (Baseline).
19. Received a licensed seasonal influenza vaccine within 180 days prior to Day 1 (Baseline) or plans to do so (outside of this study) at any time during the study.
20. Received an investigational seasonal influenza vaccine within 1 year prior to Day 1 (Baseline). Note: participants from mRNA-1010-P304 Season 1 are NOT eligible to re-enroll into Season 2.
21. Is unsure whether they received a licensed or investigational seasonal influenza vaccine within 1 year prior to Day 1 (Baseline).
22. Donated ≥450 mL of blood products within 28 days prior to Day 1 (Baseline) or plans to donate ≥450 mL of blood products within 28 days after Day 1 (Baseline).
23. Participated in a clinical study with investigational treatment within 90 days prior to Day 1 (Baseline) based on the medical history interview or plans to do so while participating in this study. See Section 10.6 Appendix 6 for KOR-specific requirement.

    Participants may continue in prior interventional study follow-up activities, provided that it does not involve further investigational treatment and/or procedures that may affect safety and/or other study endpoints, and study participation does not result in a breach of either study protocol.

    Interventions such as counseling, biofeedback, and cognitive therapy are allowed.
24. Is working or has worked as study personnel or is an immediate family member or house member of study personnel, study staff, or Sponsor personnel.
25. See Section 10.6 Appendix 6 for KOR-specific requirements.

5.3. Screen Failures

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

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

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Vital signs, including oral body temperature, must be measured prior to study intervention and as specified in the SoA (Table 1). The following events constitute criteria for temporarily delaying administration of study intervention:

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

If the participant meets these criteria, the visit should be rescheduled within the allowed window period for Screening in the SoA (Table 1), or, at the Investigator's discretion, the participant may be withdrawn from the study (Section 7.2).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to study participants during the study.

6.1. Study Intervention(s) Administered

mRNA-1010 includes mRNAs encoding for the surface glycoproteins of the influenza strains recommended by the WHO for 2024-2025 (first season) or 2025-2026 (second season) Northern Hemisphere cell- or recombinant-based vaccines. A TIV will be used in accordance with recent WHO recommendations (WHO 2023b). Optimized mRNA-1010 will be used (refer to Section 2.2 for background on optimization).

CCI [redacted]

mRNA-1010 will be administered as a single IM injection at a total mRNA dose level of 37.5 µg (see Table 3).

The active comparator administered in this study is an SD licensed inactivated seasonal influenza vaccine administered as a single IM injection (see Table 3). Licensed TIV is the preferred active comparator; however, a licensed QIV may be used as an active comparator in participating countries where licensed TIV is unavailable.

Table 3: Study Interventions Administered

Intervention Name	mRNA-1010	Fluarix, Fluarix Tetra, Influsplit® Tetra, Alpharix® Tetra
Unit Dose Strength	37.5 µg of mRNA	45 µg (TIV) or 60 µg (QIV) of protein
Dosage Volume	Single dose of 0.5 mL	Single dose of 0.5 mL
Route of Administration	IM	IM

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine.

Study Intervention Packaging and Labeling

Study intervention that is provided by the Sponsor will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH Guidance for Industry, GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.2. Preparation, Handling, Storage, and Accountability

The Investigator will designate unblinded study personnel to have no study functions other than the management, documentation, accountability, handling, preparation, and administration of study intervention (refer to Section 6.4).

- Unblinded designee(s) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only unblinded and authorized study staff may supply, handle, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the Pharmacy Manual, with access limited to designated unblinded study personnel.
- Unblinded designee(s) are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information on preparation, handling, storage, and accountability is in the Pharmacy Manual.

6.3. Assignment to Study Intervention

Randomization will be performed using an IRT system.

Approximately 56,000 participants are expected to be randomized across 2 seasons, with about CCI enrolled during the first season. A sample size reassessment may be performed at the IA, allowing for enrollment of up to 82,000 participants if needed. Participants will be randomized in a 1:1 ratio to receive a single injection of mRNA-1010 or an active comparator (Table 3). Randomization will be stratified by age category (≥50 to <65 years or ≥65 years) at Screening and influenza vaccine status in the previous influenza season (received or not received).

6.4. Blinding

As the appearance of the study interventions differ, this will be an observer-blinded study.

Study intervention preparation, administration, and accountability will be performed by designated unblinded study personnel who will not participate in any of the clinical study evaluations. The unblinded study personnel will prepare the study intervention out of view of the participant and the blinded study personnel. Unblinded study personnel will have no study functions other than the management, documentation, handling, accountability, preparation, and administration of study intervention. They will not be involved in participant evaluations or blinded data entry and will not reveal the identity of the individual study intervention assignment to either the participant or the blinded study personnel involved in the conduct of the study.

Unblinded site monitors, who are not involved in other aspects of monitoring, will be assigned as the study intervention accountability and treatment confirmation monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.

Laboratory personnel responsible for immunogenicity testing of participant samples will be blinded to study intervention assignment.

Investigators may unblind the individual study intervention assignment of any participant in case of emergency (refer to Section 6.4.1). Otherwise, the Investigator, blinded study personnel, participants, blinded site monitors, and blinded Sponsor personnel (or its designees) will remain blinded to individual study intervention assignment until the study database is locked and unblinded for the final analysis. At the preplanned IA (refer to Section 9.7.1), blinded Sponsor personnel (or its designees) who are responsible for study conduct will remain blinded at the participant level, but may be unblinded at the study intervention group level. Additionally, preidentified Sponsor personnel (or its designees) will be unblinded both at the study intervention group level and at the participant level to support IA-related activities; however, these Sponsor personnel (or its designees) will have no further responsibilities for study conduct. Study sites will remain blinded.

6.4.1. Unblinding

This is an observer-blinded study in which the Investigators are blinded to study intervention. The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may contact the Sponsor to discuss the situation prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment for the participant. If a participant's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

Sponsor safety staff may unblind the study intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's study intervention assignment, may be sent to the Investigator in accordance with local regulations and/or Sponsor policy.

6.5. Study Intervention Compliance

When participants are dosed, they will receive study intervention directly from medically qualified designated unblinded study personnel. The date and time of study intervention administration will be recorded in the source document. The identities of the study intervention and the participant will be confirmed at the time of administration by an unblinded member of the study staff other than the individual administering the study intervention.

6.6. Dose Modification

Not applicable.

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

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

6.8. Treatment of Overdose

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

6.9. Prior and Concomitant Therapy

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Recording of Prior Medications, Vaccines, and Procedures

Medications (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) and medical procedures within 28 days prior to Day 1 (Baseline) must be recorded in the eCRF. Additionally, the following will be recorded:

- Any vaccine (licensed or investigational) administered within 1 year prior to Day 1 (Baseline). For licensed influenza vaccines, detailed information regarding which vaccine was administered should be provided, if available.
- Corticosteroids, systemic immunoglobulins, or blood products within 90 days prior to Day 1 (Baseline).
- Systemic immunosuppressive or immunomodulating treatment, including long-acting biological therapies that affect immune responses within 180 days prior to Day 1 (Baseline).
- Medical procedures applicable to females of childbearing potential (eg, hysterectomy, bilateral oophorectomy).
- Historical medical procedures to treat a medical history condition prior to Day 1 (Baseline). Diagnostic procedures do not need to be recorded (eg, biopsy, colonoscopy).

6.9.2. Recording of Concomitant Medications, Vaccines, and Procedures

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

- All medications taken at the time of the Day 1 (Baseline) Visit through Day 28. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such. Any antipyretic or analgesic use recorded by participants in the Reactogenicity eDiary should be reviewed by study staff at the Day 8 Visit and recorded in the eCRF.
- All concomitant medications relevant to or for the treatment of an MAAE, AE leading to discontinuation, SAE, or AESI from Day 1 (Baseline) through Month 6 (Day 181).
- All concomitant medications that may lead to the elimination of a participant from PP analyses (Refer to Section 6.9.3) from Day 1 (Baseline) through EOS.
- All nonstudy vaccines from Day 1 (Baseline) through EOS.

- All concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) relevant to or for the treatment of protocol-defined respiratory illness (refer to Table 4) from Day 1 (Baseline) through the end of the influenza season.
- All concomitant procedures/surgeries from Day 1 (Baseline) through EOS.

6.9.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses

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 9.3.

- Any investigational or nonregistered product other than the study intervention used during the study.
- Immunosuppressants or other immune-modifying drugs administered chronically during the study.
- Intra-articular and epidural steroids or other injections with long-acting corticosteroids through Day 28.
- Long-acting biological therapies that affect immune responses (eg, infliximab) during the study.
- Any nonstudy vaccine administered through Day 14.
- Any nonstudy licensed seasonal influenza vaccine administered during the study.
- Immunoglobulins and/or any blood products administered during the study.
- Any surgical procedure through Day 28.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.10.

7.1. Discontinuation of Study Intervention

No early termination/suspension criteria are planned since the vaccine treatment is 1 day and no safety pause rules are prespecified.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). If a participant chooses to withdraw from the study, the Investigator (or designee) should document the reason for withdrawal in EDC if the participant provides one.
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of study discontinuation, if possible, an early discontinuation visit should be conducted. Refer to the Month 6 (Day 181) Visit in the SoA (Table 1) (or to the End of the Influenza Season Visit if the Month 6 [Day 181] Visit has already been conducted) for data to be collected at the time of study discontinuation. The participant will be permanently discontinued from the study at that time.
- A participant who withdraws/discontinues from the study will not be replaced.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations) unless the participant has requested destruction of samples.

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

- AE.
- Solicited AR/reactogenicity.
- Death.
- LTFU.

- Physician decision.
- Protocol deviation.
- Study terminated by Sponsor.
- Withdrawal of consent.
- Randomization by mistake.
- Other.

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study because of an SAE or AE as described in Section 8.3.6.

7.3. Lost to Follow-up

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. If contact is made, the participant should be counseled on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- The Investigator or designee must make every effort to regain contact with the participant at each missed visit. These contact attempts should be documented in the participant's medical record.
- A participant should be not considered LTFU until due diligence has been completed.
- If due diligence, as described above, has been completed and the participant continues to be unreachable, the participant will be considered LTFU.

8. STUDY ASSESSMENTS AND PROCEDURES

General considerations for study assessments and procedures include the following:

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the protocol.
- Alternate strategies for participant visits, assessments, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements, to support participants in adherence with study requirements.
- Study results that could lead to unintentional unblinding will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1).

8.1.1. Assessment of Clinical Events

For the primary and secondary efficacy endpoints, an RT-PCR-confirmed influenza infection is defined as a clinical event, potentially contributing to the efficacy data. Clinical events will be identified programmatically based on symptoms, RT-PCR test results, and similarity/antigenic match to the vaccine strains. Investigators will not receive the RT-PCR or NP swab test results performed by the central laboratory. Additional details will be provided in the SAP.

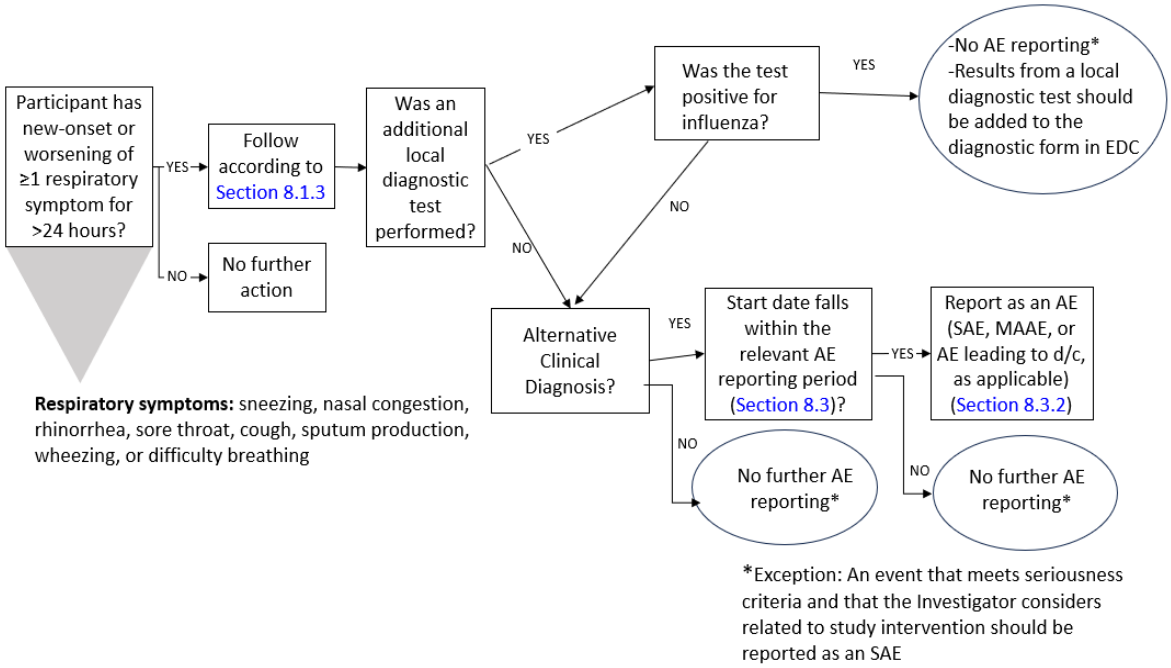
In general, protocol-defined respiratory illness events consistent with the clinical endpoint definitions (Table 4) should not be recorded as AEs or SAEs. These data will be captured as efficacy assessment data only, as these are expected endpoints.

A decision tree for reporting potential clinical events is provided in Figure 1.

- Confirmation of influenza infection by a diagnostic test performed outside of the study for clinical care will not be recorded as an AE unless the event meets seriousness criteria and the Investigator considers the event related to study intervention. Only under these circumstances, will the event be reported as an SAE (Section 8.3.2).

If a test result is negative for influenza A and B, the event will not be recorded as an AE unless an alternative clinical diagnosis is available (eg, respiratory illness due to another pathogen [eg, COVID-19, RSV, streptococcal pharyngitis]; exacerbation of asthma; congestive heart failure). These events should be recorded, evaluated, followed-up, and reported within protocol-specified reporting periods as described in Section 8.3.For SAE reporting purposes, the awareness date is the date the Investigator receives the test result or becomes aware of an alternative diagnosis (refer to Section 8.3.2).

Figure 1: Decision Tree for Reporting Potential Clinical Events



Abbreviations: AE = adverse event; EDC = electronic data capture; d/c = discontinuation; MAAE = medically attended adverse event; SAE = serious adverse event.

8.1.2. Definitions for Efficacy Assessments

Although the protocol-defined ILI case definition is used for the primary efficacy endpoint, all of the ILI case definitions provided in Table 4 are used for at least 1 secondary and/or exploratory efficacy endpoint. The protocol-defined respiratory illness case definition is used for screening as it provides high sensitivity for the detection of influenza cases.

Note: The source of the clinical symptomology that supports the case definition can be participant reported and/or from a clinical assessment.

Table 4: Case Definitions for Respiratory Illness, ILI, and Confirmed Influenza Illness

Term	Definition
Protocol-defined respiratory illness	New onset or worsening (>24 hours) of at least 1 of the following symptoms: sneezing, nasal congestion, rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing.
Protocol-defined ILI	At least 1 systemic symptom (temperature >37.2°C (>99.0°F), chills, feverish, tiredness, headaches, or myalgia) AND at least 1 respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing)
Modified CDC-defined ILI	Body temperature >37.2°C (>99.0°F) accompanied by cough and/or sore throat (DiazGranados et al 2014).
CDC-defined ILI	Body temperature ≥37.8°C (≥100°F) accompanied by cough and/or sore throat (CDC 2017).
WHO-defined ILI	An acute respiratory infection with measured fever of ≥38.0°C (100.4°F) and cough, with onset within the last 10 days (WHO 2014).
ILI as defined in a previous mRNA-1010 clinical study protocol (mRNA-1010-P302)	CCI [redacted]
RT-PCR-confirmed influenza illness	Positive influenza result by RT-PCR.
Culture-confirmed influenza illness[a]	Positive influenza result by viral culture.

Abbreviations: CDC = US Centers for Disease Control and Prevention; ILI = influenza-like illness; RT-PCR = reverse transcription polymerase chain reaction; WHO = World Health Organization.

a. Viral cultures will only be performed on samples with a positive influenza result by RT-PCR assay performed by the central laboratory.

8.1.3. Surveillance for Respiratory Illness and ILI

Surveillance for respiratory illness and ILI includes the following:

- Participants are encouraged to respond to the eDiary as soon as possible if they have any respiratory symptoms and, upon experiencing respiratory symptoms, to contact study staff (refer to Section 8.1.3.1).
- Study staff should contact participants who report experiencing respiratory symptoms as soon as possible (preferably within 24 hours) to review symptoms and confirm protocol-defined respiratory illness (refer to Section 8.1.3.2).

- For participants with protocol-defined respiratory illness:
  - An unscheduled visit will be arranged and an NP swab sample will be collected, preferably within 72 hours after symptom onset (refer to Section 8.1.3.3). Samples collected within 5 days after symptom onset are acceptable.
  - Study staff will follow up with the participant twice weekly to collect information about the duration of symptoms, healthcare usage, and concomitant medications related to the participant's respiratory illness (refer to Section 8.1.3.4).

8.1.3.1. Symptom Reporting by the Participant

At the time of consent, participants must confirm they will be willing to complete a Symptom eDiary. Participants are required to complete the eDiary twice weekly from Day 1 (Baseline) to the end of the influenza season. The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1) and will also be reminded to call the site immediately if they experience any respiratory symptoms (refer to Table 4).

- The eDiary will provide prompts to report experiencing respiratory symptoms twice weekly. Participants should contact the site if they are unable to complete the eDiary for any reason.
- Participants are encouraged to respond to the eDiary as soon as possible if they have any respiratory symptoms and, upon experiencing respiratory symptoms, to contact study staff. If they do not have any symptoms, they are encouraged to respond to the eDiary prompt at the end of the period.
- If symptoms arise or worsen after the participant has completed the eDiary entry for a given period, the participant should add an entry to the eDiary and contact the site to report symptoms.
- For participants with protocol-defined respiratory illness:
  - Oral temperature measurements should be performed daily while symptoms are ongoing, preferably at approximately the same time each day. Any body temperature >37.2°C (>99.0°F) should be reported to study staff as a possible symptom of protocol-defined ILI.
  - Participants will continue to respond to eDiary prompts twice weekly and will be followed as described in Section 8.1.3.2.

8.1.3.2. Symptom eDiary Follow-Up

If a participant does not respond to the eDiary prompts according to the SoA (Table 1), study staff will follow-up with the participant.

If a participant reports experiencing respiratory symptoms in the eDiary, study staff should contact the participant as soon as possible (preferably within 24 hours) to review symptoms and confirm protocol-defined respiratory illness (defined as new onset or worsening (>24 hours) of at least 1 of the following symptoms: sneezing, nasal congestion, rhinorrhea, sore throat, cough, sputum production, wheezing, or difficulty breathing [refer to Table 4]).

For participants with protocol-defined respiratory illness, an unscheduled illness visit will be arranged (as described in Section 8.1.3.3) and trained study staff will follow up with the participant (as described in Section 8.1.3.4).

8.1.3.3. Unscheduled Illness Visits

An unscheduled illness visit will be arranged for any participant with protocol-defined respiratory illness, preferably to occur within 72 hours after symptom onset.

During this unscheduled illness visit, the following assessments will be performed as specified in the SoA (Table 1):

- Review the history of respiratory and ILI symptoms (refer to Table 4), including approximate dates of onset.
- Vital signs measurement.
- Record any visits to nonstudy HCPs, including a healthcare visit by the participant, a mobile/home visit by an HCP, or emergency room/urgent healthcare visit in response to the episode of respiratory illness. Study personnel are encouraged to attempt to obtain information from the HCPs.
- Record any new concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) or altered doses/frequencies of existing concomitant medications resulting from the respiratory illness.
- An NP swab sample will be collected, preferably within 72 hours after symptom onset.
  - Samples collected within 5 days after symptom onset are acceptable. NP swab samples should preferably be collected prior to any antiviral therapy and may be collected at home by qualified medical personnel in lieu of a clinic visit. In the event that NP swab samples cannot be collected, any available influenza test results performed outside of the study should be captured in the eCRF.
  - Data from specimens obtained using a local diagnostic test at a healthcare visit external to the study or mobile site may be accepted if the results are obtained using Food and Drug Administration-approved kits or have laboratory developed tests within laboratories that are Clinical Laboratory Improvement Amendment (CLIA)-certified (or have similar regulatory certification for laboratories outside the US).
  - NP swab samples will be tested using an RT-PCR-based assay to determine whether influenza A and/or B strains, as well as other respiratory viruses, are present in the clinical sample. For samples that test positive for influenza in an RT-PCR assay performed by the central laboratory, additional assays, such as genetic sequencing of the virus genes and/or virus culture with subsequent antigenicity testing, will be performed to determine whether there is a similarity and/or match with the vaccine strains.
  - In participants with ongoing respiratory symptoms, additional NP swab samples are not necessary within 14 days of the last NP swab sample collection except at

the discretion of the Investigator (eg, symptom progression after a negative influenza test, evidence that symptoms represent a new case).

All clinical findings will be recorded in the eCRF.

8.1.3.4. Respiratory Illness Follow-Up

For participants with protocol-defined respiratory illness, trained study staff will contact the participant twice weekly until resolution of symptoms (or until the end of the window period for the End of the Influenza Season Visit) to update and review symptoms and concomitant medications (eg, antivirals such as Tamiflu/oseltamivir) related to the participant's respiratory illness as specified in the SoA (Table 1). In addition to the duration of symptoms, information will be collected about healthcare usage and concomitant medications related to the participant's respiratory illness (refer to Section 6.9.2). This follow-up will occur regardless of whether the participant had a positive influenza test.

8.1.3.5. End of the Influenza Season Visit

The end of the influenza season is defined in Section 4.4.1.

Trained study staff will contact the participant by telephone to conduct the End of the Influenza Season Visit according to the SoA (Table 1). For participants with ongoing protocol-defined respiratory illness, the End of the Influenza Season Visit should be scheduled within the window period and allowing for follow-up respiratory illness contacts according to the SoA (Table 1).

8.2. Safety Assessments

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

- Solicited local and systemic ARs on Day 1 (Baseline) (eDiary entry approximately 30 minutes after study intervention) and during the 6 subsequent days (through Day 7) in a subset of approximately 6000 participants.
- Unsolicited AEs observed or reported on Day 1 (Baseline) to Day 28.
- MAAEs from Day 1 (Baseline) to Month 6 (Day 181).
- AEs leading to discontinuation from Day 1 (Baseline) to Month 6 (Day 181).
- SAEs from signing the ICF to Month 6 (Day 181).

  Note: SAEs considered related to study intervention are recorded through EOS.

  Note: SAEs collected in the period from signing of the ICF to before study intervention on Day 1 (Baseline) will not be included in the safety analyses.
- AESIs from Day 1 (Baseline) to Month 6 (Day 181).
- Details of all pregnancies in participants that begin between Day 1 (Baseline) and Month 3 (Day 91).
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.

8.2.1. Physical Examinations

- At Screening, a complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. Any clinically significant finding identified during the Screening Visit should be recorded as medical history.
- On Day 1 (Baseline), physical examination will be limited to examination of the arm receiving the injection and the associated lymph node before study intervention; any abnormalities should be documented.

8.2.2. Vital Signs

Vital signs will be measured at the time points indicated in the SoA (Table 1). The participant will be seated for at least 5 minutes before all measurements are taken. On Day 1, vital sign measurements will be collected once before study intervention and again approximately 30 minutes after study intervention (before participants are discharged from the study site). If vital signs are clinically concerning, study intervention should not be administered to the participant. When applicable, vital sign measurements should be performed before blood collection.

Criteria for temporarily delaying administration of study intervention in participants with acute moderate or severe infection or fever are provided in Section 5.4.

8.2.3. Pregnancy Testing

Refer to Section 5.1 for pregnancy testing entry criteria.

A point-of-care urine pregnancy test (unless serum testing is required by local regulation or IRB/IEC) will be performed at the Screening Visit and before study intervention (if the Day 1 [Baseline] Visit is not on the same day as the Screening Visit) as specified in the SoA (Table 1). Additional serum or urine pregnancy tests may be performed at any time during the pregnancy-reporting period (through Month 3 [Day 91]), as determined necessary by the Investigator or as required by local regulation, to establish the absence of pregnancy.

8.2.4. Safety Contact

A safety contact is a telephone call made to the participant by trained study staff. This call will follow a script, which will facilitate the collection of relevant safety information. Planned timepoints for all safety contacts are provided in the SoA (Table 1). The participant will be interviewed according to the script about occurrence of AEs (refer to Section 8.2), concomitant medications/procedures (refer to Section 6.9.2), and any nonstudy vaccinations. All safety information collected during the telephone call must be documented as described by the participant in the source documents and not on the script used for the telephone call.

A safety contact may trigger an unscheduled visit.

8.2.5. Reactogenicity eDiary (Only for a Subset of Participants)

Solicited local and systemic ARs will be collected only in a subset of approximately 6000 participants (referred to as the Reactogenicity Subset).

At the time of consent, the participant must confirm they will be willing to complete a Reactogenicity eDiary (for 7-day reactogenicity). The local and systemic ARs that will be solicited by the eDiary are described in Table 6.

Solicited local and systemic reactogenicity ARs will be collected on Day 1 and during the 6 subsequent days (through Day 7). Details on the recording of solicited local and systemic ARs are included in Section 8.3.1.5.

On Day 1 (Baseline), participants will record data into the eDiary starting approximately 30 minutes after study intervention under supervision of study staff to ensure successful entry of assessments. The 30-minute observation period is an opportunity for study staff to train the participant on eDiary completion requirements. The study staff will perform any retraining as necessary.

On Day 1 (Baseline), participants will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) to the injection arm. Daily oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study staff.

The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1).

8.2.5.1. Reactogenicity eDiary Follow-Up

If a participant does not respond to the eDiary prompts according to the SoA (Table 1), the study staff will follow-up with the participant.

Study staff will review Reactogenicity eDiary entries with the participant at the Day 8 Safety Contact.

A follow-up safety call will be triggered under the following circumstances:

- If a Grade 4 solicited AR is reported, study staff should contact the participant as soon as possible.
- If a Grade 3 solicited AR is reported on 2 consecutive days, study staff should contact the participant.

Follow-up safety contacts may also be conducted at the Investigator's discretion. The results of the safety contact should be recorded in the appropriate source documentation.

Sites should have a process in place for monitoring and following up on solicited ARs.

8.3. Adverse Events: Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions of AEs, SAEs, SUSARs, AESIs, solicited ARs, and MAAEs are provided in Section 8.3.1. The time period and frequency for collecting safety information is provided in Section 8.3.2. The method of detecting AEs and SAEs is provided in Section 8.3.3. The method of recording AEs and SAEs is described in Section 8.3.4. The assessment of intensity and causality is provided in Section 8.3.5. The follow-up of AEs and SAEs is described in

Section 8.3.6. The reporting of SAEs/AESIs is described in Section 8.3.7. Regulatory reporting requirements are provided in Section 8.3.8. Pregnancy reporting is provided in Section 8.3.9.

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

Medication errors and uses outside of the study protocol are subject to the same collection/reporting rules as AEs.

8.3.1. Safety Events

AEs are defined in Section 8.3.1.1. SAEs are defined in Section 8.3.1.2. SUSARs are defined in Section 8.3.1.3. AESIs are defined in Section 8.3.1.4. Solicited ARs are defined in Section 8.3.1.5. MAAEs are defined in Section 8.3.1.6.

8.3.1.1. Adverse Event

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

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

- Unsolicited AEs are AEs that are not included in the list of predefined solicited ARs (Table 6).

Events Meeting the AE Definition

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

Events not Meeting the AE Definition

- Protocol-defined respiratory illness events consistent with the clinical endpoint definitions (Table 4) should not be recorded as AEs or SAEs except as described in Section 8.1.1.
- Signs and symptoms that are consistent with any of the solicited AR terms in Table 6 that start on or before Day 7 except as described in Section 8.3.1.5.
- Any sign, symptom, or disease identified or starting before study intervention should be recorded as medical history. If the full date is unknown, all known date information should be collected.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.3.1.2. Serious Adverse Event

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

a. Results in death.

b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

d. Results in persistent or significant disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

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

e. If exposure to a study intervention prior to conception or during pregnancy may have resulted in birth defects, congenital disorders, congenital malformations, or congenital abnormalities.

f. Other situations:

- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

8.3.1.3. Suspected Unexpected Serious Adverse Reaction

A SUSAR is an AE that is unexpected, serious, and has a reasonable possibility of a causal relationship with the study intervention.

8.3.1.4. Adverse Event of Special Interest

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

Investigators should report all events that fall into the categories presented in Table 5 as an AESI per the reporting processes in Section 8.3.7. 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 5: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia:	• Platelet count <125 × 10^9/L. • 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:	• GBS. • 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 study intervention administration as defined in Section 8.3.1.4.1.

Medical Concept	Additional Notes
Myocarditis/Pericarditis:	• Myocarditis. • Pericarditis. • Myopericarditis. See Section 8.3.1.4.2.

Abbreviations: ADEM = Acute disseminated encephalomyelitis; GBS = Guillain-Barre Syndrome; HELLP = hemolysis, elevated liver enzymes and low platelets.

8.3.1.4.1. Anaphylaxis

All cases of possible anaphylaxis associated with study intervention should be recorded as AESIs and reported as SAEs (Section 8.3.7), based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity 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:

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

8.3.1.4.2. Myocarditis and/or Pericarditis

A case of possible, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI (Section 8.3.7), even if it does not meet criteria per the CDC case definition (Section 10.4). The event should also be reported as an SAE if it meets seriousness criteria (Section 8.3.1.2).

The Investigator's medical judgment must be applied when assessing participants reporting symptoms concerning for myocarditis and/or pericarditis contained within the CDC case definition. Diagnostic evaluation (eg, ECG, echocardiogram) and laboratory testing (eg,

troponin) included in the CDC definition should promptly be obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be considered in those with positive test results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated. The Investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis that are reported in ongoing interventional clinical studies per the CEAC charter, to determine if they meet CDC criteria for "probable" or "confirmed" events. The CDC Working Case Definitions are provided in Section 10.4 as guidance and the CEAC is described in Section 10.1.6.2.

8.3.1.5. Solicited Adverse Reactions

Solicited ARs are predefined local and systemic events for assessment of reactogenicity (Table 6). The term "reactogenicity" refers to the occurrence of transient adverse effects associated with study intervention administration. In this study, solicited ARs will be collected only in the Reactogenicity Subset (~6000 participants).

Signs and symptoms that are consistent with any of the solicited AR terms in Table 6 that start on or before Day 7 should not be recorded as unsolicited AEs, unless the event meets seriousness criteria and the Investigator considers it related to study intervention, in which case the event will be reported as an SAE. Solicited ARs will be collected and assessed separately from unsolicited AEs. If a participant reports an event consistent with reactogenicity that starts after Day 7, it should not be recorded as reactogenicity in EDC, but as an AE. Causality for these events will be determined per assessment by the Investigator.

The Reactogenicity eDiary will solicit daily participant reporting of ARs using a structured checklist as described in Section 8.2.5.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 6, which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to study intervention.

If a participant missed an eDiary entry, then the reason for the missed eDiary entry should be recorded in the Missing eDiary Timepoint eCRF in the EDC.

If the event starts during the solicited AR period, but continues beyond Day 7, the participant should notify the site to provide an end date and close out the event in EDC.

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 study staff in EDC, where reactogenicity is captured:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE).
- Solicited local or systemic AR leading to discontinuation.

- Solicited local or systemic AR lasting beyond Day 7.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

Assessment of Intensity

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) has been modified to categorize local and systemic reactogenicity events (solicited ARs) observed during this study. The intensity grading scale used in this study is presented in Table 6.

Table 6: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5.0 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/ 2.5-5.0 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 ER visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER visit or hospitalization

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or >2 episodes/ 24 hours	Prevents daily activity or requires outpatient intravenous hydration	Requires ER visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires ER 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

Abbreviations: ER = emergency room.
Note: Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

8.3.1.6. Medically Attended Adverse Event

A MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up) and visits to HCPs external to the study site (eg, emergency room, urgent care, primary care physician).

8.3.2. Time Period and Frequency for Collecting of Safety Information

All solicited ARs will be collected from Day 1 (Baseline) and during the 6 subsequent days (through Day 7) in the Reactogenicity Subset.

All unsolicited AEs will be collected from Day 1 (Baseline) to Day 28 at the timepoints specified in the SoA (Table 1).

All MAAEs will be collected from Day 1 (Baseline) to Month 6 (Day 181) at the timepoints specified in the SoA (Table 1).

All AEs leading to discontinuation will be collected from Day 1 (Baseline) to Month 6 (Day 181) at the timepoints specified in the SoA (Table 1).

All SAEs will be collected from signing of the ICF to Month 6 (Day 181) at the timepoints specified in the SoA (Table 1). SAEs considered related to study intervention are collected through EOS. SAEs collected in the period from signing of the ICF to before study intervention on Day 1 (Baseline) will not be included in the safety analyses. All SAEs will be recorded and reported to the Sponsor or designee immediately after the site becomes aware of the event and under no circumstance should this exceed 24 hours, as indicated in Section 8.3.7. The date the site becomes aware of the AE is considered the awareness date; the onset date of the AE is distinct from and unaffected by the awareness date. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

All AESIs will be collected from Day 1 (Baseline) to Month 6 (Day 181) at the timepoints specified in the SoA (Table 1). All AESIs will be reported to the Sponsor in the same manner and timeframe as SAEs, as indicated in Section 8.3.7.

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

8.3.3. Method of Detecting AEs and SAEs

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.

8.3.4. AE and SAE Recording

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

8.3.5. Assessment of Intensity and Causality

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

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- **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.
- For causality assessment, the Investigator will also consult the IB and/or package insert, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.3.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts as specified in the SoA (Table 1). All AEs/SAEs/AESIs/MAAEs will be followed at least monthly until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.3). Further information on follow-up procedures is provided below:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- If a participant dies during the study, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology (if available).

- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

8.3.7. Reporting of SAEs/AESIs

AESIs will be reported to the Sponsor or designee in the same manner and timeframe as SAEs.

Reporting to the Sponsor or designee via EDC

- The primary mechanism for reporting an SAE/AESI to the Sponsor or designee will be the EDC.
- If the electronic system is unavailable, then the site will use the paper SAE/AESI data collection tool (see next section) to report the event within 24 hours of becoming aware of the event.
- The site will enter the SAE/AESI data into EDC as soon as it becomes available.
- After the study is completed at a given site, EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE/AESI from a participant or receives updated data on a previously reported SAE/AESI after EDC has been taken offline, then the site can report this information on a paper data collection tool (see next section).

Reporting to the Sponsor or designee via Paper Data Collection Tool

- If EDC is unavailable and the site needs to use a paper form to report SAEs/AESIs, email transmission of the SAE/AESI paper data collection tool may be used to transmit this information to the Sponsor.
- Initial notification via email does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.
- SAE/AESI reports should be emailed to the email address provided in Section 10.3.1.

8.3.8. Regulatory Reporting Requirements for SAEs

- Prompt notification within 24 hours by the Investigator to the Sponsor of an SAE, including those considered to be a SUSAR, is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators. For example, reports that are required to be submitted to the European Union (Individual Case Safety Reports) will be submitted via the EudraVigilance Clinical Trial Module Gateway.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB/package insert and will notify the IRB/IEC, if appropriate, according to local requirements.
- For expedited reporting purposes, the expectedness of SAEs will be assessed against the study intervention the participant received, if applicable. AE terms not listed as expected events in the IB/package insert for the investigational product and comparator will be considered unexpected.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.9. Pregnancy

- Details of all pregnancies in participants that begin between Day 1 (Baseline) and Month 3 (Day 91) will be collected. Participants who become pregnant at any time during the study should remain in the study and complete all study visits as scheduled.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the participant's pregnancy. See Section 10.3.2.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 8.3.7).
- Pregnancies must be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate (if the participant has consented) and the information will be forwarded to the Sponsor. Pregnancy-related data received after the end of the study may not be recorded in the clinical database.
- Any poststudy pregnancy-related SAE considered related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.7. While the Investigator is not obligated to actively seek this information in former participants, they may learn of an SAE through spontaneous reporting.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Future Research

Blood and NP swab samples collected throughout the study may be used for future research to further characterize safety biomarkers, immune responses to influenza vaccines, immune response across influenza virus strains, and for additional assay development in consented participants and geographies.

8.7. Biomarkers

Additional biomarkers may be evaluated using the remainder of any blood or NP swab samples collected throughout the study (Section 8.6).

8.8. Immunogenicity

Blood samples for immunogenicity assessments will be collected at the timepoints indicated in the SoA (Table 1).

- Serum antibody levels may be measured by HAI assay and/or MN assay. Measurement of antibody levels will be performed in a laboratory designated by the Sponsor.
- Measurements of T-cell responses may be performed. Measurement of T-cell responses will be performed in a laboratory designated by the Sponsor.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of the statistical analyses will be provided in the SAP, which will be finalized before the preplanned IA (refer to Section 9.7.1). If, after the study has begun, but prior to any unblinding, changes are made to the primary objectives/hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH E9). Changes to secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study.

9.1. Blinding and Responsibility for Analyses

Blinding procedures are described in Section 6.4.

An independent unblinded statistical and programming team will perform the preplanned IA.

The independent DSMB will periodically review blinded and unblinded data as described in Section 10.1.6.1.

9.2. Statistical Hypotheses

The primary efficacy objective of this study is to evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains. Cases will be counted starting 14 days after study intervention.

The null hypothesis to be tested first is that the rVE of mRNA-1010 versus an active comparator is inferior, CCI

CCI

The rVE is defined as the percent reduction in the hazard of the primary endpoint (mRNA-1010 vs active comparator). Equivalently, the null hypothesis to be tested can be formulated in terms of an HR: CCI

A stratified Cox proportional hazard model will be used to assess the HR between mRNA-1010 and an active comparator at a 1-sided adjusted significance level based on the CCI on the PP Set (defined in Section 9.3). The study will be considered to meet the primary efficacy objective by demonstrating NI of mRNA-1010 to an active comparator if the *p-value* for rejecting CCI is less than the adjusted 1-sided significance level based on the CCI at the IA or final analysis on the PP Set (see Section 9.5).

Once NI is demonstrated, rVE will be evaluated using the same endpoint for superiority. The null hypothesis to be tested is:

CCI

Equivalently, the null hypothesis is CCI

Superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be concluded if the CCI [redacted] at the IA and/or final analysis on the PP Set (see Section 9.5).

Subsequently, once superiority is demonstrated, rVE will be further evaluated using the same endpoint for super-superiority. The null hypothesis to be tested is:

CCI [redacted]

Equivalently, the null hypothesis is CCI [redacted]

Super-superiority of mRNA-1010 versus an active comparator on the primary efficacy endpoint will be concluded if the CCI [redacted] at the IA and/or final analysis on the PP Set (see Section 9.5).

If NI, superiority and super-superiority are demonstrated for the primary efficacy endpoint, then the following secondary efficacy endpoints will be evaluated for NI, superiority and super-superiority at the IA or final analysis using the adjusted 1-sided significance level based on the CCI [redacted] (see Section 9.5):

- rVE of mRNA-1010 versus an active comparator against modified CDC-defined ILI caused by any influenza A or B strains. The null hypothesis for NI is CCI [redacted] the null hypothesis for superiority is CCI [redacted] and the null hypothesis for super-superiority is CCI [redacted] where rVE is the percent reduction in the hazards of RT-PCR-confirmed modified CDC-defined ILI caused by influenza A or B strains (mRNA-1010 vs active comparator).
- rVE of mRNA-1010 versus an active comparator against protocol-defined ILI caused by influenza A or B strains with antigenic match to the vaccine strains. The null hypothesis for NI is CCI [redacted] and the null hypothesis for superiority is CCI [redacted] and the null hypothesis for super-superiority is CCI [redacted] ,where rVE is the percent reduction in the hazards of RT-PCR-confirmed protocol-defined ILI with antigenic match to the vaccine strains (mRNA-1010 vs active comparator).

CCI [redacted]

9.3. Analysis Sets

Analysis sets are defined in Table 7.

Table 7: Analysis Sets

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
FAS	All randomized participants who received any study intervention. Participants will be analyzed according to the study intervention group to which they were randomized.
PP Set	All participants in the FAS, excluding those with important protocol deviations that could adversely impact efficacy (eg, disease or therapeutic intervention that might cause suboptimal response to study intervention). The PP Set will be used as the primary analysis set for efficacy endpoints. Participants will be analyzed according to the study intervention group to which they were randomized.
Immunogenicity Subset	A prespecified subset of participants in the FAS who received TIV and have baseline and Day 29 antibody assessments by HAI assay. Participants will be analyzed according to the study intervention group to which they were randomized. The method for selection of participants for the subset will be detailed in the SAP.
PPIS	All participants in the Immunogenicity Subset who received the planned dose of study intervention and had no important protocol deviations that impact the immunogenicity assessment. Participants with RT-PCR-confirmed influenza infection between Day 1 (Baseline) and Day 29 will be removed from the PPIS. The PPIS will be used for all analyses of immunogenicity unless specified otherwise. Participants will be analyzed according to the study intervention group to which they were randomized.
Safety Set	All randomized participants who received any study intervention. The Safety Set will be used for all analyses of safety except for solicited ARs. Participants will be analyzed according to the study intervention they actually received.
Solicited Safety Subset	All randomized participants who received any study intervention and contributed any solicited AR data in the Reactogenicity eDiary. The Solicited Safety Set will be used for all analyses of solicited ARs. Participants will be analyzed according to the study intervention they actually received.

Abbreviations: AR = adverse reaction; eDiary = electronic diary; FAS = Full Analysis Set; HAI = hemagglutination inhibition; NI = noninferiority; PP = Per-Protocol; PPIS = Per-Protocol Immunogenicity Subset; RT-PCR = reverse transcription polymerase chain reaction; TIV = trivalent influenza vaccine.

9.4. Statistical Analyses

The SAP will be developed and finalized before the preplanned IA (refer to Section 9.7.1) and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

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

9.4.1. Efficacy Analyses

Efficacy analyses will be performed using the PP Set and FAS, and participants will be analyzed according to the study intervention group to which they were randomized.

9.4.1.1. Analysis of Primary Efficacy Endpoint

To assess the efficacy endpoint for the primary objective, preventing the first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains, the stratified Cox proportional hazards regression model will be used to estimate HR. The rVE (ie, 1-HR [mRNA-1010 vs active comparator]) will be estimated, along with the 2-sided 95% CI and adjusted 1-sided significance level based on the CCI [redacted] CCI [redacted]

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

Participants without RT-PCR-confirmed protocol-defined ILI will be censored at the end of the influenza season, the date of early discontinuation, or the date of death unrelated to influenza, whichever is earlier. Participants with early RT-PCR-confirmed protocol-defined ILI starting less than 14 days after study intervention will be censored at the start date of the early RT-PCR-confirmed protocol-defined ILI. The following intercurrent events are handled with the hypothetical strategy:

- Early discontinuation or death unrelated to influenza; or
- Early RT-PCR-confirmed protocol-defined ILI starting <14 days after study intervention.

The detailed estimands considerations are presented in Section 9.4.5.

The study will be considered to meet the primary efficacy objective by demonstrating NI of mRNA-1010 to an active comparator if the *p-value* for rejecting CCI [redacted] is less than the adjusted 1-sided significance level based on the CCI [redacted] at the IA or final analysis on the PP Set. The nominal alpha levels (1-sided) are CCI [redacted] at the IA and CCI [redacted] at the final analysis, respectively.

A supplementary analysis of the primary endpoint will be also performed based on the FAS using the same methods as described above.

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

In addition, Kaplan-Meier curves will be used to plot the estimated cumulative incidence rates over time by study intervention group. Participants without RT-PCR-confirmed protocol-defined ILI will be censored at the end of influenza season.

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

9.4.1.2. Analysis of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be performed using similar methods as used for the analysis of the primary efficacy endpoint.

Further details will be provided in the SAP.

9.4.2. Safety Analyses

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by study intervention group, unless otherwise specified.

The number and percentage of participants with any solicited local AR or solicited systemic AR within 7 days after study intervention will be summarized. A 2-sided exact 95% CI using the Clopper-Pearson method will be provided for the percentage of participants with any solicited AR. Solicited ARs will be coded according to MedDRA for AR terminology.

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

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

Further details will be provided in the SAP.

9.4.3. Immunogenicity Analyses

The secondary immunogenicity endpoints will be analyzed using the PPIS by study intervention group unless otherwise specified.

For each of the 3 strains, the GMT of HAI titers with corresponding 95% CI will be provided at each timepoint. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale. The GMFR of HAI titers with corresponding 95% CI at Day 29 over Day 1 (Baseline) will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

An analysis of covariance model will be carried out. The model will include the log-transformed HAI titers at Day 29 as the dependent variable, study intervention group as the fixed variable, log-transformed Day 1 (Baseline) HAI titers as a fixed covariate, and adjusting for the stratification factors. The GLSM and its corresponding 95% CI will be estimated by back-transforming the LSM estimate and 95% CI obtained from the model on the log-transformed data. The GMR and its corresponding 95% CI will be estimated similarly, from the LSM difference estimate and 95% CI obtained from the model on the log-transformed scale using back-transformation. The corresponding 2-sided 95% CI of GMR will be provided to assess the difference in immune response between study intervention groups at Day 29.

For each strain, seroconversion is defined as either a Day 1 (Baseline) HAI titer <1:10 and a postinjection titer ≥1:40 or a Day 1 (Baseline) HAI titer ≥1:10 and a minimum 4-fold rise in postinjection HAI titer.

The number and percentage of participants with seroconversion will be provided with 2-sided 95% CIs using the Clopper-Pearson method at Day 29. To compare the seroconversion rates between the study intervention groups, the Miettinen-Nurminen's method will be used to calculate the 95% CI for the difference in seroconversion rates. The seroconversion rate difference with the corresponding 95% CI at Day 29 will be provided for each strain.

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

In addition, the number and percentage of participants with an HAI titer ≥1:40 at Day 29 will be provided with 2-sided 95% CIs using the Clopper-Pearson method.

A separate analysis plan will be developed to evaluate HAI titers after study intervention (ie, Day 29 HAI titers) as CoR and CoP of influenza illness.

9.4.4. Exploratory Analyses

Analyses of exploratory endpoints evaluating rVE will be performed using similar methods as used for the analysis of the primary efficacy endpoint.

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

9.4.5. Estimands

Intercurrent event types (Table 8) and the estimand for the primary endpoint on the PP Set along with the rationale for strategies to address intercurrent events (Table 9). Additional information including a summary of the estimand for the secondary efficacy endpoint are included in the SAP.

Table 8: Intercurrent Event Types

Label	Intercurrent Event Type
IcEv1 (early discontinuation)	Early discontinuation or death unrelated to influenza
IcEv2 (early infection)	RT-PCR-confirmed protocol-defined ILI starting <14 days after study intervention

Label	Intercurrent Event Type
IcEv3 (important violation of eligibility criteria)	Important violation of eligibility criteria of inclusion and/or exclusion
IcEv4 (nonstudy influenza vaccine)	Use of alternative nonstudy Influenza vaccine during the study
IcEv5 (prohibited medications)	Use of prohibited medications deemed to impact on immunogenicity/efficacy response
IcEv6.1 (no vaccination)	Not received any study vaccine
IcEv6.2 (wrong vaccination)	Received a wrong vaccine, or a major wrong dose of the assigned vaccine

Abbreviations: IcEv = intercurrent event; ILI = influenza-like illness; IP = investigational product; PP = Per-Protocol; RT-PCR = reverse transcription polymerase chain reaction; SoA = schedule of activities.
Note: Some intercurrent events are not mutually exclusive, for example, InEv5.1 is a subset of InEv5.

Table 9: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for the PP Analysis

Objective: To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains	
Estimand Description	This estimand aims to evaluate rVE of mRNA-1010 vs active comparator, as measured by 100 x (1-HR), among participants without important protocol deviations that could impact efficacy, whether HR is the hazard ratio of mRNA-1010 vs active comparator of RT-PCR-confirmed protocol-defined ILI caused by influenza A or B strains beginning at least 14 days after study intervention.
Target Population	Adults aged ≥ 50 years who received the planned IP without any important protocol deviations that may impact the key or critical data.
Variable/Endpoint	First episode of RT-PCR-confirmed protocol-defined ILI, caused by any influenza A or B strains, beginning at least 14 days after the study intervention.
Treatment Conditions	Test: mRNA-1010 Reference: Active Comparator
Estimand Label	Primary Estimand 1
Population-Level Summary	rVE defined as 1-HR of mRNA-1010 vs active comparator HR is estimated via the Cox proportional model with the vaccination group as the independent variable, adjusted for the stratification factors (age group and influenza vaccination status in the previous season) used for the randomization.

Objective: To evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains	
Intercurrent Event Strategy	
IcEv1 (early discontinuation)	Hypothetical: censored at the time of discontinuation or death
IcEv2 (early infection)	Hypothetical: censored at the start date of the RT-PCR-confirmed protocol-defined ILI which starts <14 days after study intervention
IcEv3 (important violation of eligibility criteria)	Principal stratum
IcEv4 (alternative influenza vaccine)	Principal stratum
IcEv5 (prohibited medications)	Principal stratum
IcEv6.1 (no vaccination)	Principal stratum
IcEv6.2 (wrong vaccination)	Principal stratum
Rationale for Strategy(s)	This estimand aims to evaluate the efficacy effects of the study vaccines to prevent RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains in adults aged ≥50 years who receive the planned IP administration and comply with key protocol criteria. Hypothetical: early discontinuation (including unrelated death) will be censored at time of discontinuation (or at time of death), and early infection will be censored at the time of infection onset, handled with independent censoring. A principal stratum strategy is used for any important violation of eligibility criteria or not receiving the assigned vaccination, as well as any use of nonstudy influenza vaccine or other prohibited medication with a potential significant impact on the immune response and efficacy experience. So the analysis is conducted in a subpopulation composed of participants free from these intercurrent events to evaluate the biologic effects of the study vaccines. A hypothetical strategy is used for early discontinuation and early RT-PCR-confirmed protocol-defined ILI before Day 14 to evaluate the vaccine efficacy in the hypothetical scenarios that these events had not occurred, because either the event status would be unknow or the study vaccines have not taken effects within the 14-day incubation period. The independent censoring method will be applied because the vaccine efficacy generally cannot be perceived at an individual level but can only be evaluated with immunogenicity assay or at a population as a (relative) vaccine efficacy. Therefore, the occurrence of these event are considered unrelated to the vaccine efficacy effects.

Abbreviation: HR = hazard ratio; IcEv = intercurrent event; ILI = influenza-like illness; PP = Per-Protocol; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy.
Note: Some intercurrent events are not mutually exclusive, for example, InEv5.1 is a subset of InEv5.

9.4.6. Subgroup Analyses

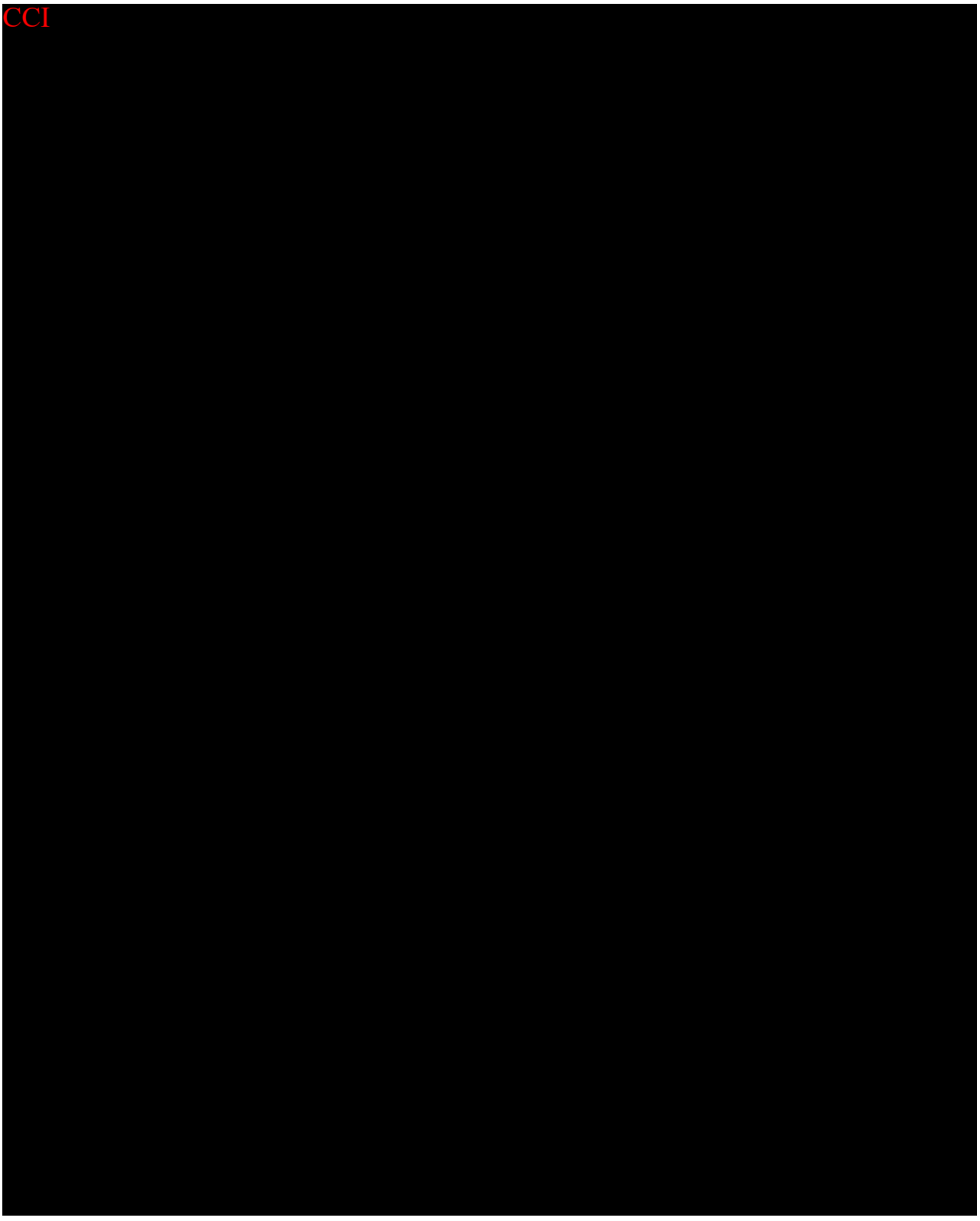
If sufficient case numbers of the primary endpoint in a subgroup (eg, age group, sex, race) are available, subgroup analysis may be performed.

9.5. CCI

CCI

CCI

Figure 2: CCI



9.6. Sample Size Determination

Sample size is driven by the total number of cases to demonstrate NI in terms of rVE (mRNA-1010 vs active comparator) to prevent the first episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study intervention caused by any influenza A or B strains.

Under the assumption of proportional hazards and with 1:1 randomization of mRNA-1010 and active comparator, a total of CCI in the PP Set will provide at least CCI power to establish an NI claim with a selected CCI assuming a true rVE of 10% using a log-rank test statistic with an overall 1-sided Type I error rate of 2.5%. Approximately 56,000 participants are needed to accrue CCI

The calculations were performed with the following additional assumptions:

CCI

Once NI is demonstrated, at the IA or final analysis, the rVE of mRNA-1010 versus the active comparator to prevent RT-PCR-confirmed protocol-defined ILI will be evaluated using the same endpoint for superiority. After superiority is demonstrated, at the IA or final analysis, the rVE will be further evaluated using the same endpoint for super-superiority of mRNA-1010 versus the active comparator with a super-superiority margin of CCI

Following the hierarchical testing procedure described in Figure 2, the NI, superiority and super-superiority hypotheses will be tested for the 2 secondary efficacy endpoints, as appropriate. CCI

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

A sample size reassessment may be performed at the IA using the promising zone method (Mehta and Pocock 2011) based on conditional powers with weighted test statistic for analysis (Cui et al 1999). Sample size increase to target CCI final analysis power up to a maximum of CCI the planned sample size (i.e. totally CCI) will be enabled when the conditional power lands in a promising zone: CCI The conditional powers for NI, superiority,

and super-superiority are calculated as the predictive probability of meeting the final analysis success criteria, i.e. 1-sided *p-value* for NI, superiority, and super-superiority, respectively, is less than the adjusted alpha level, given the efficacy data observed at IA, assuming the same data trend for the remaining observations (Mehta and Pocock 2011).

The DSMB will provide the conditional power ranges to the Sponsor. The Sponsor will have the responsibility for the decision of further enrollment. Details regarding decision of further enrollment will be provided in the SAP.

9.7. Planned Analyses

One IA and 1 final analysis are planned.

- The IA will be performed as described in Section 9.7.1.
- The final analysis is planned when all participants have completed the Month 6 (Day 181) Visit or End of the Influenza Season Visit, whichever is later.

9.7.1. Interim Analysis

An interim rVE analysis is planned at the end of the first influenza season (refer to Section 4.4.1) when approximately CCI of target cases are expected to have accrued in the PP Set. This IA may occur before the end of the first influenza season, when at least CCI of target cases have been accrued. If an IA is conducted before the end of the first season, a supportive analysis will also be performed at the end of the first season.

The purposes of the IA include: 1) Early detection of evidence of noninferiority and superiority in the rVE of mRNA-1010 versus the active comparator to prevent RT-PCR-confirmed protocol-defined ILI; 2) Sample size reassessment to enable a sample size increase in the second season to accrue up to a maximum of CCI the planned number of cases (total CCI), if the NI objective or the superiority or the super-superiority is not achieved at IA.

CCI

Under any of the above scenarios, the Sponsor will ultimately be responsible for the decision on further enrollment for the second season, including potential sample size expansion to up to CCI CCI of the original planned sample size when the conditional power lands in the CCI

CCI range. When the primary NI objective is achieved at IA, the Sponsor has the option of completing the study without further enrollment.

For the IA, the CCI will be used to preserve the 1-sided 2.5% Type 1 error rate over the IA and the final analysis. The alpha level is CCI at both the IA and the final analysis if the IA is performed with exactly CCI of the total planned cases. The actual alpha will be adjusted based on the actual information fraction calculated as the actual number of cases accrued in the PP Set across both arms divided by the total number of planned cases CCI The planned information fraction, number of cases and operating characteristics for the NI hypothesis testing at the IA and the final analysis are summarized in Table 10.

Table 10: CCI

CCI

Once NI is demonstrated at the IA, the superiority hypothesis CCI CCI will be tested in the PP Set using the same adjusted alpha level. If superiority is demonstrated at IA, the super-superiority hypothesis CCI CCI will be tested in the PP Set using the same adjusted alpha level. If NI is demonstrated at the IA, but superiority is not, superiority testing may be conducted again at the final analysis.

Similarly, the hypothesis tests planned for the 2 secondary endpoints will be conducted at IA, if NI, superiority and super-superiority for the primary endpoint have been achieved, according to the hierarchical testing order specified in Figure 2.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. 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 regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 Annex 1, Section D, No. 17, Letter a for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

The ICF will contain language that addresses the use of remaining samples for exploratory and future research. The Investigator or authorized designee will explain to each participant the objectives of exploratory and future research. Participants will be told that they are free to refuse to participate in the study and may withdraw their consent at any time and for any reason during the sample storage period.

10.1.4. Recruitment Strategy

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

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

10.1.5. Data Protection

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

- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

10.1.6.1. Data and Safety Monitoring Board

An independent DSMB will periodically review blinded and unblinded safety data at scheduled data review meetings. After each data review meeting, the DSMB will make recommendations to the Sponsor based on prespecified rules outlined in the DSMB charter.

- The DSMB will review the results of the IA.
- The Sponsor may also request that the DSMB conduct ad hoc reviews of safety events from this study or other data, including new nonclinical or clinical information related to mRNA-1010 external to this study.

The DSMB composition, its remit, and frequency of data review will be further defined in the DSMB charter and statistical analysis plan.

10.1.6.2. Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (Gargano et al 2021). The CDC Working Case Definitions are provided in Section 10.4 as guidance. 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 determine if additional action is needed. 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.

10.1.7. Dissemination of Clinical Study Data

The Sponsor shares the information about clinical trials and results on publicly accessible sites (which may include clinicaltrials.gov, euclinicaltrials.eu, and/or other national registries), based on international and local regulatory requirements, and other clinical trial disclosure commitments.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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 CRF.
- Guidance on completion of CRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

- Data recorded on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Declarations.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized study personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development.
- At the IA, the nonbinding futility rule was met (Section 9.7.1).

For site termination:

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

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

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory (FSH and highly sensitive serum hCG pregnancy tests) or by the local laboratory (highly sensitive urine hCG pregnancy tests).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Investigators must document their review of each laboratory report.

Table 11: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters
Pregnancy Testing	• Highly sensitive urine hCG pregnancy test (as needed for POCBP)[a]
Other Screening Tests	• FSH (at the discretion of the Investigator, to confirm postmenopausal status)

Abbreviations: FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; IEC = independent ethics committee; IRB = institutional review board; POCBP = person of childbearing potential.

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

10.3. Appendix 3: Safety Appendix

10.3.1. SAE Reports

When EDC is unavailable, SAE reports should be emailed to drugsafety@modernatx.com.

10.3.2. Pregnancy Forms

Pregnancy forms should be emailed to drugsafety@modernatx.com.

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

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 12 as guidance.

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

Condition	Definition	
	Probable case	**Confirmed case**
Acute myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms:[a] • 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:[a] • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.
	AND ≥1 new finding of • Troponin level above ULN (any type of troponin). • Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis.[c] • Abnormal cardiac function or wall motion abnormalities on echocardiogram. • cMRI findings consistent with myocarditis.[d]	**AND** ≥1 new finding of • Histopathologic confirmation of myocarditis.[b] • cMRI findings consistent with myocarditis[d] in the presence of troponin level above ULN (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[e]	Presence of ≥2 new or worsening of the following clinical features: • Acute chest pain.[f] • Pericardial rub on exam. • New ST-elevation or PR-depression on EKG. • New or worsening pericardial effusion on echocardiogram or MRI.	
Myopericarditis	This term may be used for participants who meet criteria for both myocarditis and pericarditis.	

Abbreviations: AV = atrioventricular; CDC = US Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Note: An independent CEAC will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events as described in Section 10.1.6.2.

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

b. 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.

c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least 1 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.

d. Using either the original or the revised Lake Louise criteria. https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihub

e. https://academic.oup.com/eurheartj/article/36/42/2921/2293375

f. 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).

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

The definitions below are in reference to biologically female participants only, not female partners (nonparticipants) of biologically male participants. Biologically male participants are not required to use any form of birth control per protocol.

Person of Childbearing Potential (POCBP)

Participants in the following categories who can become pregnant are considered POCBPs (fertile):

- Following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see PONCBP definition, below).

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

Person of Nonchildbearing Potential (PONCBP)

Participants in the following categories are considered PONCBPs:

- Premenopausal participant with permanent infertility due to one of the following:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - Documented bilateral oophorectomy.
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

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

- Postmenopausal participant
  - 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 participants not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Participants on HRT and whose menopausal status is in doubt will be required to use 1 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.

10.5.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• IUD
• IUS[c]
• Bilateral tubal occlusion/ligation
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] - Oral - Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from reproductive sexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

Abbreviations: IUD = Intrauterine device; IUS = Intrauterine hormone-releasing system; LAM = lactational amenorrhea method; POCBP = person of childbearing potential.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure from friction).

[a.] Contraceptive should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b.] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c.] Use of external condoms in addition to hormonal contraception is recommended. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

10.6. Appendix 6: Country-specific Requirements

Amendment KOR-1 is considered nonsubstantial because it neither impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Rationale for the Amendment KOR-1

This amendment incorporates requested changes from the South Korean Ministry of Food and Drug Safety to the original protocol. The Summary of Changes table describes the Exclusion criteria changes to be followed in this amendment KOR-1. The table below includes the sections modified and the corresponding rationale.

Section No. and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria No. 23	Participants in a clinical study with investigational treatment within **6 months** prior to Day 1 (Baseline) based on the medical history interview or plans to do so while participating in this study.	Request from the South Korean Ministry of Food and Drug Safety
5.2 Exclusion Criteria No. 25	Participants who reside in a collective facility (eg, elderly welfare facility).	Request from the South Korean Ministry of Food and Drug Safety
7.1 Discontinuation of Study Intervention	Added clarification that no early termination/suspension criteria are planned.	Request from the South Korean Ministry of Food and Drug Safety

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