CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, Randomized, Observer-blind, Active-Control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-based Influenza and SARS-CoV-2 Multi-component Vaccines in Healthy Adults
Protocol Number:	mRNA-1083-P101
Compound:	mRNA-1083
Brief Title:	A clinical trial to investigate how safe a new SARS-CoV-2 and influenza vaccine (mRNA-1083) is and whether it helps the immune system fight viruses in healthy adult participants
Study Phase:	Phase 1/2
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number:	IND: 29324
Date:	14 Mar 2024

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

CONFIDENTIAL

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

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled A Phase 1/2, Randomized, Observer-blind, Active-Control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-based Influenza and SARS-CoV-2 Multi-component Vaccines in Healthy Adults" dated 14 Mar 2024 and the most recent version of the mRNA-1083 Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without institutional review board (IRB) or independent ethics committee (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 clinical trial 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 clinical trial will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	14 Mar 2024
Amendment 1	16 Jan 2024
Original Protocol	08 Feb 2023

Amendment 2, 14 Mar 2024: Current Amendment

This amendment is considered to be non-substantial because it neither impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The purpose of this amendment is to provide clarifications as outlined in the table below.

The summary of changes table provided here describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. As applicable, the synopsis of Amendment 2 has been modified to correspond to changes in the body of the protocol. Additionally, minor inconsistences have been corrected.

Summary of Major Changes from Protocol Amendment 1 to Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
2.1.1 Risk Assessment	Updated Text	To align with the Company Core Data Sheet
5.2.2 Exclusion Criteria	Criterion 1 was changed to 'Participants who enrolled in Part 1 of the mRNA-1083-P101 (Phase 1/2) study'	To clarify that participants from Part 1 were excluded
	In Criterion 11, 'Participants whose values have not returned to Baseline after their convalescent period will also be excluded.' was removed.	To remove redundancy
	Criterion 23 was changed to 'Unaware whether they received an influenza vaccine during or since September 2023'	To reflect the most recent influenza season
6.10.1 Prior Medications	The following was added: 'Any seasonal influenza vaccine administered during or since September 2023 (for Part 2 of the study)'	To specify the most recent influenza season for Part 2 of the study
10.5.1 Internal Safety Team	The following was added, 'In Part 2 of the study, there will be no scheduled IST review. An ad-hoc IST review may occur as outlined by the IST charter'	To clarify the role of the IST in Part 2 of the study

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
BLA	Biologics License Application
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Clinical research organization
CSR	Clinical study report
CTFG	Clinical trial facilitation group
DHHS	Department of Health and Human Services
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG/EKG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EoS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HCP	Healthcare professional
HD	High dose
HELLP	Hemolysis, elevated liver enzymes, and low platelets
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
ILI	Influenza-like illness
IM	Intramuscular(ly)
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
IST	Internal safety team
LAM	Lactational amenorrhea method
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NA	Not applicable

Abbreviation	Definition
nAb	Neutralizing antibody
NH	Northern Hemisphere
NI	Noninferiority
NIM	Noninferiority margin
NP	Nasopharyngeal
NTD	N-terminal domain
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
POCBP	Participant(s) of childbearing potential
PP	Per protocol
PsVNA	Pseudovirus neutralization assay
PT	Preferred term
RBD	Receptor-binding domain
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SH	Southern Hemisphere
SoA	Schedule of Activities
SOC	System organ class
Tris	tris(hydroxymethyl) aminomethane
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 1/2, Randomized, Observer-blind, Active-Control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-based Influenza and SARS-CoV-2 Multi-component Vaccines in Healthy Adults

Brief Title:

A clinical trial to investigate how safe a new SARS-CoV-2 and influenza vaccine (mRNA-1083) is and whether it helps the immune system fight viruses in healthy adult participants

Regulatory Agency Identifier Number(s):

IND: 29324

Rationale:

The Sponsor is developing mRNA-1083, a lipid-encapsulated messenger ribonucleic acid (mRNA)-based prophylactic combination vaccine encoding influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigens. mRNA-1083 contains 5 to 6 mRNAs: 4 sequences encoding surface glycoprotein hemagglutinin (HA) of seasonal influenza viruses and 1 to 2 sequences encoding linked N-terminal domain (NTD) and receptor-binding domain (RBD) of SARS-CoV-2 spike proteins. mRNA-1083 encodes the respective antigens also encoded by mRNA-1010 (seasonal influenza) and mRNA-1283 (SARS-CoV-2).

The administration of the mRNA-1083 vaccine has the potential to efficiently reduce the overall burden of acute viral respiratory diseases by providing simultaneous protection against influenza and SARS-CoV-2 viruses in a convenient dosing regimen. mRNA-1083 offers greater convenience and has the potential to lead to increased compliance with vaccine recommendations, an approach which has been frequently used for pediatric vaccines (Kurosky et al 2017). Furthermore, this combined regimen could provide a public health benefit through synergistically increasing coverage rates against influenza and SARS-CoV-2 viruses.

This Phase 1/2 clinical trial aims to generate safety, reactogenicity, and immunogenicity data of multi-component influenza and SARS-CoV-2 vaccine in adults ≥18 to <80 years of age. Multiple compositions and dose levels will be evaluated.

The study is divided into 2 parts: Part 1 and Part 2. Part 1 (Phase 1/2) includes adults who are 18 to <80 years and Part 2 (Phase 2 Extension) includes adults who are 18 to <50 years.

Objectives and Endpoints:

The objectives and endpoints for the Part 1 (Phase 1/2) of the study are presented in the table below:

Objectives	Endpoints
Primary	
To evaluate the safety and reactogenicity of study intervention administration across study treatment arms	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • Unsolicited Severe AEs through 28 days after injection • Unsolicited MAAEs from Day 1 to Day 181/EoS • Unsolicited AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at Day 29	• GMT and GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥4-fold if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline titer is <LLOQ in nAb titers measured by PsVNA
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at all evaluable humoral immunogenicity time points	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above

Objectives	Endpoints
Exploratory (may be performed)	
To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
To evaluate the cellular immune responses against influenza and SARS-CoV-2 in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods • Perform targeted repertoire analysis of B-cells and T-cells after injection
To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates	• Frequency of RT-PCR-confirmed clinical influenza and COVID-19 • Assessment of immune responses to infection and viral isolates

Abbreviations: AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutination; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; RT-PCR = reverse transcription polymerase chain reaction; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2.

The objectives and endpoints for the Part 2 (Phase 2 Extension) of the study are presented below:

Objectives	Endpoints
Primary	
To evaluate the safety and reactogenicity of study intervention administration across study treatment arms	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • Unsolicited Severe AEs through 28 days after injection • Unsolicited MAAEs from Day 1 to Day 181/EoS • Unsolicited AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS

Objectives	Endpoints
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at Day 29	• GMT and GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥4-fold if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline titer is <LLOQ in nAb titers measured by PsVNA
Secondary	
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at all evaluable humoral immunogenicity time points	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
Exploratory (may be performed)	
To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

Abbreviations: AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutination; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; RT-PCR = reverse transcription polymerase chain reaction; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Overall Design:

The study is divided into 2 Parts:

Part 1 of the study will be a Phase 1/2 randomized, stratified, observer-blind, active-control study and will evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared to active-control experimental injections mRNA-1010, mRNA-1283.222, mRNA-1273.222, and licensed active-control vaccines, Fluarix and Fluzone HD (Cohort A only) in healthy adults ≥18 to <80 years of age (Cohort A is in adults ≥65 to <80 years of age and Cohort B is in adults ≥18 to <65 years of age).

Part 2 of the study will be a Phase 2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.815, mRNA-1273.815, and licensed active-control vaccine, Fluarix in healthy adults ≥18 to <50 years of age.

Brief Summary:

The study will be performed in 2 parts, and results for each part of the study will be provided as a separate clinical study report.

Part 1: The purpose of this Phase 1/2 clinical trial is to generate sufficient safety, reactogenicity, and immunogenicity data to enable selection of an mRNA-1083 vaccine composition and dose level to evaluate in a subsequent Phase 3 clinical trial in adults.

Study details include:

- Study duration: approximately up to 7 months, including the Screening period.
- Treatment duration: Study interventions are scheduled for all participants on Day 1 (Baseline).
- Visit frequency: All participants will have up to 5 in-person visits (Days 0 [Eligibility Visit], 1 [Baseline], 8, 29, 181, and unscheduled visits if appropriate) and 4 safety follow-up calls (Days 57, 91, 121, and 151).

Part 2: The purpose of this Phase 2 Extension clinical trial is to generate safety and immunogenicity data for additional mRNA-1083 compositions and dose levels in young adults ≥18 years and <50 years of age.

Study Details:

- Study duration: approximately up to 7 months, including the Screening period.
- Treatment duration: Study interventions are scheduled for all participants on Day 1 (Baseline).
- Visit frequency: All participants will have up to 4 in-person visits (Screening, Day 1, Day 29 and Day 181 and unscheduled visits if appropriate) and 3 safety follow-up calls (Days 8, 91, and 151).

Number of Participants:

Approximately 1744 participants will enroll in the overall clinical trial, with approximately 1224 participants in Part 1 and approximately 520 participants in Part 2.

Note: *Enrolled* means participants' 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 clinical trial, but do not participate in the clinical trial, 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 clinical trial activity after Screening.

Study Cohorts and Duration:

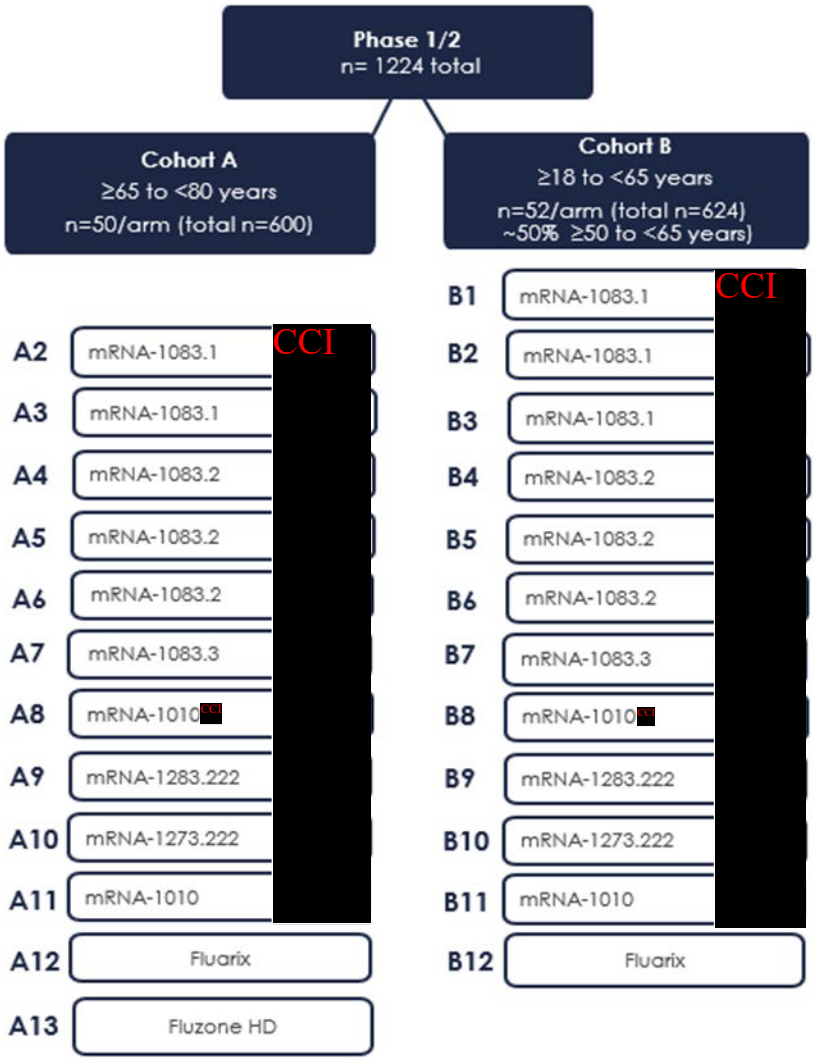
Part 1: This part of the clinical trial will enroll approximately 1224 participants into 1 of 2 age cohorts: Cohort A for participants ≥65 to <80 years of age (approximately 600 participants) or Cohort B for participants ≥18 to <65 years of age (approximately 624 participants). In Cohort A, approximately 600 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since Sept 2022). In Cohort B, approximately 624 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by the 2 age groups, ≥18 to <50 years and ≥50 to <65 years, and by influenza vaccine status in the most recent influenza season (received or not received since Sep 2022). Approximately 50% of the participants in Cohort B will be ≥50 to <65 years of age.

Part 2: This part of the clinical trial will enroll approximately 520 participants ≥18 to <50 years of age. Participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since Sep 2023).

All participants will have follow-up visits for 6 months after the study intervention administration.

1.2. Schema

Part 1:



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

Part 2:

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities (Part 1 – Phase 1/2)

Visit Number	**SCRN**	**1**	**2**	**3**	**4, 5, 6, 7**	**8**	**USV**
Type of Visit	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Month Timepoint	**NA**			**M1**	**M2-M5**	**M6**	**Up to M6**
Visit Day	**SCRN[a]**	**D1 (Baseline)[a]**	**D8**	**D29**	**D57, D91, D121, D151**	**D181/ EoS**	**NA**
Window Allowance (Days)	**-28**	**NA**	**-1 to +3**	**-7 to +3**	**±5**	**±14**	**NA**
Informed consent form, demographics, concomitant medications, medical history	X						
Inclusion/exclusion criteria	X	X					
Blood collection for safety laboratory samples[b]	X		X				
Full physical examination[c]	X						
Axillary lymph nodes assessment[d]		X					
Symptom-directed physical examination[e]		X	X	X		X	X
Vital sign measurements[f]	X	X					
Electrocardiogram[g]		X					
Pregnancy testing[h]	X	X					
Randomization		X					
Study intervention (including 60-minute, postdose observation period)		X					
Blood collection for humoral immunogenicity[i]		X		X		X	
Blood collection for cellular immunogenicity[i]		X		X			
Optional blood collection for genomics[j]		X					
Optional blood collection for transcriptomics[j]		X	X	X			
Blood sample for potential cardiac biomarker analysis[k]		X					
Nasal swab for virus detection[l]		X					X

Visit Number	SCRN	1	2	3	4, 5, 6, 7	8	USV
Type of Visit	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Month Timepoint	**NA**			**M1**	**M2-M5**	**M6**	**Up to M6**
Visit Day	**SCRN[a]**	**D1 (Baseline)[a]**	**D8**	**D29**	**D57, D91, D121, D151**	**D181/ EoS**	**NA**
Window Allowance (Days)	**-28**	**NA**	**-1 to +3**	**-7 to +3**	**±5**	**±14**	**NA**
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X					
eDiary activation for recording solicited local and systemic ARs (7 days)[m]		X					
Review of solicited AR eDiary			X				
Follow-up safety call[n]					X		
Recording of unsolicited AEs through Day 29		X	X	X			
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications associated with these events		X	X	X	X	X	X
Recording of nonstudy vaccinations	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; ECG = electrocardiogram; EoS = end of study; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SCRN = Screening; USV = unscheduled visit;.

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

b. Safety laboratory tests (see Section 10.2) will consist of total white blood cell count, hemoglobin, hematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, creatinine, alkaline phosphatase, and total bilirubin. Safety laboratory tests will be performed by the central laboratory.

c. A full physical examination, including height and weight for calculation of body mass index, will be performed at Screening. Additional physical examinations may be performed during the study at the discretion of the Investigator.

d. On the day of study intervention administration, prior to injection, axillary lymph nodes of the injection arm will be examined, and any abnormalities will be documented.

e. Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full physical examination will be performed. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during postinjection study visits should be reported as an AE.

f. Vital sign measurements: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs must be collected at Screening and on the day of injection (Day 1), once before and at least 60 minutes after injection. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination. For all vital sign measurements, participant must be seated for 5 minutes before any measurements are taken.

g. **For participants ≥18 to <51years of age only**: A 12-lead ECG will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to injection. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis and/or pericarditis occurs within the conduct of the clinical trial. The ECG output should be filed in the participant's binder. Central reading of the ECG will not be performed. Incidental significant abnormal ECG findings should contribute to the Investigator's assessment of eligibility, at their discretion, as per Exclusion Criterion 3.

h. For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. For participants of nonchildbearing potential, the follicle-stimulating hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.

i. Baseline samples for humoral and cellular immunogenicity must be collected prior to receipt of injection on Day 1. Cellular immunogenicity will be sampled and assessed in a subset of participants.

j. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Blood draws on Day 1 must occur prior to participants being administered the study intervention.

k. **For participants ≥18 to <51years of age only**: Plasma and serum samples will be collected and banked for potential future cardiac biomarker assessment.

l. A nasal swab to test for the presence of viral respiratory pathogens will be collected prior to the study intervention administration on Day 1 to document any prevaccination infection. A nasal swab should be collected through study completion for protocol-defined ILI or SARS-CoV-2 ≤7 days of symptom onset.

m. The eDiary activation and entries will be recorded by the participant starting approximately 60 minutes after injection while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection. Solicited local and systemic ARs will be recorded separately for each injection site.

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

Table 2: Schedule of Activities (Part 2 – Phase 2 Extension)

Visit Number	**SCRN**	**1**	**2**	**3**	**4, 5**	**6**	**USV**
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**NA**			**M1**	**M3-M5**	**M6**	**Up to M6**
Visit Day	**SCRN[a]**	**D1 (Baseline)[a]**	**D8**	**D29**	**D91, D151**	**D181/ EoS**	**NA**
Window Allowance (Days)	**-28**	**NA**	**-1 to +3**	**-7 to +3**	**±5**	**±14**	**NA**
Informed consent form, demographics, concomitant medications, medical history	X						
Inclusion/exclusion criteria	X	X					
Full physical examination [b]	X						
Axillary lymph nodes assessment [c]		X					
Symptom-directed physical examination [d]		X		X		X	X
Vital sign measurements [e]	X	X					
Electrocardiogram [f]		X					
Pregnancy testing [g]	X	X					
Randomization		X					
Study intervention (including 60-minute, postdose observation period)		X					
Blood collection for humoral immunogenicity [h]		X		X		X	
Optional blood collection for genomics [i]		X					
Optional blood collection for transcriptomics [i]		X		X			
Blood sample for potential cardiac biomarker analysis [j]		X					
Nasal swab for virus detection [k]		X					
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X					
eDiary activation for recording solicited ARs (7 days) [l]		X					
Review of solicited AR eDiary			X				

Visit Number	SCRN	1	2	3	4, 5	6	USV
Type of Visit	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**NA**			**M1**	**M3-M5**	**M6**	**Up to M6**
Visit Day	**SCRN[a]**	**D1 (Baseline)[a]**	**D8**	**D29**	**D91, D151**	**D181/ EoS**	**NA**
Window Allowance (Days)	**-28**	**NA**	**-1 to +3**	**-7 to +3**	**±5**	**±14**	**NA**
Follow-up safety call [m]			X		X		
Recording of unsolicited AEs through Day 29		X	X	X			
Recording of SAEs, AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications associated with these events		X	X	X	X	X	X
Recording of nonstudy vaccinations	X	X	X	X	X	X	X
Study completion						X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; BMI = body mass index; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; EoS = end of study; ILI = influenza-like illness; IM = intramuscular; M = month; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (telephone) call; SCRN = Screening; USV = unscheduled visit

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

b. A full physical examination, including height and weight for calculation of body mass index, will be performed at Screening. Additional physical examinations may be performed during the study at the discretion of the Investigator.

c. On the day of study intervention administration, prior to injection, axillary lymph nodes of the injection arm will be examined, and any abnormalities will be documented.

d. Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full physical examination will be performed. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during postinjection study visits should be reported as an AE.

e. Vital sign measurements: Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs must be collected at Screening and on the day of injection (Day 1), once before and at least 60 minutes after injection. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination. For all vital sign measurements, participant must be seated for 5 minutes before any measurements are taken.

f. A 12-lead ECG will be obtained, after 10 minutes of supine rest, at Visit 1/Day 1 prior to injection. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis and/or pericarditis occurs within the conduct of the clinical trial. The ECG output should be filed in the participant's binder. Central reading of the ECG will not be performed. Incidental significant abnormal ECG findings should contribute to the Investigator's assessment of eligibility, at their discretion, as per Exclusion Criterion 3.

g. For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injections on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. For participants of nonchildbearing potential, the follicle-stimulating hormone level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.
h. Baseline samples for humoral immunogenicity must be collected prior to receipt of injection on Day 1.
i. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. Blood draws on Day 1 must occur prior to participants being administered the study intervention.
j. Plasma and serum samples will be collected prior to the study intervention administration on Day 1 and banked for potential future cardiac biomarker assessment.
k. A nasal swab to test for the presence of viral respiratory pathogens will be collected prior to the study intervention administration on Day 1 to document any prevaccination infection.
l. The eDiary activation and entries will be recorded by the participant starting approximately 60 minutes after injection while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection. Solicited local and systemic ARs will be recorded separately for each injection site.
m. Trained study staff will call all participants to collect information related to any SAEs, MAAEs, AESIs, AEs leading to study discontinuation, information on concomitant medications associated with those events, and any nonstudy vaccinations.

2. INTRODUCTION

ModernaTX, Inc. (the Sponsor) is developing lipid nanoparticle (LNP)-mRNA-based prophylactic multi-component vaccines (also referred to as combination vaccines) against disease associated with respiratory viruses. The mRNA-1083 combination vaccine encodes antigens from influenza viruses and SARS-CoV-2 and is intended to prevent disease associated with these viruses.

Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year resulting in a severe challenge to public health (WHO 2018). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the Northern Hemisphere (NH) and Southern Hemisphere (SH) (Riedel et al 2019). Because influenza viruses continuously change through a process termed antigenic drift, the circulating viruses are actively monitored by a worldwide monitoring network coordinated by the WHO (Monto et al 2015). Based on the observed circulation patterns and antigenic changes, an expert panel recommends influenza virus strains to be used for vaccine manufacturing twice per year (once for the NH and once for the SH). Influenza A and influenza B viruses are the most relevant influenza viruses for human infection. Therefore, current vaccine recommendations include 1 influenza A H1N1 strain, 1 influenza A H3N2 strain, and 2 influenza B strains (covering the B/Victoria and B/Yamagata lineages).

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

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome. An outbreak of a novel coronavirus (later designated SARS-CoV-2, the causative agent of COVID-19) initially emerged in Wuhan, Hubei Province, China in December 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020, and COVID-19 continues to have a major global public health impact, with more than 500 million cases and 6.5 million deaths as of 17 Nov 2022 (WHO 2022).

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

The Study Is Divided into 2 Parts:

Part 1 of the study will be a Phase 1/2 randomized, stratified, observer-blind, active-control study and will evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared to active-control experimental injections mRNA-1010,

mRNA-1283.222, mRNA-1273.222, and licensed active-control vaccines, Fluarix and Fluzone HD (Cohort A only) in healthy adults ≥18 to <80 years of age (Cohort A is in adults ≥65 to <80 years of age and Cohort B is in adults ≥18 to <65 years of age).

Part 2 of the study will be a Phase 2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.815, mRNA-1273.815, and licensed active-control vaccine, Fluarix in healthy adults ≥18 to <50 years of age.

Table 3: mRNA Vaccines in mRNA-1083-P101(Part 1)

Vaccine	mRNA Encoding Influenza HA				mRNA Encoding SARS-CoV-2 Spike				CCI
	H1N1	H3N2	B/ Yamagata	B/ Victoria	Wuhan-Hu-1 RBD-NTD	BA.4/BA.5 RBD-NTD	Wuhan-Hu-1 full length	BA.4/BA.5 full length	
mRNA-1083.1	✓	✓	✓[CCI]	✓[CCI]	✓	✓			
mRNA-1083.2	✓	✓	✓[CCI]	✓[CCI]	✓	✓			
mRNA-1083.3	✓	✓	✓[CCI]	✓[CCI]	✓	✓			
mRNA-1010[CCI]	✓	✓	✓[CCI]	✓[CCI]					
mRNA-1283.222					✓	✓			
mRNA-1273.222							✓	✓	
mRNA-1010	✓	✓	✓	✓					

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid; NA = not applicable; NTD = N-terminal domain; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

CCI

Table 4: mRNA Vaccines in mRNA-1083-P101(Part 2)

Vaccine	mRNA Encoding Influenza HA				mRNA Encoding SARS-CoV-2 Spike		CCI [redacted]
	H1N1	H3N2	B/ Yamagata	B/ Victoria	Omicron XBB.1.5 RBD-NTD	Omicron XBB.1.5 full length	
mRNA-1083 (CCI)	✓	✓	✓[redacted]	✓[redacted]	✓		
mRNA-1083 (CCI)	✓	✓	✓[redacted]	✓[redacted]	✓		
mRNA-1010 CCI	✓	✓	✓[redacted]	✓[redacted]			
mRNA-1283.815					✓		
mRNA-1273.815						✓	

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid; NA = not applicable; NTD = N-terminal domain; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

CCI [redacted]

mRNA-1083

Part 1: mRNA-1083.1, mRNA-1083.2, and mRNA-1083.3)

mRNA-1083 is an LNP-encapsulated, mRNA-based, prophylactic, multi-component vaccine encoding antigens from influenza viruses and SARS-CoV-2. mRNA-1083 contains 5 to 6 mRNAs: 4 sequences that encode membrane-bound hemagglutinin (HA) of the 4 different influenza strains recommended by the CCI and 1 to 2 sequences that encode the NTD and RBD of the SARS-CoV-2 spike glycoprotein of the recommended seasonal variant(s) (Table 3 and Table 4). The NTD and RBD sequences are linked together with a short flexible linker and a transmembrane domain anchors the protein to the cell membrane. The proteins encoded by mRNA-1083 are also encoded by mRNA-1010 (influenza) and mRNA-1283 (SARS-CoV-2 bivalent), CCI Four mRNA-1083 vaccine compositions will be evaluated in this mRNA-1083-P101 study (Table 3); they contain the same 5-6 mRNAs CCI

Part 1: Contains 6 mRNA sequences that encode for the 4 different influenza strains recommended by the WHO CCI and the 2 sequences that encode the NTD and RBD of the SARS-CoV-2 spike glycoprotein of the original (Wuhan-Hu 1) and BA.4/BA.5 variants CCI .

- **mRNA-1083.1**: CCI .
- **mRNA-1083.2**: CCI .
- **mRNA-1083.3**: CCI .

Part 2: mRNA-1083 (CCI) and mRNA-1083 (CCI)

Contains 5 mRNA sequences that encode for the 4 different influenza strains recommended by the WHO CCI and the sequence that encodes the NTD and RBD of the SARS-CoV-2 spike glycoprotein of the fall/winter 2023-2024 variant XBB.1.5.

- **mRNA-1083** CCI .
- **mRNA-1083** CCI .

The Sponsor enrolled Part 1 of this study between Apr to May 2023 with a total of 630 participants dosed with mRNA-1083 drug products (277 in Cohort A and 353 in Cohort B). The IST has reviewed safety data and has not identified significant safety concerns.

The Phase 3 study completed enrollment between Oct and Nov 2023 to evaluate the safety and immunogenicity of mRNA-1083 (C µg, with CCI) vs. licensed comparators (CCI randomization) (NCT06097273). Approximately 8000 participants enrolled in this study and of those, approximately 4000 were dosed with mRNA-1083 drug

products (approximately 2000 in the ≥65-year-old age group and 2000 in the 50 to <65-year-old age group). No significant safety concerns have been identified to date.

mRNA-1010 (mRNA-1010[CCI] and mRNA-1010)

mRNA-1010 is an LNP-encapsulated, mRNA-based, prophylactic injection containing 4 mRNAs that encode membrane-bound HA of the 4 different influenza strains recommended by the WHO [CCI].

Two mRNA-1010 vaccines will be evaluated in this mRNA-1083-P101 study (Table 3 and Table 4):

- mRNA-1010[CCI] – Contains the same influenza mRNAs contained in mRNA-1083, [CCI].
- mRNA-1010 – Encodes the same influenza HA proteins as mRNA-1083, [CCI]

The Sponsor has completed a Phase 1/2 clinical trial of mRNA-1010 (NCT04956575) at dose levels up to [CCI] µg and is now conducting three Phase 3 studies at a [CCI]-µg dose level: two safety and immunogenicity clinical trials (mRNA-1010-P301, NCT05415462 and mRNA-1010-P303, NCT 05415462) and one safety and efficacy clinical trial (mRNA-1010-P302, NCT05566639). More than 15,000 adults have received mRNA-1010 ([CCI] µg) in clinical trials. No significant safety concerns have been identified to date.

mRNA-1283 (mRNA-1283.222, mRNA-1283.815)

mRNA-1283 is an LNP-encapsulated, mRNA-based prophylactic vaccine that encodes the RBD and NTD of the SARS-CoV-2 spike glycoprotein. The NTD and RBD sequences are linked together with a short flexible linker and a transmembrane domain anchors the protein to the cell membrane.

Two mRNA-1283 vaccines will be evaluated in this clinical study (Table 3 and Table 4).

- mRNA-1283.222 - contains 2 mRNAs that encode NTD-RBD of the spike proteins of the original (Wuhan-Hu-1) and BA.4/BA.5 variants of SARS-CoV-2 [CCI].
- mRNA-1283.815- encodes the linked NTD-RBD subdomains of the SARS-CoV-2 spike glycoprotein of the fall/winter 2023-2024 recommended variant XBB.1.5.

The Sponsor has evaluated mRNA-1283 as a 2-dose primary series in a Phase 1 clinical trial at dose levels up to [CCI] µg (mRNA-1283-P101; NCT04813796) and as a 1-dose booster in a Phase 2a clinical trial at dose levels up to [CCI] µg (mRNA-1283-P201; NCT05137236). The mRNA-1283-P201 clinical trial also evaluated mRNA-1283.211, a bivalent mRNA-1283 vaccine that encodes the NTD-RBD of the spike proteins from the original (Wuhan-Hu-1) and B.1.351 SARS-CoV-2 strains at [CCI], as a 1-dose booster at dose levels up to [CCI] µg.

The Sponsor is currently evaluating mRNA-1283.222 [CCI] µg and mRNA-1283.815 [CCI] µg in a Phase 3 study (NCT05815498). More than 6000 adults have received mRNA-1283 in clinical trials. No significant safety concerns have been identified to date.

mRNA-1273 (mRNA-1273.222, mRNA-1273.815)

mRNA-1273 is an LNP-encapsulated, mRNA-based prophylactic injection that encodes the full-length SARS-CoV-2 prefusion-stabilized spike glycoprotein.

In Aug 2021, the Sponsor filed a Biologics License Application (BLA) with the United States (US) Food and Drug Administration (FDA) for the full licensure of the mRNA-1273 vaccine for active immunization to prevent COVID-19 in individuals 18 years of age and older. In January 2022, the US FDA approved the BLA for SPIKEVAX™ (mRNA-1273) to prevent COVID-19 in individuals 18 years of age and older. In November 2021, the US FDA granted Emergency Use Authorization (EUA) for an mRNA-1273 booster dose ([redacted] µg) to be given at least 5 months after the primary series with mRNA-1273 in adults aged 18 years and older. In March 2022, the FDA authorized for EUA of a second booster dose of mRNA-1273 in individuals 50 years and older at least 4 months after receipt of a first booster dose. In June 2022, mRNA-1273 was granted EUA for the prevention of COVID-19 in children down to 6 months of age in the US and later universally recommended the booster for all ages. In August 2022, mRNA-1273.222 bivalent (Original + Omicron BA.4/BA.5) booster vaccine was authorized in individuals 18 years and older, followed in October 2022 for individuals 6 to 17 years of age. In September 2023, mRNA-1273.815 (Omicron variant XBB.1.5) was approved in individuals 12 years of age and older and authorized in individuals 6 months through 11 years of age.

Fluarix and Fluzone HD, licensed influenza vaccines

Fluarix and Fluzone HD are both seasonal, egg-based, quadrivalent vaccines that are licensed for the prevention of infection with influenza A and B viruses. Each vaccine contains HAs from the 4 influenza strains recommended by the WHO.

Fluarix is a standard-dose vaccine (60 µg of HA) that is approved for children and adults ages 6 months and above.

Fluzone HD is a high dose vaccine, containing 4 times the amount of antigen (240 µg of HA) than the standard-dose vaccine. In the US, Fluzone HD is approved for adults ≥65 years of age and is preferentially recommended for use in that age group.

2.1. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mRNA-1083 may be found in the Investigator's Brochure (IB).

2.1.1. Risk Assessment

As with all injectable vaccines, immediate systemic allergic reactions to vaccination, ranging from mild allergic reactions (eg, urticaria) to systemic allergic reactions (eg, anaphylaxis) can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2022). Since the authorization of the mRNA-1273 vaccine for coronavirus disease 2019 (COVID-19), the US CDC estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precautionary measure, all participants will remain under observation at the clinic for at least 60 minutes after study intervention administration.

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

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

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

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following study intervention administration have been observed in early phase clinical studies with similar mRNA-based study interventions. These abnormalities were without clinical symptoms or signs and returned toward Baseline values over time. The clinical significance of these observations is unknown.

In the postauthorization setting, there have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in adolescents and young males, within 7 to 14 days primarily after the second dose of the vaccine but also after subsequent doses of the vaccine. These are typically mild cases and individuals tend to recover within a short time following conservative treatment. Healthcare professionals (HPCs) and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021). As mentioned above, the risk of myocarditis and pericarditis is largely confined to vaccine recipients younger than 50 years of age. Therefore, a Baseline ECG and blood will be collected and banked for potential future cardiac biomarker assessment in ≥18 to <51 before vaccination to provide a comparison should any suspected or confirmed case of myocarditis or pericarditis occur.

A completed interim analysis of Part 1 of this study showed that all three mRNA-1083 compositions and doses in mRNA-1083-P101 were generally well tolerated. The majority of solicited ARs were Grade 1 or Grade 2 in severity, and most had an onset within 1 to 2 days after vaccination. In the mRNA-1083 study arms, participants 18 to <50 years old reported a higher frequency of solicited ARs than those in either the 50 to <65 or 65 to <80-year age groups. Overall, mRNA-1083 was observed to have an acceptable safety profile with no safety concerns identified.

In a completed Phase 3 study of the mRNA-1273 injection for COVID-19 in 30,420 healthy adults, the most frequently reported ARs after any dose of study intervention were pain at the injection site, fatigue, headache, myalgia, arthralgia, and chills. The majority of local and systemic ARs had a median duration of 1 to 3 days. Adverse reactions from clinical studies with

mRNA-1273 occurring in ≥1% of recipients include injection site rash, injection site urticaria, rash, and delayed injection site reactions.

CCI [redacted]

The Sponsor has completed a Phase 1/2 clinical trial of mRNA-1010 (NCT04956575) at dose levels up to CCI µg and is now conducting three Phase 3 studies at a CCI -µg dose level: mRNA-two safety and immunogenicity clinical trials (mRNA-1010-P301, NCT05415462 and mRNA-1010-P303, NCT 05415462) and one safety and efficacy clinical trial (mRNA-1010-P302, NCT05566639). More than 15,000 adults have received mRNA-1010 (CCI µg) in clinical trials. No significant safety concerns have been identified to date. Based on the final analysis of the Phase 1/2 trial, the most common solicited local AR in the mRNA-1010 groups was injection site pain and the most common solicited systemic ARs in the CCI µg mRNA-1010 groups were fatigue, myalgia, and headache.

Further details are provided in the current IB.

2.1.2. Benefit Assessment

The following benefits may accrue to participants:

- Participants will have a Baseline (Day 1) evaluation for respiratory pathogens, including influenza virus and SARS-CoV-2. For Part 1 that is conducted during the influenza season, there is ongoing access to evaluation for ILI and/or COVID-19 throughout the clinical trial.
- The clinical trial will contribute to the development of a potentially efficacious vaccine against seasonal influenza virus and SARS-CoV-2 together as a single injection.
- For participants who receive licensed vaccines (mRNA-1273, Fluzone HD, Fluarix) may have protection against influenza and/or SARS-CoV-2 and its variants.

2.1.3. Overall Benefit/Risk Conclusion

The clinical study aggregate safety data for mRNA-1010, mRNA-1273, and mRNA-1283 injections demonstrate a similar, consistent and acceptable safety profile supportive of the clinical development of the Sponsor mRNA vaccine platform.

Data from the mRNA-1010-P101 clinical trial, doses tested ranged from CCI µg of mRNA-1010) showed no significant safety concerns regarding mRNA-1010. The mRNA-1010-P301 (Phase 3, dose tested CCI µg) clinical trial has also been completed. Additionally, there are two more Phase 3 studies evaluating mRNA-1010 CCI µg (mRNA-1010-P302 [NCT05566639], and mRNA-1010-P303 [NCT05827978]) currently ongoing. Over 15,000 participants have received mRNA-1010 at CCI mcg in clinical studies. No significant safety concerns have been identified.

Safety from the completed interim analyses of mRNA-1283 injection for COVID-19 in adults 18 years and older in mRNA-1283-P101 (dose levels up to CCI µg) and in mRNA-1283-201 (dose

levels up to [redacted] µg) revealed no significant safety concerns. The safety and reactogenicity profiles of mRNA-1283 ([redacted] µg) and mRNA-1283.11 ([redacted] µg) were overall similar to mRNA-1273 ([redacted] µg). The Sponsor is currently evaluating mRNA-1283.222 [redacted] µg and mRNA-1283.815 [redacted] µg in a Phase 3 study (NCT05815498). More than 6000 adults have received mRNA-1283 in clinical trials. No significant safety concerns have been identified to date.

Safety and efficacy have been established for mRNA-1273. In the post-authorization period, there have been very rare reports of anaphylaxis following mRNA-1273 administration. In addition, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines.

The combined administration of mRNA-1010 and mRNA-1283 as mRNA-1083 may or may not offer protection against seasonal influenza and/or COVID-19, respectively.

Considering the nonclinical data for the combined administration of mRNA-1010 and mRNA-1283 vaccines and the clinical safety and immunogenicity data for mRNA-1010, mRNA-1283, mRNA-1273.222, and other mRNA vaccines manufactured to date by the Sponsor that contain the proprietary SM-102 lipid formulation, the Sponsor considers the potential benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

3.1. Part 1

The objectives and endpoints for the Part 1 (Phase 1/2) of the study are presented in the table below:

Objectives	Endpoints
Primary	
To evaluate the safety and reactogenicity of study intervention administration across study treatment arms	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • Unsolicited severe AEs through 28 days after injection • Unsolicited MAAEs from Day 1 to Day 181/EoS • Unsolicited AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS
Secondary	
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at Day 29	• GMT and GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥4-fold if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline titer is <LLOQ in nAb titers measured by PsVNA
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at all evaluable humoral immunogenicity time points	• GMT and GMFR at all evaluable timepoints compared with Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
Exploratory (may be performed)	
To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable timepoints compared with Day 1 by HAI for influenza and PsVNA for SARS-CoV-2

Objectives	Endpoints
	• Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable timepoints compared with Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
To evaluate the cellular immune responses against influenza and SARS-CoV-2 in a subset of participants	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods • Perform targeted repertoire analysis of B-cells and T-cells after injection
To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses
To assess the occurrence of clinical influenza and COVID-19 in study participants and characterize their immune response to infection and viral isolates	• Frequency of RT-PCR-confirmed clinical influenza and COVID-19 • Assessment of immune responses to infection and viral isolates

Abbreviations: AE = adverse event; AR = adverse reaction;; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutination; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; RT-PCR = reverse transcription polymerase chain reaction; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2.

3.2. Part 2

The objectives and endpoints for the Part 2 (Phase 2) of the study are presented below:

Objectives	Endpoints
Primary	
To evaluate the safety and reactogenicity of study intervention administration across study treatment arms	• Solicited local and systemic ARs through 7 days after injection • Unsolicited AEs through 28 days after injection • Unsolicited Severe AEs through 28 days after injection • Unsolicited MAAEs from Day 1 to Day 181/EoS • Unsolicited AESIs from Day 1 to Day 181/EoS • SAEs from Day 1 to Day 181/EoS • Unsolicited AEs leading to discontinuation from Day 1 to Day 181/EoS

Objectives	Endpoints
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at Day 29	• GMT and GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, defined as a Day 29 titer CCI if Baseline is CCI or a 4-fold or greater rise if Baseline is CCI in anti-HA antibodies measured by HAI assay • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 titer ≥4-fold if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline titer is <LLOQ in nAb titers measured by PsVNA
Secondary	
To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment arms at all evaluable humoral immunogenicity time points	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
Exploratory (may be performed)	
To evaluate the humoral immune responses to vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by HAI for influenza and PsVNA for SARS-CoV-2 • Influenza: Percentage of participants with seroconversion, as defined above • SARS-CoV-2: Percentage of participants with seroresponse, as defined above
To evaluate the humoral immune responses against vaccine-matched and vaccine-mismatched strains for influenza and SARS-CoV-2 across study treatment arms	• GMT and GMFR at all evaluable time points compared to Day 1 by alternative methods, including, but not limited to: microneutralization assay for influenza or ligand-binding assay for SARS-CoV-2
To further characterize the immune response to influenza and SARS-CoV-2 across study treatment arms	• Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses

Abbreviations: AE = adverse event; AR = adverse reaction;; COVID-19 = coronavirus disease 2019; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HA = hemagglutination; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; RT-PCR = reverse transcription polymerase chain reaction; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2.

4. STUDY DESIGN

4.1. Overall Design

The study is divided into 2 parts:

Part 1 of the study will be a Phase 1/2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.222, mRNA-1273.222, and licensed active-control vaccines, Fluarix and Fluzone® HD (Cohort A only) in healthy adults ≥18 to <80 years of age (Cohort A is in adults ≥65 to <80 years of age and Cohort B is in adults ≥18 to <65 years of age).

Approximately, 1224 participants will be enrolled into 1 of 2 age cohorts: Cohort A for adults ≥65 to <80 years of age or Cohort B for adults ≥18 to <65 year of age. In Cohort A, approximately 600 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since September 2022). In Cohort B, approximately 624 participants will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by 2 age groups: ≥18 to <50 years and ≥50 to <65 years of age and by influenza vaccine status in the most recent influenza season (received or not received since September 2022). Approximately 50% of the participants in Cohort B will be ≥50 to <65 years of age.

Part 2 of the study will be a Phase 2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels compared with active-control vaccines mRNA-1010, mRNA-1283.815, mRNA-1273.815, and licensed active-control vaccine, Fluarix in young healthy adults ≥18 to <50 years of age.

Approximately, 520 participants between ≥18 to <50 years of age will be randomized (in equal allocation ratio) into the investigational treatment arms, stratified by influenza vaccine status in the most recent influenza season (received or not received since Sept 2023).

The study will be performed in 2 parts, and results for each part of the study will be provided as a separate clinical study report.

4.2. Scientific Rationale for Study Design

The Sponsor is developing mRNA-1083, a lipid-encapsulated mRNA-based prophylactic combination vaccine encoding influenza and SARS-CoV-2 antigens. mRNA-1083 contains 5 to 6 mRNAs: 4 sequences encoding surface glycoprotein hemagglutinin (HA) of seasonal influenza viruses and 1 to 2 sequences encoding linked NTD and RBD of SARS-CoV-2 spike proteins. mRNA-1083 encodes the respective antigens also encoded by mRNA-1010 (seasonal influenza) and mRNA-1283 (SARS-CoV-2 booster).

The administration of the mRNA-1083 vaccine has the potential to efficiently reduce the overall burden of acute viral respiratory diseases by providing simultaneous protection against influenza and SARS-CoV-2 viruses in a convenient dosing regimen. mRNA-1083 offers greater convenience and has the potential to lead to increased compliance with vaccine recommendations, an approach which has been frequently used for pediatric vaccines

(Kurosky et al 2017). Furthermore, this combined regimen could provide a public health benefit through synergistically increasing coverage rates against influenza and SARS-CoV-2 viruses.

This clinical trial aims to generate safety, reactogenicity, and immunogenicity data of the mRNA-1083 multicomponent influenza and SARS-CoV-2 vaccine in adults aged ≥18 to <80 years.

The study is divided into 2 parts: Part 1 and Part 2. Part 1 (Phase 1/2) includes adults who are 18 to <80 years and Part 2 (Phase 2 Extension) includes adults who are 18 to <50 years.

4.3. Justification for Dose

The selected dose levels in this clinical trial are based on the clinical experience with the component vaccines mRNA-1010 and mRNA-1283, which were evaluated for safety up to CCI µg and CCI µg, respectively. In clinical trials, at least 15,000 adults have been dosed with mRNA-1010 and approximately 6000 participants have been dosed with mRNA-1283.

All of the proposed dosages of mRNA-1083 are lower than maximum dosages of the mRNA-1010 and mRNA-1283 components studied previously in clinical studies.

CCI

4.4. End of Study Definition

For each of the study (Part 1 and Part 2), a participant is considered to have completed the clinical trial once they have completed all periods of the clinical trial including the last scheduled procedure as shown in the Schedule of Assessments (SoA), Section 1.3.

The EoS is defined as completion of the last visit of the last participant in the clinical trial or last scheduled procedure as shown in the SoA for the last participant in each part of the clinical trial globally.

5. STUDY POPULATION

This clinical trial will enroll adult participants ≥18 to <80 years of age. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Part 1 (Phase 1/2)

5.1.1. Inclusion Criteria

Participants are eligible to be included in the clinical trial only if all the following criteria apply:

Age

1. Adults ≥18 to <80 years of age at the time of consent.

Weight

2. Body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2 (inclusive) at the Screening Visit.

Type of Participant and Disease Characteristics

3. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
4. Healthy as determined by medical evaluation, including medical history, physical examination, and laboratory tests.

Sex and Contraceptive/Barrier Requirements

5. Participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized as described in Section 10.6. A FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. Participants of childbearing potential may be enrolled in the study if they fulfill all of the following criteria:

    - Have a negative pregnancy test at the Screening Visit and on the day of study intervention administration.
    - Have practiced adequate contraception, as described in Section 10.6, or have abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
    - Has agreed to continue adequate contraception, as described in Section 10.6, or abstain from all activities that could result in pregnancy through 90 days following study intervention administration.

7. Is not currently breast/chestfeeding.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusion Criteria

9. Fully vaccinated for COVID-19 primary series according to the locally authorized or approved regimen, and their last COVID-19 vaccine (primary series or booster) was ≥120 days prior to Day 1.

5.1.2. Exclusion Criteria

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

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
2. Clinical screening laboratory values (white blood cell count, hemoglobin, hematocrit, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, alkaline phosphatase, and total bilirubin) >Grade 1 or platelets ≥Grade 1 (DHHS 2007).
3. Significant, progressive, unstable, or uncontrolled clinical condition, including any condition that may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures per Investigator judgment.
4. Participants who have undergone surgical procedures within 28 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention administration are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
5. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunocompromizing/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:

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

6. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
7. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA or influenza vaccines or any components of the mRNA or influenza vaccines, including egg protein.
8. Has coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.
9. Diagnosis of malignancy within previous 5 years (excluding nonmelanoma skin cancer).
10. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the clinical trial or could interfere with the interpretation of study results.
11. Has a history of myocarditis, pericarditis, or myopericarditis.
12. Has a history of Guillain-Barre syndrome.
13. Participant has known history of SARS-CoV-2 infection within ≤90 days prior to Day 1.
14. Tested positive for influenza by local health authority-approved testing methods ≤150 days prior to Day 1.

Prior/Concomitant Therapy

15. Received systemic immunosuppressants for >14 days in total within 180 days prior to Screening Visit (for glucocorticoids ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the clinical trial (including intra-articular steroid injections). Inhaled, nasal, and topical steroids are allowed.
16. Received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study intervention administration or plans to receive a vaccine authorized or approved by a local health agency within 28 days after study intervention administration.
17. Received a seasonal influenza vaccine or any other investigational influenza vaccine within 150 days prior to Day 1.
18. Treated with antiviral therapies for influenza (eg, Tamiflu®) within 150 days prior to the Day 1.
19. Treated with any other non-influenza antiviral therapies (including antivirals for treating individuals with HIV or in at-risk individuals as pre-exposure prophylaxis) within 14 days prior to Day 1 or plans to use antiviral therapies within 28 days of study intervention administration.
20. Has received systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the clinical trial.

Prior/Concurrent Clinical Study Experience

21. Participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this clinical trial. Participants may continue in prior interventional study follow-up activities if it does not involve further investigational treatment. **Note**: Interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary.

Other Exclusion Criteria

22. Unaware whether they received an influenza vaccine during or since September 2022.
23. Has had close contact to someone with COVID-19 as defined by the CDC in the past 10 days prior to Day 1.
24. 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 Day 1.
25. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the clinical trial.
26. Working or has worked as study personnel, is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel, or resides in a nursing home.

5.2. Part 2 (Phase 2 Extension)

5.2.1. Inclusion Criteria

Participants are eligible to be included in the clinical trial only if all the following criteria apply:

Age

1. Adults ≥18 to <50 years of age at the time of consent.

Weight

2. Body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2 (inclusive) at the Screening Visit.

Type of Participant and Disease Characteristics

3. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
4. Healthy as determined by medical evaluation, including medical history, and physical examination.

Sex and Contraceptive/Barrier Requirements

5. Participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized as described in Section 10.6. A FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. Participants of childbearing potential may be enrolled in the study if they fulfill all of the following criteria:
   - Have a negative pregnancy test at the Screening Visit and on the day of study intervention administration.
   - Have practiced highly effective contraception, as described in Section 10.6, or have abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
   - Has agreed to continue adequate contraception, as described in Section 10.6, or abstain from all activities that could result in pregnancy through 90 days following study intervention administration.
7. Is not currently breast/chestfeeding.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusion Criteria

9. Have received at least 2 doses of locally authorized or approved COVID-19 vaccines and last dose was >= 90 days prior to Day 1.

5.2.2. Exclusion Criteria

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

Medical Conditions

1. Participants who enrolled in Part 1 of the mRNA-1083-P101 (Phase 1/2) study.

2. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
3. Significant, progressive, unstable, or uncontrolled clinical condition, including any condition that may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures per Investigator judgment (including but not limited to the following examples: IBD, CKD Grade ≥2 or higher), CHF).
4. Participants who have undergone surgical procedures within 28 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study intervention administration are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
5. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunocompromizing/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:

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

6. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
7. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA or influenza vaccines or any components of the mRNA or influenza vaccines, including egg protein.
8. Has coagulopathy or bleeding disorder considered a contraindication to IM injection or phlebotomy.
9. Any malignancy within previous 5 years (excluding nonmelanoma skin cancer).
10. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the clinical trial or could interfere with the interpretation of study results.
11. Has a history of myocarditis, pericarditis, or myopericarditis with onset within 90 days prior to Day 1 or whose values have not returned to Baseline clinical status.
12. Has a history of Guillain-Barre syndrome.
13. Participant has known history of SARS-CoV-2 infection within ≤90 days prior to Day 1.
14. Tested positive for influenza by local health authority-approved testing methods ≤150 days prior to Day 1.

Prior/Concomitant Therapy

15. Received systemic immunosuppressants for >14 days in total within 180 days prior to Screening Visit (for glucocorticoids ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the clinical trial (including intra-articular steroid injections). Inhaled, nasal, and topical steroids are allowed.
16. Received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study intervention administration or plans to receive a vaccine

authorized or approved by a local health agency within 28 days after study intervention administration.
17. Received a seasonal influenza vaccine ≤150 days prior to Day 1.
18. Received any investigational seasonal influenza vaccine study ≤12 months prior to Day 1
19. Treated with antiviral therapies for influenza (eg, Tamiflu®) within 150 days prior to the Day 1.
20. Treated with any other non-influenza antiviral therapies (including antivirals for treating individuals with HIV or in at-risk individuals as pre-exposure prophylaxis) within 14 days prior to Day 1 or plans to use antiviral therapies within 28 days of study intervention administration.
21. Has received systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the clinical trial.

Prior/Concurrent Clinical Study Experience

22. Participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this clinical trial. Participants may continue in prior interventional study follow-up activities if it does not involve further investigational treatment. **Note**: Interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary.

Other Exclusion Criteria

23. Unaware whether they received an influenza vaccine during or since September 2023.
24. Has had close contact to someone with COVID-19 as defined by the CDC in the past 10 days prior to Day 1.
25. 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 Day 1.
26. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the clinical trial.

Working or has worked as study personnel, is an immediate family member or household member of study personnel, study site staff, or Sponsor personnel, or resides in a nursing home.

5.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

Participants in the clinical trial should defer vaccination with licensed seasonal influenza vaccine or an authorized/licensed COVID-19 vaccine until after completion of their Day 29 visit, and ideally until Day 181. If such vaccines are available, participants should discuss with the Investigators prior to receiving these nonstudy vaccines.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of

Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

The Sponsor is using its mRNA-based platform to develop a custom-manufactured LNP-encapsulated, mRNA-based vaccines against diseases caused by influenza virus types A and B and SARS-CoV-2. The mRNA vaccines to be used in this clinical study are shown in Table 3 (Part 1) and Table 4 (Part 2). The mRNAs comprising each vaccine are formulated in a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG200-DMG. All injections are administered intramuscularly (IM).

6.1.1. Part 1 (Phase 1/2)

In Part 1 of the study, all participants will receive a single IM injection of study intervention (Table 5) administered in a deltoid muscle on Day 1.

The components of the mRNA vaccines to be used in Part 1 of are shown in Table 3.

The term investigational product (IP) in Part 1 of the study refers to the mRNA-1083 (mRNA-1083.1, mRNA-1083.2, mRNA-1083.3). Non-IP experimental comparators administered in this clinical trial are mRNA-1010CCI, mRNA-1010, mRNA-1283.222, and mRNA-1273.222 vaccines. Fluarix and Fluzone HD are licensed vaccine comparators.

Table 5: Study Arm(s) and Interventions (Part 1 – Phase 1/2)

Cohort A Arms: (≥65 to <80 years), n=50/arm, 600 total	Cohort B Arms: (≥18 to <65 years), n=52/arm, 624 total	Intervention	Total mRNA Dose (µg)[5] CCI	Intervention Type
NA	B1	mRNA-1083.1	CCI	IP
A2	B2	mRNA-1083.1		IP
A3	B3	mRNA-1083.1		IP
A4	B4	mRNA-1083.2		IP
A5	B5	mRNA-1083.2		IP
A6	B6	mRNA-1083.2		IP
A7	B7	mRNA-1083.3		IP
A8	B8	mRNA-1010CCI		Non-IP experimental comparator
A9	B9	mRNA-1283.222		Non-IP experimental comparator
A10	B10	mRNA-1273.222		Non-IP experimental comparator

Cohort A Arms: (≥65 to <80 years), n=50/arm, 600 total	Cohort B Arms: (≥18 to <65 years), n=52/arm, 624 total	Intervention	Total mRNA Dose (µg)[1] CCI	Intervention Type
A11	B11	mRNA-1010	CCI	Non-IP experimental comparator
A12	B12	Fluarix		Licensed vaccine comparator
A13	NA	Fluzone HD		Licensed vaccine comparator

[1] Total mRNA dose is rounded to the nearest C µg.

CCI

Abbreviations: HD = high dose; IP = investigational product; mRNA = messenger ribonucleic acid; NA = not applicable; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2

6.1.2. Part 2 (Phase 2 - Extension)

In Part 1 of the study, all participants will receive a single IM injection of study intervention (Table 6) administered in a deltoid muscle on Day 1.

The components of the mRNA vaccines to be used in Part 2 are shown in Table 4.

The term IP in Part 2 of the study refers to mRNA-1083 (CCI and mRNA-1083 CCI). Non-IP experimental comparators administered in this clinical trial are mRNA-1010CCI, mRNA-1283.815 and mRNA-1273.815 vaccines. Fluarix is the licensed vaccine comparator.

Table 6: Study Arm(s) and Interventions (Part 2 – Phase 2 Extension)

Part 2 Arm: (≥18 to <50 years), n=40/arm, 520 total	Intervention	CCI	Intervention Type
1	mRNA-1083 CCI		IP
2	mRNA-1083 CCI		IP
3	mRNA-1083 CCI		IP
4	mRNA-1083 CCI		IP
5	mRNA-1083 CCI		IP
6	mRNA-1083 CCI		IP
7	mRNA-1083 CCI		IP
8	mRNA-1083 CCI		IP
9	mRNA-1010CCI		Non-IP experimental comparator
10	mRNA-1010CCI		Non-IP experimental comparator
11	mRNA-1283.815		Non-IP experimental comparator
12	mRNA-1273.815		Licensed vaccine comparator
13	Fluarix		Licensed vaccine comparator

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

See full prescribing information for detailed information for the preparation, handling, and storage of Fluarix (Glaxosmithkline Biologicals) and Fluzone HD (Sanofi Pasteur Inc).

6.2.1. Preparation of Study Injection

The IP, non-IP, and experimental comparators preparation instructions are detailed in the Pharmacy Manual.

6.2.2. Clinical Study Material Packaging and Labeling

All IPs used in this clinical trial will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP guidelines, guidelines for Quality System Regulations, and applicable regulations. For further direction, refer to the Pharmacy Manual.

6.2.3. Clinical Study Material Storage

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

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

6.2.4. Clinical Study Material Accountability

It is the Investigator’s responsibility that the IP accountability study staff maintain accurate records in an IP accountability log of receipt of all IP, site IP inventory, IP dispensing, IP injections, and return to the Sponsor or alternative disposition of used and unused IP vials.

A site monitor will review the inventory and accountability log during site visits and at the completion of the clinical trial. For further direction, refer to the Pharmacy Manual.

6.2.5. Clinical Study Material Handling and Disposal

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

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

6.3. Assignment to Study Intervention

Randomization will be performed using an interactive response technology (IRT).

6.4. Blinding

The treatment assignment, including the injection site and the corresponding vaccine administered, will be concealed by having the delegated unblinded study personnel prepare the study intervention in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

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

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the clinical trial, the Investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified timepoint(s) for analysis as outlined in Section 9.1.

6.5. Study Intervention Compliance

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

6.6. Dose Modification

No dose modifications will be made to the study interventions as planned.

6.7. Criteria for Temporarily Delaying Study Vaccination

Body temperature must be measured before study intervention administration. The following events constitute criteria for delay of study intervention administration, and if either of these events occur at the time scheduled for dosing, the participant may be injected at a later date within the time window specified in the SoA (Table 1), or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7.2):

- 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 fever ≥38.0°C (100.4°F) 72 hours prior to or at the Screening Visit or Day 1 may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number. If the Investigator determines that the participant's health on the day of dosing temporarily precludes study intervention administration, the visit should be rescheduled within the allowed interval for that visit.

If a participant takes a prohibited drug therapy, study intervention administration could be delayed within the visit window based on the joint decision of the Investigator and the CRO's medical monitor (Section 6.10.3).

6.8. Treatment of Overdose

As study intervention is to be administered by a healthcare professional (HCP), it is unlikely that an overdose will occur, as each participant will receive a single injection. However, in the event of an overdose, the Investigator should:

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

Dose deviations will be tracked as protocol deviations (Section 10.1.6).

6.9. Continued Access to Study Investigational Product After the End of the Study

Study intervention administration consists of a single injection; as such, there will be no access to study intervention after the end of the clinical trial.

6.10. Prior and Concomitant Therapy

6.10.1. Prior Medications

- Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.
- Historical use of facial injections or dermal fillers.
- Any seasonal influenza vaccine administered during or since September 2022 (for Part 1 of the study).

  Any seasonal influenza vaccine administered during or since September 2023 (for Part 2 of the study).
- Any authorized or investigational COVID-19 vaccine at any time before study intervention administration.

6.10.2. Concomitant Medications and Therapies

At study site, study staff must record the following information in the eCRF after questioning participants regarding any prohibited or allowed medications taken or non-study vaccinations received:

- All non-study vaccinations administered within the period starting 28 days before the study intervention administration and through EoS.
- All concomitant medications taken through 28 days after study intervention 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.
- Systemic steroids (≥10 mg/day of prednisone or equivalent), immunosuppressants, immunoglobulins, or long-acting biological therapies that affect immune responses (eg, infliximab), or blood products administered at any time during the clinical trial period after study intervention administration through EoS.
- Any concomitant medications used to prevent or treat either COVID-19 or influenza through EoS.
- Antiviral and antiretroviral medications through EoS.
- Any concomitant medications relevant to or for the treatment of an SAE, AESI, or an MAAE from Day 1 through EoS.
- Any antipyretic or analgesic medications taken to treat or prevent fever or pain, as indicated in the participant's eDiary.

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

6.10.3. Prohibited Therapy

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the clinical trial but may determine a participant's evaluability in the per protocol (PP) analysis (analysis sets are described in Section 9.3.2):

- Any investigational or nonregistered product (drug or vaccine) other than the study interventions used during the clinical trial period.
- Immunosuppressants administered during the clinical trial period. For corticosteroids, ≥10 mg/day of prednisone or equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- An authorized or licensed vaccine administered during the period from 28 days before through 28 days after vaccination.
- Immunoglobulins or long-acting biological therapies that affect immune responses (eg, infliximab) or any blood products administered during the clinical trial period.
- Antiviral and antiretroviral medications.

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

Discontinuation of specific sites or of the clinical trial as a whole are detailed in Section 10.1.14.

7.1. Pause Rules

Study pause rules will be continuously monitored during all periods of the clinical trial by the Investigators and the study team, as well as the IST as warranted. The study team or IST may request that the clinical trial be paused due to a safety concern, further study intervention will be suspended, but all other planned procedures relating to safety, reactogenicity, and immunogenicity assessments will continue as described in the study protocol. An unblinded statistician will support the determination if study pause rules have been met. The Sponsor will notify the Center for Biologics Evaluation and Research within 48 hours in the event of a study pause.

- The occurrence of any of the events listed in Table 7, regardless of treatment group, will result in immediate suspension of dosing and enrollment. An unscheduled IST will be convened to assess specific data concerns and to make recommendations.
- The occurrence of safety events listed in Table 7 will pause study intervention administration based on defined threshold levels, which are aggregate incidences relative to the number of exposed participants within a treatment group.

Table 7: Pause Rule Criteria, Events, and Thresholds

Pause Rule	Event	Number of Participants[a]
Single Event		
1	Any SAE that cannot be reasonably attributed to a cause other than study intervention	≥1
2	Any Grade 4[b] systemic or local solicited AR that cannot be reasonably attributed to a cause other than study intervention	≥1
3	Any case of myocarditis and/or pericarditis that cannot be reasonably attributed to a cause other than study intervention	≥1
Proportion of Participants		
4	Any severe unsolicited nonserious AE that cannot be reasonably attributed to a cause other than the study intervention (independent of within or not within the same system organ class)	≥2 of the initial 10 participants in the same study arm or ≥20% of participants within the same study arm after the initial 10 participants have been dosed
5	Any Grade 3 solicited local AR lasting more than 48 hours that cannot be reasonable attributed to a	≥2 of the initial 10 participants in the same study arm or ≥20% of participants within the same study

Pause Rule	Event	Number of Participants[a]
	cause other than the study intervention, starting within the 7-day post-injection period[b]	arm after the initial 10 participants have been dosed[c]
6	Any Grade 3 solicited systemic AR lasting more than 48 hours (24 hours for fever) that cannot be reasonably attributed to a cause other than vaccination, starting within the 7-day post-injection period[b]	≥2 of the initial 10 participants in the same study arm or ≥20% of participants within the same study arm after the initial 10 participants have been dosed[c]

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

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

b. Grading of parameters will be based on the US FDA Guidance for Industry "Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials" (DHHS 2007).

c. Reactogenicity eDiary data confirmed by the Investigator as being entered by the participant in error will not contribute toward a stopping rule.

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

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

7.2. Discontinuation of Study Intervention

Participants who withdraw or are withdrawn from the clinical trial will not be replaced. From an analysis perspective, a "withdrawal" from the clinical trial refers to a situation wherein a participant does not return for the final visit foreseen in the protocol.

Participants can withdraw consent and withdraw from the clinical trial at any time, for any reason, without prejudice. The Investigator will request that the participant complete all study procedures pending at the time of withdrawal.

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

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

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

- AE

- Death
- Lost to follow-up (LTFU)
- Other
- Physician decision
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by participant

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

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

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (see Section 10.1.9).

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the clinical trial.
- 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 source document.

If the registered/certified letter is signed by the participant but no other contact is established, the participant is considered to be noncompliant with study visits or procedures and will be considered to have withdrawn from the clinical trial.

If due diligence, as described above, has been completed, and the participant continues to be unreachable, the participant will be considered LTFU.

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF (as detailed in Section 10.1.4). Participants will undergo study procedures at the timepoints specified in the SoA (Table 1 for Part 1 and Table 2 for Part 2). A participant can also be seen for an unscheduled visit at any time during the clinical trial, at the discretion of the Investigator. Reasons for an unscheduled visit may include, but are not limited to, reactogenicity issues, symptoms of potential ILI and/or COVID-19, or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review electronic diaries (eDiaries) requirements, or follow-up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency," Investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoA (Table 1 for Part 1 and Table 2 for Part 2). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the clinical trial.
- 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.
- 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.
- The Screening Visit and Day 1 visit will not be performed on the same day for Part 1 of the study but may be completed on the same day for Part 2. Additionally, the Screening Visit assessments may be performed over multiple visits if within the 28-day Screening window.

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

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

8.1. 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. Clinically significant findings that were present prior to the signature of the informed consent will also be included in EDC.

8.2. Immunogenicity Assessments

8.2.1. Part 1 (Phase 1/2)

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

- Influenza: Serum antibody level as measured by HAI assay and potentially serum neutralizing antibody (nAb) level as measured by microneutralization assay.
- SARS-CoV-2: Serum nAb titers as measured by pseudovirus neutralization assay (PsVNA) assay and potentially serum binding antibody titers by enzyme-linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.
- Cellular immunogenicity in a subset of participants.

This clinical trial is not powered for efficacy assessment, but any reports of clinical influenza or COVID-19 will be summarized by study group as an exploratory descriptive analysis.

8.2.2. Part 2 (Phase 2 Extension)

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

- Influenza: Serum antibody level as measured by HAI assay and potentially serum neutralizing antibody (nAb) level as measured by microneutralization assay.
- SARS-CoV-2: Serum nAb titers as measured by pseudovirus neutralization assay (PsVNA) assay and potentially serum binding antibody titers by enzyme-linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.

8.3. Safety Assessments

8.3.1. Part 1 (Phase 1/2)

Safety assessments will include monitoring and recording of the following for each participant according to the SoA:

- Solicited local and systemic ARs that occur during the 7 days following study intervention administration (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.

- Unsolicited AEs observed or reported during the 28 days following study intervention administration (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- Unsolicited AEs leading to discontinuation from dosing and/or study participation from Day 1 through EoS or discontinuation from the clinical trial.
- Unsolicited MAAEs from Day 1 through EoS or discontinuation from the clinical trial.
- SAEs from Day 1 through EoS or discontinuation from the clinical trial.
- Unsolicited AESIs from Day 1 through EoS or discontinuation from the clinical trial.
- Details of all pregnancies in participants will be collected postinjection and until the end of their participation in the clinical trial. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after the end of the clinical trial may not be collected in the clinical database.
- Results of safety laboratory tests.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.
- **For participants ≥18 to <51 years of age only**: 12-lead electrocardiogram (ECG) obtained at Visit 1/Day 1 prior to injection.

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

8.3.2. Part 2 (Phase 2 Extension)

Safety assessments will include monitoring and recording of the following for each participant according to the SoA:

- Solicited local and systemic ARs that occur during the 7 days following study intervention administration (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following study intervention administration (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- Unsolicited AEs leading to discontinuation from dosing and/or study participation from Day 1 through EoS or discontinuation from the clinical trial.
- Unsolicited MAAEs from Day 1 through EoS or discontinuation from the clinical trial.
- SAEs from Day 1 through EoS or discontinuation from the clinical trial.
- Unsolicited AESIs from Day 1 through EoS or discontinuation from the clinical trial.

- Details of all pregnancies in participants will be collected postinjection and until the end of their participation in the clinical trial. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after the end of the clinical trial may not be collected in the clinical database.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.
- 12-lead ECG obtained at Visit 1/Day 1 prior to injection.

Planned timepoints for all safety assessments are provided in the SoA (Table 2).

8.3.3. Physical Examinations (Part 1 and Part 2)

- A complete physical examination will include, at a minimum, assessments of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, musculoskeletal system, and extremities. Height and weight will also be measured and recorded. At Screening, the BMI will be calculated using the formula weight (kg) / (height [m])^2.
- On the day of injection (Day 1), prior to injection, axillary lymph nodes of the injection arm(s) will be examined, and any abnormalities will be documented.
- Symptom-directed physical examinations will be performed at all clinic visits, except at Screening, where a full examination will be performed. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant finding identified by an HCP during postinjection study visits should be reported as an AE. Investigators should also pay special attention to clinical signs related to previous serious illnesses.

8.3.4. Vital Signs (Part 1 and Part 2)

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the timepoints indicated in the SoA (Table 1 and Table 2). On the day of study intervention administration, vital sign measurements will be collected once before and at least 60 minutes after study intervention. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

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

Participants who are febrile (body temperature ≥38.0°C/100.4°F) before injection on Day 1 should be rescheduled within the relevant window period to receive the injection. Participants

who are afebrile with minor illnesses may be administered study intervention at the discretion of the Investigator.

When procedures overlap and are scheduled to occur at the same timepoint, the order of procedures should be vital sign measurements and then blood collection.

8.3.5. Electrocardiograms (Part 1 and Part 2)

For participants aged ≥18 to <51 only, a 12-lead ECG will be obtained, after 10 minutes of supine rest, as outlined in the SoA (Table 1 and Table 2). Skin preparation should be thorough and electrode placement should be according to standard 12-lead ECG procedure. The purpose of the ECG is to serve as a Baseline comparison, should it be necessary, for subsequent clinical evaluation of suspected myocarditis and/or pericarditis. The ECG output should be filed in the participant's binder, and the Investigator will not be expected to document an ECG reading. Central reading of the ECG will not be performed. Clinically significant abnormal ECG findings, if incidentally observed by the Investigator, may contribute to Investigator's assessment of eligibility, at his or her discretion, as per Part 1 Exclusion Criterion 3 and Part 2 Exclusion Criterion 3.

8.3.6. Clinical Safety Laboratory Tests (Part 1)

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).

Safety laboratory tests will consist of white blood cell count, hemoglobin, hematocrit, platelets, AST, ALT, creatinine, alkaline phosphatase, and total bilirubin.

Additional blood samples for safety laboratory tests may be taken at the discretion of the Investigator if warranted to ensure participant's safety.

- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the clinical trial as an AE. The laboratory results must be retained with source documents.
- All Screening laboratory results must be reviewed prior to dosing of any study intervention to ensure that the participant's laboratory values meet all inclusion and exclusion criteria.
- All laboratory tests with values considered clinically significantly abnormal during participation in the clinical trial should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or medical monitor. If clinically significant abnormal values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

8.3.7. Assessment for Respiratory Viral Infection

8.3.7.1. Part 1 (Phase 1/2)

During the clinical trial, participants might experience symptoms consistent with ILI or SARS-CoV-2 infection. All participants will provide nasal swab samples before the injection on

Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments. Throughout the clinical trial, the participant will be instructed to contact the study site if they have symptoms suggestive of ILI (Section 10.3.7) or SARS-CoV-2 (Section 10.3.8). An unscheduled visit for symptom assessment and nasal swab for viral respiratory pathogens will be conducted within 7 days of the onset of any potential ILI or SARS-CoV-2 symptoms.

Planned timepoints for all safety and immunogenicity assessments are provided in the SoA (Table 1).

8.3.7.2. Part 2 (Phase 2 Extension)

All participants will provide nasal swab samples before the injection on Day 1 for assessment of infection with respiratory pathogens, including influenza viruses and SARS-CoV-2, as influenza or COVID-19 symptoms may confound reactogenicity assessments.

8.3.8. Pregnancy Testing (Part 1 and Part 2)

Participants who have a positive pregnancy test at Screening must not be enrolled.

Planned timepoints for pregnancy testing are provided in the SoA (Table 1 and Table 2).

For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before injection. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. For participants of nonchildbearing potential, the FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status (please see Section 10.6 for details).

Additional pregnancy testing during the clinical trial may also be performed if required by local regulatory requirements.

8.3.9. Safety Telephone Calls (Part 1 and Part 2)

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls will follow a schedule for each participant, as shown in the SoA (Table 1 and Table 2). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from study participation, concomitant medications associated with those events, and any nonstudy vaccinations. All safety information collected from the phone call must be documented in the source documents as described by the participant and not documented on the script used for the phone call. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event. A safety telephone call may trigger an unscheduled visit.

8.3.10. Electronic Diaries (Part 1 and Part 2)

At the time of consent, participants must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or a device that will be provided at the time of enrollment. The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements).

Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided with an eDiary device to record solicited ARs (Section 10.3.3) on Day 1. Participants will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

On Day 1 (dosing day), study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants to assess body temperature and injection site reactions, respectively, for recording solicited ARs in the eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

On Day 1 (injection day), participants will activate their eDiary and record data into the eDiary starting approximately 1 hour after the injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of study intervention administration and for 6 days following study intervention administration, for a total of 7 days.

Participants will record the following data in the eDiary during the 7 days following study intervention administration:

- Solicited local and systemic ARs (Section 10.3.3). ARs beyond Day 7 should be reviewed either during the next scheduled telephone call or at the following study site visit.
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Other measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever.

Study site staff (or delegate) will review all eDiary data with participants during the Day 8 visit (Visit 2) after vaccination. However, if a Grade 3 or Grade 4 AR is reported at any time during the first 7 days after vaccination, the site will contact the participant in sufficient time to determine if a potential pause rule has been met (as per Section 7.1). The sites should have a process in place for monitoring and follow-up of potential pause rule events on nonbusiness days while dosing is actively taking place on the study. The site should report potential pause rule events or to make clarifications in the EDC when there are discrepancies between the participant's reported Grade 3 or above solicited AR on eDiary and the site's assessment.

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

The definitions of AEs and SAEs can be found in Section 10.3.1 and Section 10.3.2, respectively. The definitions of unsolicited and solicited adverse events, as well as MAAEs, are found in Section 10.3.3 and Section 10.3.4, respectively. The definition of AESI can be found in Section 10.3.6.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, of special interest, considered related to the study intervention or study procedures, or that caused the participant to discontinue the clinical trial. 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 unsolicited AEs will be collected from the day of study intervention administration through 28 days postinjection.

All AEs leading to study discontinuation, MAAE, SAEs, and AESIs will be collected from the start of study intervention administration until EoS visit at the timepoints specified in the SoA (Table 1 and Table 2).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours of becoming aware of the event via the EDC. If a site receives a report of a new SAE or AESI from a study participant or receives updated data on a previously reported SAE or AESI and the eCRF has been taken offline, then the site can report this information on a paper SAE/AESI form via the contact information provided on the form (Section 10.3.10).

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

Investigators are not obligated to actively seek AEs or SAEs after EoS participation. However, if the Investigator learns of any SAE at any time after a participant has withdrawn from or completed the clinical trial and the Investigator considers the event to be reasonably related to the study intervention administration or study participation, the Investigator must promptly notify the Sponsor.

Active and passive surveillance for ILI and COVID-19 will be conducted from Day 1 through EoS. Participants who develop ILI or COVID-19 will be followed through 30 days from the onset of ILI, even if Day 30 is beyond EoS.

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 clinical trial, it will be recorded and reported as an AE.

8.4.2. Method of Detecting AEs and SAEs

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

AEs may be collected as follows:

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

8.4.3. Eliciting and Documenting Adverse Events

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

At every study site visit or telephone contact, participants will be asked if they had any changes in their health or illnesses (including ILI and COVID-19 symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any nonstudy vaccinations.

In addition to participant observations, physical examination findings or data relevant to participant safety that are classified as AEs will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.3). All contacts, or contact attempts, concerning follow-up of AEs/SAEs should be recorded in the participant's source documentation.

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, IRB or IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected SAEs (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

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 their local IRB/IEC if appropriate according to local requirements.

8.4.5. Pregnancy

Details of all participant pregnancies will be collected after the start of study intervention. Participants who become pregnant at any time during the clinical trial should remain in the clinical trial and complete all study visits as scheduled.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered as SAEs. The Investigator must immediately report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence, using the SAE Mailbox or the SAE Fax line (Section 10.3.10). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome. This follow-up should occur even if intended duration of the safety follow-up for the clinical trial has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this clinical trial.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this clinical trial.

8.7. Genetics

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

The ICF will contain a separate consent form that addresses the use of this sample.

8.8. Biomarkers

Transcriptomic and genomic samples will be part of the optional biomarker assessment as per the SoA once consented by the study participant. Exploratory assessments may include assessment of biomarkers for safety, reactogenicity, and inflammation. Serologic markers of disease severity, immune response to SARS-CoV-2 or influenza, reverse transcription polymerase chain reaction (RT-PCR) of nasal swab samples, genetic sequences of SARS-CoV-2 or influenza strains isolated from participants' samples, and genomic and transcriptomic samples may also be evaluated. Samples will be collected according to the schedule described in the SoA (Table 1 and Table 2) and as detailed in the laboratory manual provided separately to sites.

Plasma and serum samples for potential cardiac biomarker analysis will be collected and banked from participants ≥18 to <51 years of age according to the schedule described in the SoA (Table 1 and Table 2) and as detailed in the laboratory manual provided separately to sites. If indicated, and requested by ModernaTX, testing of cardiac biomarkers may be performed.

The Sponsor may store samples for the time period specified in the ICF to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by the Sponsor or in collaboration with others such as universities or other companies to contribute to the understanding of vaccine response or other diseases, the development of related or new treatments, or research methods.

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 clinical trial.

9. STATISTICAL CONSIDERATIONS

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

9.1. Blinding and Responsibility for Analyses

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

- Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than 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 study site personnel involved in the conduct of the clinical trial unless this information is necessary in the case of an emergency.
- Unblinded medically qualified study site personnel will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.
- An independent unblinded statistical and programming team will perform the preplanned interim analysis (Section 9.6). Sponsor team members will be prespecified to be unblinded to the interim analysis results and will not communicate the results to the blinded Investigators, study site staff, clinical monitors, or participants.
- The IST will review unblinded safety data provided by the independent unblinded statistician to safeguard the interests of clinical study participants and to help ensure the integrity of the clinical trial. The IST will review unblinded statistical outputs for ad hoc safety reviews triggered by pause rules, should this occur. Section 10.5 provides additional information on IST and safety review.

The treatment assignment, including the injection site and the corresponding vaccine administered, 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 staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is

completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

9.2. Statistical Hypotheses

This clinical trial does not have formal statistical hypothesis testing planned for the primary objectives (safety and reactogenicity). The total sample sizes planned for Part 1 and Part 2 are considered sufficient to provide descriptive summary of the safety and reactogenicity across study treatment arms within each age Cohort for respective parts.

9.3. Sample Size Determination

9.3.1. Part 1

Approximately 1224 participants will be enrolled at an evenly allocated ratio across the 12 treatment arms in Cohort A for adults ≥65 to <80 years of age and 12 treatment arms in Cohort B for adults ≥18 to <65 years of aged, with 50 participants planned for each arm in Cohort A (600 participants in total) and 52 participants planned for each arm in Cohort B (624 participants in total) (Table 8). Approximately 50 participants in each group receiving an investigational injection have approximately 87% (or 92%) probability to observe at least 1 participant with an AE given the true underlying incidence rate of AE is 4% (or 5%).

Table 8: Probability of AEs Based on Sample Size(Part 1)

n	True AE Rate	Probability of 0 AE	Probability of at Least 1 AE Observed
50	2.0%	36.4%	63.6%
50	3.0%	21.8%	78.2%
50	4.0%	13.0%	87.0%
50	5.0%	7.7%	92.3%

9.3.2. Part 2

Approximately, 520 participants will be enrolled at an evenly allocated ratio across the 13 treatment arms in Part 2 for adults ≥18 to <50 years of age, with 40 participants planned for each arm. Approximately 40 participants in each group receiving an investigational injection have approximately 80.5% (or 87.1%) probability to observe at least 1 participant with an AE given the true underlying incidence rate of AE is 4% (or 5%).

Table 9: Probability of AEs Based on Sample Size (Part 2)

n	True AE Rate	Probability of 0 AE	Probability of at Least 1 AE Observed
40	2.0%	44.6%	55.4%
40	3.0%	29.6%	70.4%
40	4.0%	19.5%	80.5%
40	5.0%	12.9%	87.1%

9.4. Analysis Sets

For the purposes of analysis, the following analysis sets are defined in Table 10.

Table 10: Populations for Analyses

Analysis Sets	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.
Full Analysis Set[a]	The FAS consists of all participants who are randomly assigned and receive the study intervention.
Per Protocol Set[b]	The PP Set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a Baseline and at least 1 post-injection assessment at Day 29, have no documented infection (confirmed by RT-PCR test) of either influenza or SARS-CoV-2 on Day 1 and up to Day 29, and have no major protocol deviations that affect the immune response.
Safety Set[c]	The Safety Set consists of all participants who are randomly assigned and receive the study intervention.
Solicited Safety Set[d]	The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data.

Abbreviations: AR = adverse reaction; FAS = full analysis set; PP = per protocol; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV 2 = severe acute respiratory syndrome coronavirus 2.

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

9.5. Statistical Analyses

The statistical analyses in this clinical trial will be planned and performed on the data collected.

The SAP will be developed and finalized before the interim analyses. The SAP will describe the preplanned statistical analysis details and the participant populations to be included in the analyses. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Immunogenicity Analyses

The analysis population of immunogenicity will be the PP Set.

For the immunogenicity endpoints, geometric mean of specific antibody titers with corresponding 95% confidence interval (CI) at each timepoint and geometric mean fold rise (GMFR) of specific antibody titers with corresponding 95% CI at each post-Baseline timepoint over pre-injection Baseline at Day 1 will be provided by treatment arm. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For participants in the groups receiving mRNA-1083, mRNA-1010 or influenza injections, seroconversion rate from Baseline will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each post-Baseline timepoint. Rate of seroconversion is defined as the proportion of participants with either a pre-injection HAI titer CCI and a post-injection HAI titer CCI, or a pre-injection HAI titer CCI and a minimum 4-fold rise in post-injection HAI antibody titer.

For participants in the groups receiving mRNA-1083, mRNA-1283, or mRNA-1273 injections, seroresponse is defined as either participants with GMFR in nAb titers of ≥4-fold at Day 29 compared with Day 1 in those with Baseline titer ≥LLOQ, or Day 29 titer ≥4 × LLOQ if Baseline titer is <LLOQ.

Between-group comparisons will be evaluated for the immunogenicity endpoints (GMT and seroconversion/seroresponse rate difference) in the PP Set; details will be provided in the SAP.

9.5.2. Efficacy Analyses (Part 1 Only)

Analyses of RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed symptomatic SARS-CoV-2 (COVID-19) will be performed on the FAS. The participants will be summarized according to the study treatment groups to which they are randomized into.

Frequency of RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed symptomatic SARS-CoV-2 observed among the participants in the FAS will be summarized according to the treatment groups as randomized.

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 treatment group. Participants will be included in the treatment group corresponding to what they actually received.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to withdrawal from study participation.

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

The number and percentage of participants with unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to withdrawal from study participation will be summarized. Unsolicited AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and presented by MedDRA system organ class (SOC) and preferred term (PT).

Solicited ARs will be coded by SOC and PT according to the MedDRA for AR terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used in this clinical trial with modification for rash, solicited ARs, and vital signs.

The number of events of unsolicited AEs, SAEs, AESIs, MAAEs, severe AEs, and AEs leading to withdrawal from study participation will be reported in summarization tables accordingly.

Table 11 summarizes the analysis strategy for safety parameters. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Table 11: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants	Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	✓	–	✓
Any unsolicited AE	✓	✓	–
Any unsolicited treatment-related AE	✓	✓	–
Any SAE	✓	✓	–
Any treatment-related SAE	✓	✓	–
Any unsolicited AESI	✓	✓	–
Any unsolicited treatment-related AESI	✓	✓	–
Any unsolicited MAAE	✓	✓	–
Any unsolicited treatment-related MAAE	✓	✓	–
Any unsolicited severe AE	✓	✓	–
Any unsolicited treatment-related severe AE	✓	✓	–
Any unsolicited AE leading to withdrawal from study participation	✓	✓	–

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; SAE = serious adverse event.
Notes: 95% CI using the Clopper-Pearson method, ✓=results will be provided.

9.5.4. Exploratory Analyses

Analyses of the exploratory endpoints (if any) will be described in the SAP.

9.6. Planned Analyses

The analysis for each part of the study (Part 1 and Part 2), will be performed independently and reported in a separate CSR.

Part 1:

An interim analysis of safety, reactogenicity, and immunogenicity is planned after all the participants in Cohort A and B have completed the Day 29 visit.

In addition, another interim analysis for reactogenicity only may be performed after all the participants in Cohort A and B have completed the Day 8 visit.

The potential interim analysis as of completion of Day 8 may be performed by an independent team of unblinded statistician and programmers. The interim analysis as of completion of Day 29 will be performed by the study statistician and programmers. The group-level unblinded summary data of the interim analyses may be reviewed by the Sponsor project team for safety

monitoring and/or clinical development planning purposes for the mRNA-1083 project. More details will be documented in the study data blinding plan.

The final analysis of Part 1 will be performed after all the participants in both Cohort A and Cohort B in Part 1 have completed the Day 181/EoS visit.

Part 2:

An interim analysis of safety, reactogenicity, and immunogenicity is planned after all participants have completed the Day 29 visit.

The interim analysis as of completion of Day 29 will be performed by the study statistician and programmers. The group-level unblinded summary data of the interim analyses may be reviewed by the Sponsor project team for safety monitoring and/or clinical development planning purposes for the mRNA-1083 project. More details will be documented in the study data blinding plan.

The final analysis of Part 2 will be performed after all participants in Part 2 have completed the Day 181/EoS visit.

9.6.1. Multiplicity

No multiplicity adjustment will be needed for either within each of the interim and final analyses or between the interim analyses and the final analysis because there will not be formal statistical hypothesis testing planned for the primary objective (safety and reactogenicity) and the interim and final analyses will be based on descriptive summaries using observed data.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This clinical trial 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 clinical trial 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 clinical trial 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 clinical trial 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. Audits and Inspections

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

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

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

10.1.3. Financial Disclosure

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

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.

10.1.4. Informed Consent Process

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

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

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

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

No participant should be obliged to participate in the clinical trial. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the clinical trial. The information must make clear that refusal to participate in the clinical trial or withdrawal from the clinical trial at any stage is without any prejudice to the participant's subsequent care.

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

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

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

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

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

10.1.5. Protocol Amendments

No change or amendment to this protocol may be made by the Investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case, the IRB(s)/IEC(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may affect the conduct of the clinical trial, potential benefit of the clinical trial, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed by the Investigator(s), and approved by the relevant IRB(s)/IEC(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s)/IEC(s) must be provided to the Sponsor before the clinical trial is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the clinical trial is to be conducted. These administrative changes will be released by the Sponsor, agreed by the Investigator(s), and notified to the IRB(s)/IEC(s).

10.1.6. Protocol Deviations

The noncompliance may be either on the part of the participant, the Investigator, or the study site staff (or delegate). As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations to the Sponsor or its designee. All deviations must be addressed in study source documents and reported to the study monitor. Protocol deviations must be sent to the reviewing IRB/IEC per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements.

10.1.7. 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, 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.

10.1.8. Data Protection

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

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

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

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

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

The Investigator and all employees and coworkers involved with this clinical trial may not disclose or use for any purpose other than performance of the clinical trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the

clinical trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

10.1.9. Sample Retention and Future Biomedical Research

The Sponsor may store samples for the time frame specified in the ICF to achieve study objectives. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the clinical trial, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity and include humoral and cellular immune assay methodologies to measure responses to influenza and/or SARS-CoV-2 on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1083 as well as to determine how changes in biomarkers may relate to exposure to mRNA vaccines and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.1.10. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include, but are not limited to, clinicaltrials.gov and clinicaltrialsregister.eu (EU.CTR), as well as other national registries.

10.1.11. Data Quality Assurance

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

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring); methods; responsibilities; and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this clinical trial including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the clinical trial is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this clinical trial must be retained by the Investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

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

10.1.12. Data Collection and Management

This clinical trial will be conducted in compliance with ICH CGP guidelines. This clinical trial will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This clinical trial will use electronic data collection to collect data directly from the investigational site using eCRFs. The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHO - Drug Reference List.

10.1.13. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, eDiaries, medical, and hospital records, Screening logs, ICFs, telephone contact logs, and

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

Data reported on the 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 clinical trial. Also, current medical records must be available.

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

10.1.14. Study and Site Start and Closure

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

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

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

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

- Continuation of the clinical trial represents a significant medical risk to participants.
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.

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.

10.1.15. Publication Policy

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

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 12 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the clinical trial as determined necessary by the Investigator or required by local regulations. If a local sample is clinically indicated, 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.

Investigators must document their review of each laboratory safety report.

Table 12: Protocol-required Safety Laboratory Tests (Part 1)

Laboratory Tests	Parameters
Hematology	• White blood cell (WBC) count
	• Platelet count
	• Hematocrit
	• Hemoglobin
Clinical Chemistry[a]	• Creatinine • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase[b] • Total bilirubin
Pregnancy Testing	• Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for participants of childbearing potential)[c]
Other Screening Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed in participants of nonchildbearing potential only)[d]

a. All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN or ALT [or AST] ≥3 × ULN must be reported to Sponsor in an expedited manner.
b. If alkaline phosphatase is elevated, consider fractionating.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
d. For participants assigned female at birth and of nonchildbearing potential, the FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm menopausal status.

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 defined as any untoward medical occurrence associated with the use of a drug/vaccine in humans, whether or not considered related to the drug/vaccine.

Events Meeting the Adverse Event Definition

Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition, after the study intervention.

- New conditions detected or diagnosed after the study intervention even though they may have been present before the start of the clinical trial.

Events NOT Meeting the Adverse Event Definition

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

An unsolicited AE (Section 10.3.4) is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after vaccination).

10.3.2. Definition of Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- **Results in death**
  A death that occurs during the clinical trial or that comes to the attention of the Investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study intervention.
- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least 1 overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE

regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as AEs; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE. Procedures planned before study entry (eg, hospitalization for preplanned surgical procedure) are not considered SAEs.

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect.**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or 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 medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.3.3. Solicited Adverse Reactions

Solicited ARs are predefined local (at the injection site) and systemic events/symptoms that participants are specifically asked, and which are noted by the participant in their eDiary.

The solicited ARs for this clinical trial include selected signs and symptoms that are typically associated with vaccine reactogenicity. Reactogenicity refers to the occurrence and intensity of local and systemic ARs commonly following vaccination. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.3.10). Participants will record such occurrences in an eDiary on the day of vaccination and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 13 modified from the Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

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

Table 13: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 10 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/ induration (hardness)	<25 mm/ <2.5 cm	25 to 50 mm/ 2.5 to 5 cm	51 to 100 mm/ 5.1 to 10 cm	>100 mm/ >10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
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 to 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

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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 to 38.4°C 100.4 to 101.1°F	38.5 to 38.9°C 101.2 to 102.0°F	39.0 to 40.0°C 102.1 to 104.0°F	>40.0°C >104.0°F

Note: Events listed above but starting >7 days post study intervention administration will be recorded on the AE page of the electronic case report form (eCRF). Causality for each event will be determined per assessment by the Investigator.

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

- Solicited local or systemic AR that results in a visit to an HCP (MAAE; Section 10.3.4)
- Solicited local or systemic AR leading to the participant withdrawing from the clinical trial or the participant being withdrawn from the clinical trial by the Investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days post-injection
- Solicited local or systemic AR that otherwise meets the definition of an SAE

Additionally:

- If a participant reported a solicited AR during the solicited period and did not record the event in the eDiary, the event should be recorded on the Reactogenicity page of the eCRF.
- If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant should notify the site to provide an end date to close out the event on the Reactogenicity page of the eCRF.
- If the participant reported an event after the solicited period (ie, after Day 7), it should be recorded as an AE on the AE page of the eCRF.

10.3.4. Definition of Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a participant eDiary 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 participants 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 participants and by review of available medical records at the next visit.

10.3.5. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, COVID-19 [Section 10.3.8]) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. An unscheduled visit for assessment of protocol-defined ILI is not considered an MAAE unless additional medical evaluation, including examinations/testing not required PP and/or treatment is provided during the visit. All MAAEs will be collected through the entire study period.

10.3.6. Adverse Events of Special Interest

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

Section 10.4 (Appendix 4) provides a list of AESIs pertinent to this clinical trial.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on a paper SAE/AESI form using the SAE Mailbox, or the SAE Fax line (Section 10.3.10).

10.3.6.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours per Section 10.3.10. The Investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as described below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

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

- Anaphylaxis is a clinical syndrome characterized by the following:
- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:

Skin/mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, and red and itchy eyes.

Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, and 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, and rhinorrhea.

Gastrointestinal: diarrhea, abdominal pain, nausea, and vomiting.

10.3.6.2. Myocarditis/Pericarditis/Myopericarditis

Any case that has either a high clinical index of suspicion for myocarditis or pericarditis, or which is considered to be a confirmed case of myocarditis, pericarditis, or myopericarditis, should be reported as an AESI. The event should also be reported as an SAE if it meets seriousness criteria (see Section 10.3.2). The CDC has developed a working case definition for myocarditis, pericarditis, and myopericarditis, which is provided to inform the evaluation of suspected cases (see Section 10.3.6.2). The CDC document is intended for guidance only; the Investigator is expected to apply medical judgment in the evaluation of suspected cases, which may be prompted by a participant reporting symptoms concerning for myocarditis and/or pericarditis (per the CDC case definition).

Similarly, the diagnostic work up (eg, ECG, echocardiogram) and laboratory testing (eg, troponin) outlined in the CDC definition should be considered as a guidance to the Investigator, and promptly obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be considered in those with positive tests results or clinically significant symptoms without other identifiable causes. The Investigator must 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 should continue to be followed in the clinical trial for safety as per the protocol assuming consent is not withdrawn.

In the event that a case is evaluated for myocarditis, pericarditis, or myopericarditis, and the Investigator considers that the findings do not support the diagnosis of myocarditis, pericarditis, or myopericarditis, the case should not be reported as an AESI.

An independent Cardiac Event Adjudication Committee (CEAC) that includes cardiologists will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events and make recommendations to the Sponsor. (Gargano et al 2021). The CEAC operates under the rules of an approved charter. Details

regarding the CEAC composition, responsibilities, procedures, and frequency of data review is defined in its charter.

The CDC case definition is provided in Section 10.7 (Appendix 7) as guidance.

10.3.7. Influenza-Like Illness

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

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

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

An RT-PCR-confirmed ILI is defined as a positive influenza result by RT-PCR done at any setting during the study period.

10.3.8. Suspicion of SARS-CoV-2 Infection

SARS-CoV-2 should be suspected if the participant experiences any one of the symptoms listed below lasting at least 48 hours (except for fever and/or respiratory symptoms) (CDC 2020b):

- Fever (temperature ≥38.0°C [100.4°F]) or chills (of any duration, including ≤48 hours)
- Cough (of any duration, including ≤48 hours)
- Shortness of breath and/or difficulty breathing (of any duration, including ≤48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste and/or smell
- Sore throat, congestion, or runny nose
- Nausea or vomiting
- Diarrhea

Symptomatic COVID-19 is defined by the presence of one of the CDC-listed symptoms (CDC 2020c) and a positive RT-PCR test on a respiratory sample. Asymptomatic SARS-CoV-2

infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test result at the time of enrollment, with the serologic assay detecting previously resolved SARS-CoV-2 infections that may have occurred between visits, and the RT-PCR to detect active viral infection at the time of a visit. If participants are confirmed to have SARS-CoV-2 infection and are symptomatic or asymptomatic, the Investigator will notify the participants' primary care physicians of the diagnosis and the local public health authorities as required per local regulations.

If the participant had known exposure to COVID-19 (eg, exposure to someone with a confirmed case of COVID-19), it will be captured in the COVID-19 exposure form, and the participant will continue to follow all remaining study assessments as scheduled. Likewise, participants with a confirmed case of COVID-19 will continue to follow all remaining study assessments as scheduled.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 7.3.

All unsolicited AEs reported or observed during the clinical trial will be recorded on the AE page of the eCRF. All unsolicited AEs will be collected from start of study intervention through 28 days after injection.

All SAEs reported or observed during the clinical trial will be recorded on the SAE page of the eCRF. All SAEs will be collected from the start of study intervention until EoS visit at the timepoints specified in the SoA (Table 1).

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AEs of special interest (as defined in Section 10.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

10.3.9.1. Assessment of Intensity

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

measurements observed during this clinical trial. Specific criteria for local and systemic reactogenicity events are presented in Section 10.3.3.

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

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

Study staff (or delegate) should elicit from the participant, the impact of AEs on the participant's activities of daily living to assess severity and should document it appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

10.3.9.2. Assessment of Causality

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

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

10.3.10. Reporting of 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.

Any AE considered serious by the Investigator or that meets SAE criteria (Section 10.3.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC. The Investigator will assess whether there is a reasonable possibility that the study intervention caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as required per the applicable regulations. The Investigator is responsible for notifying the IRB/IEC directly.

If the eCRF is unavailable at the time of the SAE, the event should be reported using the provided study-specific paper SAE/AESI Reporting Form and sent via the email address or fax number on the form.

Regulatory reporting requirements for SAEs are described in Section 8.4.4.

10.4. Appendix 4: Adverse Events of Special Interest

The Investigator's medical judgment must be applied to assess an event as an AESI, as most AESIs are based on medical concepts.

Table 14 does not provide a comprehensive list of terms. The table describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, PP, even when they occur during/following COVID infection.

Please note: COVID-19 itself is not an AESI.

Table 14: Adverse Events of Special Interest

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology • DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	• Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) • DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	• New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	• Any event of appendicitis
Rhabdomyolysis	• New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome (ARDS)	• New onset of ARDS/respiratory failure due to acute inflammatory lung injury • DOES NOT INCLUDE nonspecific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	• New onset of thrombosis, thromboembolic event, or nontraumatic hemorrhage/bleeding disorder (eg, stroke, deep vein thrombosis [DVT], pulmonary embolism, disseminated intravascular coagulation [DIC], etc.)

Medical Concept	Additional Notes
Acute cardiovascular injury	• New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by electrocardiogram (eg, atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. • DOES NOT INCLUDE transient sinus tachycardia/bradycardia, nonspecific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	• New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc; • Increase in serum creatinine by ≥0.3 mg/dL (or ≥26.5 μmol/L) within 48 hours; **OR** • Increase in serum creatinine to ≥1.5 times Baseline, known or presumed to have occurred within prior 7 days.
Acute liver injury	• New onset <u>in the absence of a clear, alternate etiology</u>, such as trauma, tumor, hepatotoxic medications/substances, etc: • >3-fold elevation above the upper normal limit for alanine aminotransferase or aspartate aminotransferase; **OR** • >2-fold elevation above the upper normal limit for total serum bilirubin or gamma-glutamyl transferase (GGT) or alkaline phosphatase
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rash • Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	• Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) • Kawasaki's disease • Hemophagocytic lymphohistiocytosis (HLH)

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet count <150 × 10^9/L • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
Acute aseptic arthritis	• Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or polymerase chain reaction test. • DOES NOT INCLUDE new onset of chronic arthritic conditions.
New onset, or worsening, of the following neurological diseases	• Guillain-Barre Syndrome • Acute disseminated encephalomyelitis (ADEM) • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures, including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis associated with study intervention administration as defined PP • Follow reporting procedures in protocol Section 10.3.6.1
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome • Myalgic encephalomyelitis • Post viral fatigue syndrome • Myasthenia gravis

10.5. Appendix 5: Safety Oversight and Committees Structure

10.5.1. Internal Safety Team

Safety monitoring for this clinical trial will include the blinded study team members, inclusive of at a minimum, the Sponsor's medical monitor, a CRO medical monitor and an unblinded IST. The IST is comprised of the Sponsor's physicians, who will not otherwise be involved in the conduct of the clinical trial. The study team will conduct ongoing blinded safety reviews during the clinical trial and will be responsible for notifying the IST of potential safety signal events or the triggering of pause rules. An unblinded statistician will support the determination if study pause rules have been met.

For each Cohort, a scheduled IST safety review will occur after at least 10 participants/arm reach Day 8 (~120 in Cohort A and ~120 in Cohort B). The scheduled IST safety review for each

Cohort may be combined into 1 session for both Cohort A and B if the recruitment rate and the timing of the participants reaching Day 8 are close to each other. Enrollment will be ongoing while this review is conducted if no pause rules have been met and the study team has not identified any safety concerns. Additional ad hoc IST review may occur as outlined by the IST charter.

In Part 2 of the study, there will be no scheduled IST review. An ad-hoc IST review may occur as outlined by the IST charter.

10.5.2. Cardiac Event Adjudication Committee

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

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

10.6. Appendix 6: Contraceptive and Barrier Guidance

Definitions:

Participant of Childbearing Potential

1. Participants are considered participants of childbearing potential (POCBP) (fertile) from the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Participant of Non-Childbearing Potential

1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Participants on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the clinical trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
2. Permanent sterilization methods (for the purpose of this clinical trial) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Documented bilateral tubal ligation
3. 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.

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

Contraception Guidance:

Highly effective contraception is defined as consistent and correct use of a contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a participant's monogamous partner prior to entry into the clinical trial

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the 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[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from 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 clinical trial and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• External or internal condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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

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.] External condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
[d.] Considered effective, but not highly effective - failure rate of ≥1% per year.

10.7. Appendix 7: CDC Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

The CDC working case definition of pericarditis, myocarditis, and myopericarditis to be used in this clinical trial is presented in Table 15.

Table 15: CDC Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable Case**	**Confirmed Case**
	Presence of ≥1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope	Presence of ≥1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope
	OR	**OR**
	Infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy	Infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy
	AND	**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[c] • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[d]	≥1 new finding of • Histopathologic confirmation of myocarditis[b] • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	AND	**AND**
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings

Condition	Definition
Acute pericarditis[d]	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain[f] • pericardial rub on exam • new ST-elevation or PR-depression on ECG • 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; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI=magnetic resonance imaging.

Note: An independent Cardiac Event Adjudication Committee (CEAC) comprised of medically qualified personnel, including cardiologists, will review reported 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.

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

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

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

d. Using either the original or the revised Lake Louise criteria (Ferreira et al 2018).

e. Adler et al 2015.

f. Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur (Gargano et al 2021).

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1, 16 January 2024

This amendment is considered to be substantial because it impacts the design/methodology of the study.

Overall Rationale for the Amendment:

The purpose of this amendment is to add a Phase 2 Extension study (Part 2) in participants aged 18 to <50 years to evaluate the safety, reactogenicity, and immunogenicity of two compositions of mRNA-1083 (CCI [redacted]) at 4 different dose levels for each composition as compared to mRNA-1010[CCI] mRNA-1283, mRNA-1273, and Fluarix®.

The summary of changes table provided here describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. As applicable, the synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes from Original protocol to protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Signature Page, Protocol Amendment Summary of Changes, Header	Updated the protocol version and date, as applicable.	To reflect the current version.
Section 1.1 (Protocol Synopsis)	Protocol synopsis was updated to align with changes in the relevant sections of the protocol.	To align with changes in relevant sections of protocol.
Section 1.2 (Schema)	Study schema was divided into two parts. Part 2 study schema was added.	To provide the study schema for each part of the study.
Section 1.3 (Schedule of activities)	Part 2 SOA was added	To provide the assessments for Part 2 of the study.
Section 2	Text has been included to clarify that the study is now divided into 2 parts. Details about Part 2 of the study are added. Table 4 was added to provide description of vaccines that are used in Part 2 of the study. Text regarding the mRNA-1083 vaccines used in Part 2 of the study was updated.	To give general update on the how the study is divided into 2 parts. To give clarity on vaccines that will be used in Part 2 of the study.
Section 2.1.1 (Risk assessment)	Text was updated to include details about the interim analysis for Part 1 of the study.	To provide updated data.

Section # and Name	Description of Change	Brief Rationale
	Also, details regarding the completed Phase 1/2 study for mRNA-1010 was added	
Section 2.1.2 (Benefit assessment)	Text was updated vaccines that are being administered to the participant and their intended benefit	To clarify on the vaccines that are being administered
Section 2.1.3 (Overall Benefit/Risk conclusion)	Details regarding the completed study for mRNA-1010 and interim analysis for mRNA-1083 Part 1were added	To provide updated data
Section 3 (Objectives and endpoints)	New section (Part 2) has been created to provide the objectives and endpoints of the newly added Phase 2 part of the study. Section 3 now includes 2 subsections to separate objectives for the 2 study parts (Phase 1/2 and Phase 2). The originally planned objectives and endpoints (for the Phase 1/2 part) are now tabulated under Section 3.1 (Phase 1/2).	Provided the objectives and endpoints of the Phase 2 part of the study.
Section 4.1 (General design)	Added design, duration, randomization, treatment groups, and dosing, assessment procedures for Part 2 of the study.	Provided information on the specific Part 2 of the study.
Section 4.3 (Justification for Dose)	Updated the number of participants who were dosed with mRNA-1283	To provide updated data
Section 5 (Study Population)	Added inclusion and exclusion criteria for Part 2 Section 5.2.1 and Section 5.2.2, respectively. Inclusion criteria 6 for Part 1 was revised to update use of contraception from adequate to highly effective.	Provided a list of the inclusion and exclusion criteria for participant eligibility for Part 2. To align with the appendix 10.6 which gives highly effective methods of contraception.
Section 6 (Study interventions and concomitant therapy) Section 6.1 (Study interventions administered) Section 6.2 (Preparation, handling, storage, and accountability)	Text has been updated to include information on the IPs administered in Part 2 of the study. Details for the clinical study materials were removed.	Provided information on the IPs administered in the Part 2. The instructions on storage, handling, preparation, processing, and accountability of the products administered were removed, as they are available in a Pharmacy Manual.

Section # and Name	Description of Change	Brief Rationale
Section 6.10.3 (Prohibited therapy)	Text was updated from "Immunosuppressants administered chronically (more than 14 days in total) during the clinical trial period. For corticosteroids, ≥10 mg/day of prednisone or equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed" to "Immunosuppressants administered during the clinical trial period. For corticosteroids, ≥10 mg/day of prednisone or equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed."	To provide clarity on the immunosuppressants that are prohibited.
Section 8.2 (Immunogenicity Assessments), Section 8.3 (Safety Assessments) and Section 8.3 (Biomarkers)	Text has been updated to include safety, immunogenicity, and biomarker assessments to be performed for Part 2 of the study.	Provided text on the assessments and procedures planned for Part 2 of the study.
Section 9.3 (Sample Size Determination)	A sample size of 520 participants (40 participants in each of the 13 arms) is planned for the Part 2 and corresponding text has been added.	Added per the addition of the Part 2 of the study.
Section 9.5.2 (Efficacy Analysis)	The efficacy analysis will be limited to Part 1 of the study. Text was updated from "Efficacy analyses will be performed on the FAS" to "Analyses of RT-PCR-confirmed protocol-defined ILI and RT-PCR-confirmed symptomatic SARS-CoV-2 (COVID-19) will be performed on the FAS."	To provide clarity of the efficacy analysis being performed will be limited to Part 1.
Section 9.6 (Planned Analyses)	Added text for the planned IA for Part 2 of the study.	To provide information on the IA for Part 2 of the study.
Section 10.2 (Clinical laboratory tests)	Table title was updated to clarify that the clinical laboratory tests will be performed in both Part 1 and Part 2.	Added per the addition of the Part 2 of the study.
Section 10.6 (Contraceptive and Barrier guidance)	Contraception guidance was updated from adequate to highly effective.	To align with available contraception guidance.
Throughout the protocol	Minor formatting and edits were made for consistency.	Minor formatting and edits were made for consistency and clarity.

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