CLINICAL STUDY PROTOCOL

Protocol Title:

A Phase 2, randomized, active-controlled, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

Protocol Number: mRNA-CRID-004

Date: 12 Apr 2023

Compound: mRNA-1010 variations

Brief Title:

Study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

Study Phase: Phase 2

Sponsor Name:

ModernaTX, Inc.

Legal Registered Address:

200 Technology Square

Cambridge, MA 02139

Regulatory Agency Identifier Number(s):

Registry	ID
FDA	IND 028259

Approval Date: 12-Apr-2023

Sponsor Signatory:

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

PPD

Date

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2, randomized, active-controlled, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age" dated 12 Apr 2023 and the most recent version of the mRNA-1010 IB.

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

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staff and members of the IRB/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

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Definition
AE	adverse event
AESI	adverse events of special interest
AFAB	assigned female at birth
AR	adverse reaction
AxMP	auxiliary medicinal products
BMI	body mass index
C	clinic
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
D	day
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EKG	electrocardiogram
EoS	end-of-study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator’s Brochure

Abbreviation or Specialist Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IM	intramuscular(ly)
IMP	investigational medicinal product
IRB	institutional review board
IST	internal safety team
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LTFU	lost to follow-up
M	month
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NH	Northern Hemisphere
NIMP	noninvestigational medicinal product
NP	nasopharyngeal
POCBP	person of childbearing potential
PONCBP	person of nonchildbearing potential
PP	per protocol
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	safety call
SoA	Schedule of Assessments
ULOQ	upper limit of quantification
USV	unscheduled visit
UTR	untranslated region
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 2, randomized, active-controlled, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

Brief Title:

Study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

Regulatory Agency Identifier Number:

Registry	ID
FDA	IND 028259

Rationale:

The aim of this Phase 2 study is to identify common or unique adaptive and innate immune signals or inflammatory biomarkers with predictive value for mRNA vaccine-induced immunogenicity and/or reactogenicity to support the Sponsor's mRNA-based vaccine platform and mRNA-1010 vaccine development. This study will be performed in an exploratory manner CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1010 vaccine candidate variations.	• Solicited local and systemic ARs through 7 days after study intervention. • Unsolicited AEs through 28 days after study intervention. • Medically attended AEs from Day 1 to EoS. • AESIs from Day 1 to EoS. • SAEs from Day 1 to EoS. • AEs leading to study or treatment discontinuation from Day 1 to EoS.

Objectives	Endpoints
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 vaccine candidate variations at evaluable humoral immunogenicity timepoints.	• GMT at indicated timepoints as measured by HAI assay. • GMFR, comparing each timepoint with D1 (Baseline) as measured by HAI assay. • Percentage of participants with seroresponsea for mRNA-1010 at indicated timepoints, as measured by HAI assay.
CCI [redacted]	

Abbreviations: AE=adverse event; AESI=adverse events of special interest; AR=adverse reaction; D=day; EoS=end-of-study; GMFR=geometric mean fold rise; GMT=geometric mean titer; HAI=hemagglutination inhibition; LLOQ=lower limit of quantification; SAE=serious adverse event.

a. Vaccine seroresponse is defined as an increase of antibody titers and concentrations from predose below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if predose is ≥LLOQ.

Overall Design Synopsis:

This will be a randomized, observer-blind, Phase 2 study to evaluate the safety, reactogenicity and immunogenicity of mRNA-1010 vaccine candidate variations using a systems biology approach in healthy adults 18 to 49 years of age.

Approximately 270 participants will be randomly assigned in a ratio of 2:1:2:1:1:2 to one of 6 study arms to receive one of the following treatments:

- mRNA-1010 at 1 dose level CCI [redacted] administered as a single dose.
- mRNA-1010.4 at 1 of 2 dose levels CCI [redacted] administered as a single dose.
- mRNA-1010.6 at 1 of 3 dose levels CCI [redacted] administered as a single dose.

CCI [redacted]

Enrollment in the study arms will proceed in parallel.

Except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors, all personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding or EoS.

Safety monitoring for this study will include the blinded study team members, including, at least, the Sponsor Medical Monitor, a CRO Medical Monitor, and an unblinded IST. The unblinded IST will comprise 3 members who are not directly involved in the conduct of this study. The

study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the unblinded IST in case of potential safety signal events. Details regarding composition, responsibilities, and procedures of the IST will be presented in the IST charter.

An independent CEAC of medically qualified personnel, including cardiologists, will review all suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events which are reported in ongoing interventional clinical trials per the CEAC charter.

Brief Summary:

The study aims to identify common or unique adaptive and innate immune signals or inflammatory biomarkers with predictive value for immunogenicity and/or reactogenicity of mRNA-1010, mRNA-1010.4 and mRNA-1010.6 in healthy adult participants 18 to 49 years of age.

Study details include:

- Study visits for all participants will consist of a Screening Visit (up to 28 days before the D1 visit), a Study Intervention Visit at D1, and Clinic Visits CCI [redacted]
- All participants will be asked to complete an eDiary for solicited ARs for 7 days (ie, the day of study intervention dosing and 6 subsequent days).
- Frequent blood samples will be collected for the first 7 days to support the exploratory objective of the study.
- Collection of all AEs will be through 28 days after study intervention dosing (ie, the day of study intervention dosing and 27 subsequent days). Collection of MAAEs, AESI, SAEs, and AEs leading to discontinuation from study participation will continue through CCI [redacted]/EoS.

Number of Participants:

Approximately 270 participants will be enrolled.

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

Study Arms and Duration:

- The study will comprise 6 study arms.
- The total duration of study participation is up to 7 months from the Screening Visit.

1.2. Schema

Not Applicable.

1.3. Schedule of Activities

The SoA is listed in Table 1.

Table 1: Schedule of Activities

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
ICF, demographics, concomitant medications, medical history	X	X											
Inclusion/exclusion criteria	X	X											
Physical examination[d]	X	X											
Vital signs[e]	X	X											
Pregnancy testing[f]	X	X											
Blood for humoral immunogenicity[g]		X				X	X		X			X	

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI [redacted]											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI [redacted]											
CCI [redacted]													
NP swab for virus detection[h]		X											X
Randomization		X											
Study intervention (including 30-minute postdosing observation period)		X											
eDiary activation for recording solicited ARs (7 days)[i]		X											

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
Review of eDiary ARs[j]						X							
Follow-up safety calls[k]								X		X	X		
Unsolicited AEs[l]		X	X	X	X	X	X						
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
AESIs, MAAEs, and AEs leading to withdrawal from the study[m]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and nonstudy vaccinations[m]		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BMI=body mass index; C=clinic; COVID-19=coronavirus disease 2019; D=Day; EoS=end-of-study; eDiary=electronic diary; FDA=Food and Drug Administration; FSH=follicle-stimulating hormone; ICF=informed consent form; M=month; MAAE=medically attended AE; NA=not applicable; NP=nasopharyngeal; SAE=serious adverse event; SC=safety call; USV=unscheduled visit.

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

a. Participants may experience AEs that necessitate a USV. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study.
b. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window. If a participant returns for the D1 visit more than 28 days after their Screening Visit for any reason and continues to provide consent to participate in the study, the participant may be rescreened, for study eligibility. All assessments for eligibility must be repeated.
c. A blood draw will be collected at 6 hours post vaccine injection on D1.
d. A full physical examination, including height, weight, and BMI will be performed at Screening. Symptom-directed physical examinations may be performed at other timepoints at discretion of the Investigator. On each dosing day before injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.
e. Vital signs measurements: Systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once at least 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
f. A pregnancy test either via blood or point-of-care urine test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. 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.
g. D1 (Baseline) blood samples for CCI [redacted]
h. An NP swab specimen for viral respiratory pathogens will be collected prior to the study intervention administration on Day 1. At USVs participants with symptoms of respiratory tract infection may be tested by NP swab for respiratory viruses at the Investigator's discretion to include influenza, RSV and SARS-CoV-2, which may impact analyses of reactogenicity and immunogenicity.
i. eDiary entries will be recorded by the participant at approximately 30 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day, preferably in the evening and at the same time each day, on the day of vaccination and for 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution.
j. Solicited ARs recorded in the eDiaries that is ongoing beyond 7 days after injection will be followed up by the study site staff at the next scheduled telephone call or at the next study site visit. Any medication recorded in eDiaries that is taken to prevent or treat pain or fever will also be reviewed at this time.
k. Trained study personnel will call all participants to collect information relating to any MAAEs, AESIs, AEs leading to withdrawal from the study, SAEs, information on concomitant medications associated with those events; receipt of any nonstudy vaccinations; and receipt of any systemic steroids, immunosuppressive therapies (drugs or biologics), immunoglobulins, and/or blood products.
l. All unsolicited AEs will be recorded starting the day of each study intervention, and through 28 days following each study intervention.
m. All concomitant medications will be recorded through 28 days after vaccination. All concomitant medications relevant to or for the treatment of the SAE, AESI, MAAE, or AE leading to study withdrawal will be recorded from D1 through EoS. Any nonstudy vaccinations will be recorded from D1 through EoS.

2. INTRODUCTION

2.1. Study Rationale

The aim of this Phase 2 study is to identify common or unique adaptive and innate immune signals or inflammatory biomarkers with predictive value for mRNA vaccine-induced immunogenicity and/or reactogenicity to support the Sponsor's mRNA-based vaccine platform and mRNA-1010 vaccine development. CCI [redacted]

2.2. Background

ModernaTX, Inc. (the Sponsor) has developed a proprietary vaccine platform based on mRNA delivered through LNPs. The platform is based on the principle and observations that cells in vivo can take up LNP-encapsulated mRNA, translate it, and then express protein antigen(s) on the cell surface or secrete the antigens. The intracellularly delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Strongly encouraged by the successful development of its mRNA-based SARS-CoV-2 vaccine (mRNA-1273; Spikevax®), the Sponsor is currently using the mRNA/LNP-based vaccine delivery platform to develop vaccines against multiple viruses, including influenza (mRNA-1010), RSV (mRNA-1345), and cytomegalovirus (mRNA-1647).

mRNA-1010 is an LNP-encapsulated, mRNA-based, prophylactic vaccine containing 4 mRNAs in an equivalent mRNA mass ratio that encode membrane-bound HA of the 4 different influenza strains, recommended by the WHO for 2022-2023 NH cell or recombinant based vaccines. The Sponsor has completed a Phase 1/2 study of mRNA-1010 (NCT04956575) at dose levels up to CCI and is now conducting several Phase 3 studies at a CCI dose level (NCT05415462 and NCT05566639).

This study will evaluate several versions of the Sponsor's seasonal influenza mRNA vaccine candidate (mRNA-1010) that are currently being evaluated in separate clinical Phase 1/2 (mRNA-1083-P101) and Phase 3 development studies (mRNA-1010-P303) for their ability to further optimize the immunogenicity and tolerability of the mRNA-1010 vaccine. CCI [redacted]

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

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

There have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 vaccines, including mRNA vaccines. The majority

of the cases have been reported in adolescents and young males shortly 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 (including rest, NSAIDs, and/or colchicine). Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021). It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of other non-COVID mRNA vaccines.

Safety and reactogenicity data from multiple studies with mRNA-1010 (NCT04956575, NCT05415462, and NCT05566639) have revealed no safety concerns to date. Additional details are provided in the IB.

2.3.2. Benefit Assessment

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

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

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1010 vaccine candidate variations.	• Solicited local and systemic ARs through 7 days after study intervention. • Unsolicited AEs through 28 days after study intervention. • Medically attended AEs from Day 1 to EoS. • AESIs from Day 1 to EoS. • SAEs from Day 1 to EoS. • AEs leading to study or treatment discontinuation from Day 1 to EoS.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1010 vaccine candidate variations at evaluable humoral immunogenicity timepoints.	• GMT at indicated timepoints as measured by HAI assay. • GMFR, comparing each timepoint with D1 (Baseline) as measured by HAI assay. • Percentage of participants with seroresponsea for mRNA-1010 at indicated timepoints, as measured by HAI assay.
CCI [redacted]	

Abbreviations: AE=adverse event; AESI=adverse events of special interest; AR=adverse reaction; D=day; EoS=end-of-study; GMFR=geometric mean fold rise; GMT=geometric mean titer; HAI=hemagglutination inhibition; LLOQ=lower limit of quantification; SAE=serious adverse event.

a. Vaccine seroresponse is defined as an increase of antibody titers and concentrations from predose below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if predose is ≥LLOQ.

4. STUDY DESIGN

4.1. Overall Design

This will be a randomized, observer-blind, Phase 2 study to evaluate the safety, reactogenicity and immunogenicity of mRNA-1010 vaccine candidate variations using a systems biology approach in healthy adults 18 to 49 years of age.

Three mRNA-1010 vaccine candidate versions will be evaluated (Table 3):

- mRNA-1010: CCI [redacted]
- mRNA-1010.4: CCI [redacted]
- mRNA-1010.6: CCI [redacted]

CCI [redacted]

This study will initially enroll approximately 270 participants 18 to 49 years of age. Participants will be randomly assigned to study arms 1, 2, 3, 4, 5, and 6 in a ratio of 2:1:2:1:1:2 to receive a single dose of 1 of the 3 mRNA-1010 vaccine candidate variations (ie, mRNA-1010, mRNA-1010.4, or mRNA-1010.6). Randomization will be stratified by receipt of a 2022-2023 NH influenza vaccine (Yes/No). The different arms will include different dose levels for mRNA-1010.4 and mRNA-1010.6. See Table 4 for study arms and number of participants per study arm.

Except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors, all personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding.

Study visits for all participants will consist of a Screening Visit (up to 28 days before the D1 visit), a Study Intervention Visit at D1, and Clinic Visits CCI [redacted] The duration of study participation for all participants is up to 7 months from the Screening Visit. Refer to the SoA (Table 1), for more details.

Safety Oversight

Safety monitoring for this study will include the blinded study team members, including, at least, the Sponsor Medical Monitor, a CRO Medical Monitor, a Clinical Safety Physician, and an unblinded IST. The unblinded IST will comprise 3 members who are not directly involved in the conduct of this study. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the unblinded IST in case of potential safety signal events. Details regarding composition, responsibilities, and procedures of the IST will be presented in the IST charter.

An independent CEAC of medically qualified personnel, including cardiologists, will review all suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events which are reported in ongoing interventional clinical trials per the CEAC charter (Gargano et al 2021).

4.2. Scientific Rationale for Study Design

The study is designed as a randomized, observer-blind dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age. The randomized and observer-blind design will ensure unbiased collection of safety and immunogenicity data.

This study will evaluate several versions of the Sponsor's seasonal influenza mRNA vaccine candidate (mRNA-1010). CCI [redacted]

This study will be performed in an exploratory manner CCI [redacted]

4.3. Justification for Dose

Participants will receive either 1 dose level of mRNA-1010 CCI [redacted] 1 of 2 dose levels of mRNA-1010.4 CCI [redacted]); or 1 of 3 dose levels of mRNA-1010.6 CCI [redacted] administered on Day 1 (refer to Table 3).

The selected dose levels in this study are based on the observed reactogenicity and immunogenicity profiles in clinical Phase 1/2 and Phase 3 studies conducted with mRNA-1010

At least 15,000 adults have been dosed with mRNA-1010. No safety concerns were identified with mRNA-1010 dose levels up to CCI [redacted]

4.4. End-of-Study Definition

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

A participant is considered to have completed the study if he or she has completed all parts of the study, including the last visit or scheduled procedure as shown in the SoA (Table 1).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Adults 18 to 49 years of age at the time of consent (Screening Visit) who, in the opinion of the Investigator, are in good health based on review of medical history and physical examination performed at screening.

Sex and Contraceptive/Barrier Requirements

2. A participant AFAB is eligible to participate if not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a PONCBP as defined in Clinical Study Protocol, Appendix 4.

     OR

   - Is a POCBP and using an acceptable contraceptive method as described in Appendix 4 at least 28 days before the dose of study intervention and for at least 3 months after the dose of study intervention. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the dose of study intervention.

     A POCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at the Screening Visit and again before the dose of study intervention if Day 1 is not on the same day as the Screening Visit (see Section 8.3.3).

     - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. If the serum pregnancy result is positive, the participant must be excluded from participation.

     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.

Informed Consent

3. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
4. Participant has provided written informed consent for participation in this study, including all evaluations and procedures as specified in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

5. Participant has had close contact with someone with laboratory-confirmed influenza infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu®) within the past 5 days prior to D1.
6. Participant has tested positive for influenza by local health authority-approved testing methods within 150 days prior to D1.
7. Is acutely ill or febrile (temperature ≥38.0°C/100.4°F) within 72 hours prior to or at the Screening Visit or D1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
8. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
9. Asymptomatic conditions and conditions with no evidence of end-organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time-course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, because of immunosuppressive therapies (drugs or biologics) used to treat them, at the discretion of the Investigator.
    - Participants who have undergone surgical procedures within 7 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study injection are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
10. Any medical, psychiatric, or occupational condition, including reported history of substance abuse, that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the Investigator's judgment.
11. Has a current or previous diagnosis of congenital or acquired immunodeficiency, to include HIV, immunosuppressive condition or immune-mediated (autoimmune) disease, asplenia, or recurrent severe infections, that requires treatment with systemic immunosuppressive drugs or biologics. Participants who use topical corticosteroids or other immunosuppressive agents (eg, topical calcineurin inhibitor) may be eligible for participation at the discretion of the Investigator.
12. History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of mRNA vaccines or any components of the mRNA-1010 or influenza vaccines, including egg protein.

13. Any history of myocarditis or pericarditis.
14. Reported history of coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.
15. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
16. Diagnosis of malignancy within the previous 2 years (excluding nonmelanoma skin cancer).
17. History of Guillain-Barre syndrome.

Prior/Concomitant Therapy

18. Has received systemic immunosuppressive therapy (drugs or biologics) for more than 14 days within 180 days prior to Screening (for corticosteroids ≥10 mg/day of prednisone equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled, nasal, and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study intervention dosing.
19. Has received or plans to receive any licensed/authorized vaccine (to include SARS-CoV-2 vaccine) ≤28 days prior to or within 28 days after study intervention.
20. Has received a licensed seasonal influenza vaccine within 5 months (150 days) prior to D1.
21. Has participated in any investigational seasonal influenza vaccine study within 12 months prior to D1.
22. Is not aware of having received a seasonal influenza vaccine in the most recent influenza season (in the prior 12 months).
23. Has been treated with antiviral therapies for influenza (eg, Tamiflu®) within 150 days prior to D1.
24. Has received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or plans to receive the treatment during the study. In addition, participants who have received long-acting biological therapies that affect immune responses (eg, infliximab) within 90 days prior to the Screening Visit/Day 1, or plan to receive them, are also excluded.

Prior/Concurrent Clinical Study Experience

25. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
26. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to participate in an interventional clinical trial of an investigational vaccine or drug while participating in this study.

Other Exclusion Criteria

27. Is working or has worked as study personnel or is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 once if they will be eligible upon rescreening.

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Body temperature (oral temperature preferred) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may receive the study intervention at a later date, or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7.1):

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

Participants with a minor illness without fever, as assessed by the Investigator, can be vaccinated.

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

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1. Study Interventions Administered

The study interventions administered are listed in Table 3.

Table 3: Study Interventions Administered

Intervention Label	**mRNA-1010**	**mRNA-1010.4**	**mRNA-1010.6**
Intervention Description	LNP dispersion encoding 4 seasonal influenza vaccine antigens, HAs, from the influenza strains recommended by the WHO for 2022-2023 NH cell- or recombinant-based influenza vaccines. All mRNAs are formulated in LNPs composed of 4 lipids and provided as a sterile liquid for injection, white to off white dispersion in appearance, in Tris buffer with sucrose, and sodium acetate at pH 7.5.		
Type	Vaccine		
Appearance	White to off-white dispersion for injection		
Dosage Strengths	CCI [redacted] Single Dose	CCI [redacted] CCI [redacted] Single Dose	CCI [redacted] CCI [redacted] CCI [redacted] Single Dose
Route of Administration	IM Injection		
Use	Experimental		
IMP and NIMP/AxMP	IMP		
Packaging and Labeling	All study interventions will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.		

Abbreviations: AxMP=auxiliary medicinal products; CFR=code of federal regulation; GCP=good clinical practice: GMP=good manufacturing practice; HA=hemagglutinin; ICH=International Council for Harmonisation; IM=intramuscular; IMP=investigational medicinal product; LNP=lipid nanoparticles; NH=Northern Hemisphere; NIMP=noninvestigational medicinal product.

Study Arms and Dosing Regimens

The study arms and dosing regimens are listed in Table 4.

Table 4: Study Arms and Dosing Regimens

Study Arm	Group Name	Antigens	Dose (Total)	N (Total)	Dose Schedule
1	mRNA-1010 (Single dose)	Influenza HA, quadrivalent for NH	CCI	60	D1
2	mRNA-1010.4 (Single dose)			30	D1
3	mRNA-1010.4 (Single dose)			60	D1
4	mRNA-1010.6 (Single dose)			30	D1
5	mRNA-1010.6 (Single dose)			30	D1
6	mRNA-1010.6 (Single dose)			60	D1

Abbreviations: D=day; HA=hemagglutinin; mRNA=messenger ribonucleic acid; N=number; NH=Northern Hemisphere.

6.2. Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

   Note: *Enrolled* means participants', or their legally acceptable representatives', agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed as summarized in the SoA (Table 1).

Returned study intervention should not be redispensed to the participants.

6.4. Blinding

Refer to Section 9.1 for additional details on blinding.

This is an observer-blinded study. Except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors, all personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding or EoS.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' 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, at the Investigator's discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's 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 intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report identifying the participant's intervention assignment may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.5. Study Intervention Compliance

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

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

6.6. Dose Modification

No dose modifications are allowed.

6.7. Continued Access to Study Intervention after End-of-Study

There will be no access to study intervention after EoS.

6.8. Treatment of Overdose

Because the study intervention is to be administered by a healthcare provider, it is unlikely that an overdose will occur.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the last safety follow-up visit.
- Report any signs or symptoms associated with the overdose as an AE and record details in the relevant AE/SAE sections in the eCRF.
- Document the quantity of the excess dose in the eCRF.

Dose deviations will be tracked as protocol deviations.

6.9. Prior and Concomitant Therapy

Prior Medications and Therapies

The following prior medications and therapies must be recorded in the eCRF:

- All prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent.
- Any licensed seasonal influenza vaccine administered in the prior 12 months.
- Any licensed/authorized or investigational COVID-19 vaccine administered at any time before study intervention administration.
- Any investigational influenza or RSV vaccine administered at any time before study intervention administration.

6.9.1. Concomitant Medications and Therapies

At each study visit (including SCs), study site staff must question the participant regarding any medications taken and nonstudy vaccinations received by the participant and record the following information in the eCRF along with the reason for use, dates of administration including start and end dates and dosage information including dose and frequency:

- All concomitant medications administered through 28 days (the day of study vaccination and the subsequent 27 days) after study vaccine administration. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- All nonstudy vaccinations administered from Screening through EoS.
- Systemic steroids, immunosuppressive therapy (drugs or biologics), immunoglobulins, and/or blood products administered from Screening through EoS.
- Any concomitant medications or vaccines relevant to or for the treatment of an AESI, MAAE, or AE leading to study or treatment discontinuation will be recorded from the first dose at Day 1 through the EoS.
- Any concomitant medications or vaccines relevant to or for the treatment of a SAE will be recorded from the signing of ICF through the EoS.

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

The participant will be asked in the eDiary if they have taken any antipyretic or analgesic medication to treat or prevent fever or pain within 7 days after the study vaccination, including the days of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the study visits after vaccination or via other participant interactions (eg, telephone calls).

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

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

All medication and interventions necessary for the appropriate care of the study participant should be administered and appropriately documented along with the AE for which the treatment was initiated.

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

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

- Any investigational or nonregistered product (drug or vaccine) other than the study vaccine used during the study period.
- Systemic immunosuppressive therapy (drugs or biologics) administered chronically (ie, more than 14 days in total) during the study period. For glucocorticosteroids, this will mean that prednisone ≥10 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed. Intra-articular and epidural steroid injections within 28 days after study intervention dosing.
- An authorized or licensed vaccine, including SARS-CoV-2 vaccine, administered 28 days before and after study intervention.

- Long-acting immunosuppressive therapy (drugs or biologics) administered at any time during the study period (eg, infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

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

Not applicable.

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).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1). See the SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- A participant who withdraws from the study will not be replaced.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit foreseen in the protocol. All data collected until the date of withdrawal or last contact of the participant will be used for the analysis. A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Information relative to the withdrawal will be documented in the 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.
- SAR/reactogenicity.

- Death.
- LTFU.
- Noncompliance with study procedures.
- Physician decision.
- Pregnancy.
- Protocol deviation.
- Screen failure.
- Study terminated by Sponsor.
- Withdrawal by participant.
- Other.

Participants who are withdrawn from the study because of an AE (including SAE, MAAE and AESI) or SAR/Reactogenicity event 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 AE/SAE/AESI/MAAE or SAR/reactogenicity event until resolution of the event.

7.3. Lost to Follow-up

If a participant does not complete a visit within the time window specified in the SoA (Table 1), every effort should still be made to complete the assessments for that visit (even though outside of the defined visit window); the participant will continue with subsequent scheduled study visits per their original schedule (ie, relative to their Day 1 visit). If a participant still does not complete the visit after all these efforts, the visit will be classified as missed and all safety requirements of the missed visit will be captured and included in the subsequent visit.

A participant will be considered LTFU if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

- A participant should be not considered LTFU until due diligence has been completed.

7.4. Pause Rules

Not applicable.

8. STUDY ASSESSMENTS AND PROCEDURES

- Before performing any study procedures, all potential participants will sign an ICF (Section 10.1.3).
- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- Study results that could unblind the study will not be reported to investigative sites or other blinded 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.
- If a visit cannot be scheduled within the indicated allowable window and/or the participant misses the visit, this is considered a protocol deviation. However, the visit should still be completed, if possible, to collect study data. Subsequent visits should be scheduled at the originally planned number of days after D1 defined in the SoA (Table 1).

8.1. Demography

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

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

8.2. Immunogenicity Assessments

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

- Vaccine-specific humoral immune responses, including serum antibody levels as measured by the HAI assay. CCI [redacted]
- CCI [redacted]

8.3. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant (see the SoA [Table 1] for details):

- Solicited local and systemic ARs that occur during the 7 days following vaccine administration (ie, the day of study injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each vaccine administration (ie, the day of study injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AESIs, MAAEs, and AEs leading to discontinuation from study participation from D1 (poststudy intervention dosing) through EoS or discontinuation from the study.
- SAEs from the signing of ICF through EoS or discontinuation from the study.
- Vital sign measurements before and after study injection.
- Physical examination findings.
- Occurrences of pregnancy in participants will be collected after the start of study intervention and until the end of their participation in the study. All pregnancies must be followed to end of pregnancy. Pregnancy details and outcome data are to be collected beyond EoS, when required (ie, for pregnancies continuing beyond the EoS visit).
- Concomitant medications and nonstudy vaccinations.

8.3.1. Physical Examinations

- Physical examination including height, weight, and BMI will be performed at the timepoints indicated in the SoA (Table 1).
- A full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and

musculoskeletal system and extremities. Height and weight will also be measured and recorded as outlined in the SoA (Table 1).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- On the day of study intervention administration, before administration, the arm receiving the injection should be examined, and the associated lymph node(s) should be evaluated.

8.3.2. Vital Signs

- Vital signs will be measured at the timepoints indicated in the SoA (Table 1).
- Vital sign measurements include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (oral being the preferred route).
- The participant will be seated for at least 5 minutes before all measurements are taken.
- On study intervention day, vital sign measurements will be collected once before study vaccine injection and at least 30 minutes after study vaccine injection (before participants are discharged from the study site). If vital signs are clinically concerning, participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection.
- Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.
- Participants who are febrile (fever is defined as a body temperature ≥38.0°C/100.4°F) before injection on dosing day must be rescheduled. Criteria for delay of study vaccine are provided in Section 5.4. Participants who are afebrile with minor illnesses may be injected at the discretion of the Investigator. If fever is clinically concerning, participant should not be dosed.
- Abnormal vital sign measurements should be assessed by the Investigator to determine clinical significance and whether it should be reported as an AE. The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at Baseline, is considered stable, or until the Investigator determines that follow-up is no longer medically necessary.

8.3.3. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted for all POCBP at the Screening Visit and before study intervention dosing on Day 1, if Day 1 is not at the same day as the Screening Visit (Table 1).
- The FSH level may be measured at the Screening Visit as necessary, and at the discretion of the Investigator, to confirm postmenopausal status (Table 1).

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.4. Assessments for Respiratory Viral Infections

NP swab specimen(s) for viral respiratory pathogens will be collected prior to study intervention dosing on Day 1. At USVs participants with symptoms of respiratory tract infection may be tested by NP swab for respiratory viruses at the Investigator's discretion, to include influenza, RSV and SARS-CoV-2, which may impact analyses of reactogenicity and immunogenicity.

8.3.5. Safety Calls

An SC is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. SCs will follow a schedule for each participant, as shown in the SoA (Table 1). The participant will be interviewed according to the script about occurrence of MAAEs, SAEs, AESIs, AEs leading to withdrawal from the study, and concomitant medications associated with those events; receipt of any nonstudy vaccinations, and receipt of any systemic steroids, immunosuppressive therapy (drugs or biologics), immunoglobulins, and/or blood products. All safety information collected from the telephone call must be documented in the source documents as described by the participant and not documented on the script used for the telephone call. An unscheduled follow-up SC may be triggered if an eDiary record results in identification of a relevant safety event. An SC may trigger a USV.

8.3.6. Use of Electronic Diaries

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

Solicited local and systemic reactogenicity ARs will be collected on the day of each study intervention and during the 7 days after study intervention (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.4.6.

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

At each dosing visit, participants will be instructed or reminded on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) side as the injection arm during the 7 days after study intervention. Daily oral temperature measurement should be performed at approximately the same time each day using the thermometer provided by the site staff.

The participant will be trained on how to complete the eDiary questions according to the SoA (Table 1) and also reminded to call the site immediately if they experience any new signs or symptoms.

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

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator and any qualified designees shall be responsible for following up all AEs or SAEs or that caused the participant to discontinue the study intervention or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

All SAEs will be collected from the signing of ICF until the last day of study participation at the timepoints specified in the SoA (Table 1).

All, AESIs, MAAEs, and AEs leading to withdrawal from the study will be collected from the start of study intervention until the last day of study participation at the timepoints specified in the SoA (Table 1).

All other (unsolicited) AEs will be collected from the time of the administration of study vaccination through 28 days (the day of study vaccination and the subsequent 27 days) (see the SoA [Table 1]).

Solicited ARs will be collected during the solicited period, for 7 days (the day of study vaccination and the subsequent 6 days).

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

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.5. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE 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.

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 10.3.2 and Section 10.3.4, respectively) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.3), even if the event continues beyond the participant's EoS visit. Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB 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 investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB for investigational product 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.

8.4.5. Pregnancy

- The effects of the study intervention on the unborn child and/or newborn baby are not known. Therefore, is important that study participants are not pregnant and do not become pregnant during the study.
- Pregnancy testing is scheduled to occur at the Screening Visit and Day 1, if Day 1 is not at the same day as the Screening Visit (Table 1). Participants who have a positive pregnancy test at the Screening Visit must not be enrolled and participants who have a positive pregnancy test at Day 1 must not receive the study intervention. Additional pregnancy testing may also be performed at any time during the study if required by local regulatory requirements, or at the discretion of the Investigator.
- Details of all pregnancies in participants will be collected after the start of study intervention and until the end of their participation in the study.
- 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 pregnancy.
- Participants who have a positive pregnancy test after receiving study intervention should remain in the study and be followed-up for safety.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (refer to Section 10.3).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 10.3).
- The participant will be followed to determine the outcome of the pregnancy. General pregnancy and outcome data may be collected beyond EoS (ie, for pregnancies continuing beyond EoS visit).

8.4.6. Solicited Adverse Reactions

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

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Appendix 3 (Section 10.3.5), which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

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

- Solicited local or systemic ARs that were not recorded in the eDiary but reported to the study site/Investigator and is Grade 1 or greater.
- Solicited local or systemic AR that results in a visit to a healthcare practitioner including USVs at the study site (MAAE).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (AE leading to discontinuation).
- Solicited local or systemic AR lasting beyond 7 days postinjection.
- Solicited local or systemic AR that leads to participant discontinuation from study intervention.
- Solicited local or systemic AR that otherwise meets the definition of an SAE (Section 10.3.2).

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

If the event starts during the solicited period, but continues beyond 7 days after dosing, the participants should notify the site to provide an end date and close out the event in the EDC where reactogenicity is collected.

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

8.4.7. Medically Attended Adverse Events

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

8.4.8. Adverse Events of Special Interest

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

AESI for this protocol are listed in Appendix 5.

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in Appendix 3.

8.4.8.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as AESIs and reported as an SAE (Appendix 3), 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 multiorgan 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.

8.4.8.2. Myocarditis and/or Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI per Investigator's medical assessment, even if it does not meet criteria per the CDC case definition below. The event should also be reported as an SAE if it meets seriousness criteria (Section 10.3.2).

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, EKG, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition (Table 9) should promptly be obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be obtained 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. Participants with events of

myocarditis and/or pericarditis will be discontinued from further vaccination but should continue to be followed in the study for safety as per the protocol.

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis which are reported in ongoing interventional clinical trials per the CEAC charter to determine if they meet CDC criteria for "probable" or "confirmed" events. (Section 10.1.6.2).

The CDC Working Case Definitions are provided in Appendix 6 as guidance.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

CCI [redacted]

8.8. Biomarkers

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

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 clinical database lock for the study and treatment unblinding. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

9.1. Blinding and Responsibility for Analyses

Blinding during the study will be conducted as described in Section 6.4, with the following exceptions:

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded study site staff will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned primary analysis and the IA (Section 9.6.1). Sponsor team members will be unblinded for the primary analysis and the IA results and will not communicate the results to the blinded Investigators, study site staff, clinical monitors, or participants.
- The IST may review unblinded data, as appropriate, to safeguard the interests of clinical study participants and to help ensure the integrity of the study.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the study intervention in a secure location that is not accessible or visible to other study site staff. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study site staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

The procedure for breaking the blind in the case of a medical emergency is provided in Section 6.4.

9.2. Statistical Hypotheses

No formal hypotheses will be tested in this study.

9.3. Sample Size Determination

As there will be no hypothesis testing in this study, the number of proposed participants in Section 4.1 is considered sufficient to provide a descriptive summary of the safety, reactogenicity, and immunogenicity of the mRNA-1010 vaccine product variables.

With 60 participants in the CCI study arms, there is an approximately 95% probability to observe at least 1 participant with an AE if the true incidence of the AE is 5%; if the true incidence rate is 3%, then the probability to observe an AE is approximately 84%.

With 30 participants in the CCI [redacted] study arms, there is an approximately 95% probability to observe at least 1 participant with an AE if the true incidence of the AE is 9.5%; if the true incidence rate is 7.5%, then the probability to observe an AE is approximately 90%.

9.4. Analysis Sets

Analysis sets are listed in Table 5.

Table 5: Analysis Sets

Participant Analysis Set	Description
Randomization Analysis Set	The Randomization Analysis Set consists of all participants who are randomized.
FAS	The FAS consists of all randomized participants who receive the study intervention. Participants will be included in the study arm to which the participant is randomized.
PPS for Immunogenicity	The PPS consists of all participants in the FAS who comply with the injection schedule, comply with the timing of immunogenicity blood sampling to have a Baseline (D1) and at least 1 postinjection assessment, and have no major protocol deviations which impact the immune response. The PPS will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified.
Safety Set	Safety Set consists of all participants who receive one dose of study intervention. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the study arm corresponding to the study intervention that they actually received.
Solicited Safety Set	The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the treatment group corresponding to the study intervention that they actually received.

Abbreviation: AR=adverse reaction; D=day; FAS=full analysis set; PPS=per protocol set.

9.5. Statistical Analyses

The SAP for the primary and secondary endpoints will be developed and finalized before database lock and will describe the preplanned statistical analysis details, data derivations, the

participant populations to be included in the analyses, and procedures for accounting for missing data.

9.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, sex, race, ethnicity, height, weight, and BMI) and Baseline characteristics will be summarized by injection group and overall.

Summary statistics (mean and standard deviation for continuous variables, and number and percentage for categorical variables) will be provided.

9.5.2. Immunogenicity Analyses

The analyses of immunogenicity will be based on the PPS. If the number of participants in the FAS and PPS differ (defined as the difference divided by the total number of participants in the PPS) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS. All immunogenicity analyses will be provided by study arm, at each timepoint unless otherwise specified.

For the immunogenicity endpoints, the GM of antibody titers as measured by HAI assay with corresponding 95% CI at each timepoint will be provided by study arm. The GMFR of antibody titers as measured by HAI assay with corresponding 95% CI at each postdose timepoint over predose (D1) will be provided by study arm. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back-transformed to the original scale. Descriptive summary statistics, including median, minimum, and maximum will also be provided. For calculation of GMTs reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the ULOQ will be converted to the ULOQ.

Vaccine seroresponse rate will be provided with a 2-sided 95% CI using the Clopper-Pearson method by study arm. Vaccine seroresponse is defined as an increase of neutralizing antibody titers from predose below the LLOQ to ≥4 × LLOQ or at least a 4-fold rise if predose is ≥LLOQ. The number and percentage of participants with >2-, 3-fold increases from Baseline (if ≥LLOQ) or with >2-, 3-fold increases from LLOQ (if <LLOQ) will also be analyzed with 2-sided 95% CI using the Clopper-Pearson method by study arm, at each postdose timepoint. Further details will be described in the SAP.

9.5.3. Safety Analyses

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

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

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, with any solicited AR during the 7-day follow-up period after vaccination, and with Grade 3 or higher solicited AR will be provided. A 2-sided 95% exact CI using the

Clopper-Pearson method will be provided for the percentage of participants with any solicited AR.

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

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

9.5.4. Exploratory Analyses

CCI [redacted]

9.6. Planned Analyses

There will be at least one IA and a final CSR for this study.

9.6.1. Interim Analysis

CCI [redacted]

9.6.2. Final Clinical Study Report

The final CSR will include full unblinded analyses of all safety and immunogenicity with individual unblinded listings through EoS.

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 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

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

addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

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 written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The ICF will require the participant to clearly indicate whether or not the participant agrees to allow any remaining specimens to be used for exploratory research.

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

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. Internal Safety team

The Sponsor's independent IST comprises 3 members, including clinical development physicians/clinicians and a safety physician, who are not involved in the study, and will oversee the safety of study participants in addition to the clinical development team in charge of the study. The IST may perform unblinded safety data reviews due to safety concerns that arise during the study, or as requested on ad hoc bases by the study team. Details regarding the composition, responsibilities, and procedures of the IST will be described in a charter.

10.1.6.2. Cardiac Event Adjudication Committee

An independent CEAC comprising medically qualified personnel, including cardiologists, will review all suspected cases of myocarditis and pericarditis, to determine if they meet CDC criteria for "probable" or "confirmed" events, which are reported in ongoing interventional clinical trials per the CEAC charter (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then 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 the charter.

10.1.7. Dissemination of Clinical Study Data

The Sponsor shares information about clinical studies and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These

websites include clinicaltrials.gov, European Union clinical trial register, and some national registries.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 the CRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- 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 on-site monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- 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 reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Agreement.

- 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 site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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.

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 CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 6 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)[1]
Other Screening Tests	• FSH and estradiol (as needed in PONCBP only)

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

NOTES:

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

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

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, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

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

10.3.2. Definition of SAE

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

a. Results in death.
b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

d. Results in persistent or significant disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3. Definition of MAAE

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

10.3.4. Definition of AESI

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

The AESIs defined for this protocol can be found in Section 10.5.

10.3.5. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- 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 the EDC entry.
- 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.

Assessment of Intensity

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

- Mild:
  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.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this trial. The intensity grading scale used in this trial is presented in Table 7.

Table 7: Adult and Adolescent Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	<38.0°C <100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	>40.0°C >104.0°F

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

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 product information, 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.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded 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.

10.3.6. Reporting of SAEs/AESI

NOTE: AESI will be reported in the same way as SAEs

SAE Reporting to the Sponsor or designee via an Electronic Data Collection Tool

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

SAE Reporting to the Sponsor or designee via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- Initial notification via email or fax does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.
- SAE reports should be emailed to drugsafety@modernatx.com.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Person of Childbearing Potential

Persons AFAB are considered POCBP (fertile) following menarche:

- From the time of menarche until becoming postmenopausal unless permanently sterile.
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Persons AFAB on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
  - Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

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

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

Person of Nonchildbearing Potential

Persons AFAB in the following categories are considered PONCBP:

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

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

2. Postmenopausal persons AFAB:

    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        i. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
        ii. Persons AFAB on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. 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.
• IUD.
• IUS.
• Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a medical cause). • *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the 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.* Note: documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: Oral. Intravaginal. Transdermal. Injectable.
Progestogen-only hormone contraception associated with inhibition of ovulation: Oral. Injectable.

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

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

10.5. Appendix 5: Adverse Event of Special Interest

Investigators should report all events that fall into the categories presented in Table 8 as an AESI per the reporting processes in Section 10.3.6. The following AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines or the vaccine platform.

Table 8: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $<125 \times 10^9$. • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome.
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome. • ADEM. • Idiopathic peripheral facial nerve palsy (Bell's palsy). • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions.
Anaphylaxis	• Anaphylaxis associated with IP administration as defined per protocol in Section 8.4.8.1. • Follow reporting procedures in Section 10.3.6.
Myocarditis/Pericarditis	• Myocarditis. • Pericarditis. • Myopericarditis.

Abbreviations: ADEM=acute disseminated encephalomyelitis; HELLP=hemolysis, elevated liver enzymes and low platelets; IP=investigational product.

10.6. Appendix 6: 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 9 as guidance.

Table 9: Case Definitions of Probably and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms:* • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.	Presence of ≥1 new or worsening of the following clinical symptoms:* • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.
	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.	**OR,** infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.
	AND ≥1 new finding of • Troponin level above upper limit of normal (any type of troponin). • Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[§]. • Abnormal cardiac function or wall motion abnormalities on echocardiogram. • cMRI findings consistent with myocarditis[¶].	**AND** ≥1 new finding of • Histopathologic confirmation of myocarditis[†]. • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin).

Condition	Definition	
	AND • No other identifiable cause of the symptoms and findings.	**AND** • No other identifiable cause of the symptoms and findings.
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • Acute chest pain††. • Pericardial rub on exam. • New ST-elevation or PR-depression on EKG. • New or worsening pericardial effusion on echocardiogram or MRI.	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

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

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

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

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

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon.

** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon.

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

Reference: (Gargano et al 2021).

11. REFERENCES

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