CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized, Observer-blind, Active-control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1083 (SARS-CoV-2 and Influenza) Vaccine in Healthy Adult Participants, ≥50 Years of Age
Protocol Number:	mRNA-1083-P301
Amendment Number:	1
Date:	22 Mar 2024
Compound:	mRNA-1083
Brief Title:	A clinical study 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, ≥50 years of age.
Study Phase:	Phase 3
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Number:	IND: 29324

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 3, Randomized, Observer-blind, Active-control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1083 (SARS-CoV-2 and influenza) Vaccine in Healthy Adult Participants ≥50 Years of Age" 22 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 IRB/IEC approval except to eliminate an immediate risk to participants.

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

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

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	22 Mar 2024
Original Protocol	21 Sep 2023

Amendment 1, 22 Mar 2024

This amendment is considered to be substantial because it impacts the objectives and endpoints of the study.

Overall Rationale for the Amendment:

The purpose of this amendment is to add a new secondary objective and endpoint for both Cohort A and Cohort B to evaluate the humoral immune responses for influenza using microneutralization assay at the Day 29 timepoint.

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.

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)	Updated the protocol synopsis to align with changes in the relevant sections of the protocol.	To align with changes in the relevant sections of protocol.
Section 3 (Objectives and Endpoints)	Clarified the endpoints for the secondary objective of evaluating the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2, by separating the Day 29 GM level by HAI assay and PsVNA, respectively.	To clarify the superiority analysis plan for humoral responses for influenza and SAR-CoV-2 by indicating the endpoints for each, separately for Cohorts A and B.
	Added text to specify a new secondary objective and endpoint to evaluate the humoral immune responses for influenza using GM level and GMFR at Day 29 compared with Day 1 by microneutralization assay.	To provide the updated secondary objective and endpoint for Cohorts A and B.
	Deleted the exploratory objective and endpoint to evaluate the humoral	To avoid redundancy with other secondary and exploratory

Section # and Name	Description of Change	Brief Rationale
	immune responses for influenza and SARS-CoV-2 across treatment arms using alternative methods.	endpoints evaluating the immune response, for Cohorts A and B.
	Deleted the exploratory objective and endpoint to further characterize the immune response across treatment arms.	To avoid redundancy with other secondary and exploratory endpoints evaluating the immune response, for Cohorts A and B.
Section 8.2 (Immunogenicity Assessments)	Clarified that the influenza serum nAb levels by microneutralization assay will be measured in a subset of participants.	To align with changes in the secondary objectives for Cohorts A and B.
Section 9.2 (Statistical Hypotheses)	Added new header for the secondary endpoint and updated hypotheses content regarding superiority success criteria.	To align with changes in the secondary objectives for Cohort A and B.
Section 9.3 (Sample Size Determination)	Added sampling strategy for the new secondary objective assessing humoral immune responses for influenza by microneutralization assay.	To provide updated sampling strategy.
Section 9.4 (Analysis Sets)	Added the new analysis set, Per Protocol Immunogenicity Set for microneutralization assay.	To provide updated Analysis Sets.
Section 9.5.1 (Immunogenicity Analyses)	Updated ANCOVA model description with log transformed Baseline HAI or PsVNA levels as an additional fixed covariate.	To adjust for Baseline titer in the ANCOVA model.
	Updated the confidence intervals to 95% CI for immunogenicity endpoints other than GMR and SCR/SRR difference for Cohorts A and B.	To clarify that 97.5% CI is only applicable to GMR and SCR/SRR difference due to multiplicity control. The other immunogenicity endpoints should use 95% CI.
	Separated the superiority testing sequence for influenza and SARS-CoV-2.	To clarify the superiority analyses for influenza and SARS-CoV-2.
Section 9.6 (Planned Analyses)	Removed analyses other than the primary.	To focus on the planned primary analyses timepoint.
Section 10.8 (Appendix 8: Scoring the Edmonton Frail Scale)	Deleted Section 10.8. The EFS example was not the licensed version of the EFS questionnaire that was utilized for participants in Cohort A.	To ensure clarity regarding the EFS. The EFS example provided in the original protocol was not the licensed version of the EFS questionnaire utilized for participants in Cohort A.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EFS = Edmonton Frail Scale; GM = geometric mean; GMFR = geometric mean fold rise; GMR = geometric mean ratio; HAI = hemagglutination inhibition; mRNA = messenger ribonucleic acid; PsVNA = pseudovirus neutralization assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Adverse reaction
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
CSR	Clinical study report
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EFS	Edmonton Frail Scale
EoS	End of study
EQ-5D-5L	EuroQol 5-dimension 5-level
EQ-VAS	EuroQol – visual analog scale
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLSM	Geometric least squares mean
GMFR	Geometric mean fold rise
GM	Geometric mean
GMR	Geometric mean ratio

Abbreviation	Definition
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HCP	Healthcare professional
HD	High dose
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IM	Intramuscular(ly)
IRB	Institutional review board
IRT	Interactive response technology
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	Multisystem inflammatory syndrome in adults
MIS-C	Multisystem inflammatory syndrome in children
mRNA	Messenger ribonucleic acid
NA	Not applicable
nAb	Neutralizing antibody
NH	Northern Hemisphere
NI	Noninferiority
NIM	Noninferiority margin
NP	Nasopharyngeal
NTD	N-terminal domain
OTC	Over-the -counter
PCR	Polymerase chain reaction

Abbreviation	Definition
PP	Per Protocol
PPIS	Per Protocol Immunogenicity Set
PsVNA	Pseudovirus neutralization assay
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
SCR	Seroconversion rate
SD	Standard deviation
SH	Southern Hemisphere
SoA	Schedule of Activities
SRR	Seroresponse rate
WHO	World Health Organization
WPAI:GH	Work Productivity and Activity Impairment: General Health

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 3, Randomized, Observer-blind, Active-control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1083 (SARS-CoV-2 and influenza) Vaccine in Healthy Adult Participants, ≥50 Years of Age

Brief Title:

A clinical study 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 ≥50 years of age.

Regulatory Agency Identifier Number(s): IND 29324

Rationale:

This Phase 3 study aims to evaluate the safety, reactogenicity, and immunogenicity of the mRNA-1083 multi-component influenza (A/H1N1, A/H3N2, B/Victoria, B/Yamagata) and SARS-CoV-2 (Omicron XBB.1.5) vaccine for adults aged 50 years and older. Multiple compositions and dose levels of mRNA-1083 were evaluated in a Phase 1/2 clinical study (NCT05827926). Based on Day 29 safety and immunogenicity data obtained during the Phase 1/2 study, 40 µg mRNA-1083 was selected for adults ≥50 years of age to be further evaluated in this Phase 3 study. mRNA-1083 will be compared to co-administered licensed influenza and licensed COVID-19 vaccines. As the recommended licensed influenza vaccines are different for adults aged 65 and older versus those younger than 65 years, the mRNA-1083 vaccine will be independently evaluated against the licensed influenza comparators in 2 cohorts, Cohort A (≥65 years of age) and Cohort B (≥50 to <65 years). The licensed COVID-19 comparator will be the same for both cohorts, aligning with current recommendations for adults.

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 single injection. 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. Furthermore, this combined regimen could provide a public health benefit through synergistically increasing coverage rates against influenza and SARS-CoV-2 viruses.

Objectives and Endpoints:

Cohort A (≥65 years of age)

Objectives	Endpoints
Primary	
• To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched	• GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29

Objectives	Endpoints
strains for influenza and SARS-CoV-2 at Day 29.	post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the safety and reactogenicity of study injections across treatment arms.	• Solicited local and systemic ARs through 7 days after study injection. • Unsolicited AEs through 28 days after study injection. • MAAEs from Day 1 through Day 181 (Month 6) or EoS. • AESIs from Day 1 through Day 181 (Month 6) or EoS. • SAEs from the time of informed consent through Day 181 (Month 6) or EoS. • AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.
Secondary	
• To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza. • GM level at Day 29 by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.	• GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.

Objectives	Endpoints
• To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.	• GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza in a subset of participants.
Exploratory (may be performed)	
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 to vaccine-mismatched strains for influenza and SARS-CoV-2 across treatment arms.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 characterize other health outcomes during the first 7 days after study injections.	• Describe EQ-5D-5L health questionnaire utility score through 7 days after study injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reactions; COVID-19 = coronavirus disease 2019; EoS = End of Study; EQ-5D-5L = EuroQol 5-dimension 5-level; GM = geometric mean; GMFR = geometric mean fold rise; HAI = hemagglutination inhibition; HA = hemagglutinin; LLOQ = lower limit of quantification; MAAE = medically attended AE; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Cohort B (≥50 to <65 years)

Objectives	Endpoints
Primary	
• To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the safety and reactogenicity of study injections across treatment arms.	• Solicited local and systemic ARs through 7 days after each study injection. • Unsolicited AEs through 28 days after each study injection. • MAAEs from Day 1 through Day 181 (Month 6) or EoS. • AESIs from Day 1 through Day 181 (Month 6) or EoS. • SAEs from the time of informed consent through Day 181 (Month 6) or EoS. • AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.
Secondary	
• To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza. • GM level at Day 29 by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is

Objectives	Endpoints
	<LLOQ in the nAb values measured by PsVNA.
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.	• GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.
• To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.	• GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza in a subset of participants.
Exploratory (may be performed)	
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 to vaccine-mismatched strains for influenza and SARS-CoV-2 across treatment arms.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 characterize other health outcomes during the first 7 days after study injections.	• Describe EQ-5D-5L health questionnaire utility score daily from Day 1 through 7 days after study injection. • Describe WPAI:GH V2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity impairment through 7 days after study injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reactions; COVID-19 = coronavirus disease 2019; EoS = End of Study; EQ-5D-5L = EuroQol 5-dimension 5-level; GM = geometric mean; GMFR = geometric mean fold rise; HAI = hemagglutination inhibition; HA = hemagglutinin; LLOQ = lower limit of quantification; MAAE = medically attended AE; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WPAI:GH = Work Productivity and Activity Impairment: General Health.

Overall Design Synopsis:

This study will be a Phase 3, randomized, stratified, observer-blind, active-control study conducted in 2 age-group substudies: Cohort A (≥65 years of age) and Cohort B (50 to <65 year of age). Each of the 2 independent substudies has its own separate hypotheses and statistical analyses, and its own multiplicity control for overall Type I error rate (2-sided alpha of 5%) for the co-primary endpoints within the substudy.

Brief Summary:

The purpose of this Phase 3 clinical study is to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1083 as compared with active control, co-administered licensed influenza and SAR-CoV-2 vaccines, in 2 independent age-group sub-study cohorts, healthy adults 65 years and older (Cohort A) and healthy adults 50 to <65 years of age (Cohort B).

Study details include:

- Study duration: approximately 6 months, including the Screening period.
- Treatment duration: Study injections are scheduled for all participants on Day 1 (Baseline).
- Visit frequency:
  - All participants will have scheduled in-person clinic visits for Screening and on Day 1 (Baseline) and Day 29 (Month 1).
  - All participants will have a safety follow-up call on Days 8 and 91 (Month 3).
  - On Day 181 (Month 6), at least 800 participants per substudy cohort will have an in-person clinic visit for sample collection. All remaining participants will have a safety follow-up call.

Number of Participants:

Overall, the study will enroll approximately 8000 participants with approximately 4000 participants (in a 1:1 ratio) in Cohort A and approximately 4000 participants (in a 1:1 ratio) in Cohort B.

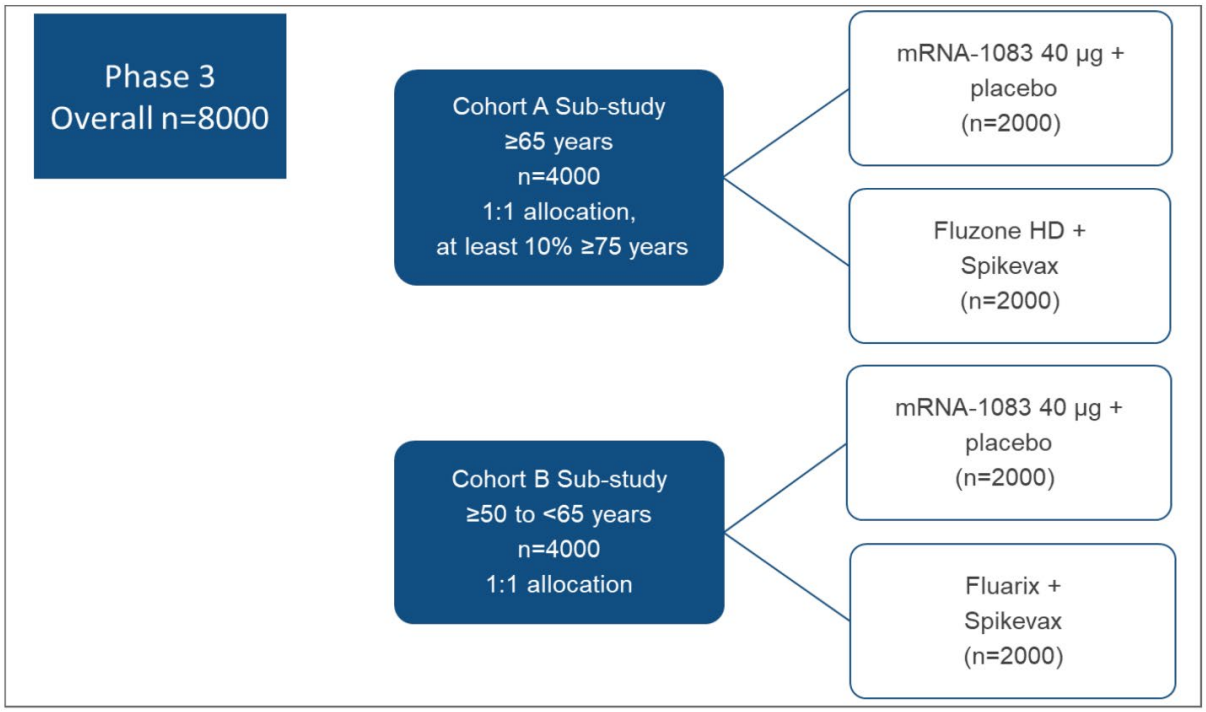
Study Arms and Duration:

- Cohort A will evaluate the safety, reactogenicity, and immunogenicity of 40 µg mRNA-1083 vaccine as compared with co-administered active licensed comparator vaccines (Fluzone® HD and Spikevax™) in healthy adults ≥65 years of age. Randomization will be stratified by age groups (65 to <75 years and ≥75 years of age where at least 10% of participants are ≥75 years of age) and the influenza vaccine status in the most recent influenza season (received or not received since September 2022).
- Cohort B will evaluate the safety, reactogenicity, and immunogenicity of 40 µg mRNA-1083 vaccine as compared with co-administered active licensed comparator vaccines (Fluarix® and Spikevax) in healthy adults 50 to <65 years of age. Randomization will be stratified by the influenza vaccine status in the most recent influenza season (received or not received since September 2022).

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

1.2. Schema

Figure 1: Study Schematic and Participant Disposition



Abbreviations: HD = High dose, n = number

1.3. Schedule of Activities

Table 1: Schedule of Activities

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	**C**
Month Timepoint				**Month 1**	**Month 3**	**Month 6**	**Up to Month 6**
Study Visit	**SCRN[a]**	**Day 1 (Baseline)[a]**	**Day 8**	**Day 29**	**Day 91**	**Day 181 (EoS)[b]**	**USV**
Window Allowance (Days)	**-42**	**NA**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
ICF, demographics, concomitant medications, medical history[c]	X						
Inclusion/exclusion criteria	X	X					
Physical examination[d]	X	X		X			
Vital sign measurement[e]	X	X					
Pregnancy testing[f]	X	X					
Randomization		X					
Study injection (including 30-minute postdosing observation period)[g]		X					
Collection of EFS[h]		X					
Blood collection for humoral immunogenicity[i]		X[j]		X		X	
Optional blood collection for future research sample (genomics)		X[j]					
Optional blood collection for future research sample (transcriptomics)		X[j]		X			
NP swab for virus detection[k]		X					
Blood collection for SARS-CoV-2 antibodies, nucleocapsid		X[j]					
eDiary activation for recording solicited ARs		X					
Solicited AR eDiary Reporting[l]		~30 min postinjection and then daily Day 1 through Day 7					

Visit Number	**SCRN**	**1**	**2**	**3**	**4**	**5**	**USV**
Type of Visit/Contact	**C**	**C**	**SC**	**C**	**SC**	**SC/C**	**C**
Month Timepoint				**Month 1**	**Month 3**	**Month 6**	**Up to Month 6**
Study Visit	**SCRN[a]**	**Day 1 (Baseline)[a]**	**Day 8**	**Day 29**	**Day 91**	**Day 181 (EoS)[b]**	**USV**
Window Allowance (Days)	**-42**	**NA**	**±3**	**-7 to +3**	**±5**	**±14**	**NA**
Review of eDiary for solicited ARs		X	X				
Follow-up safety call[m]			X		X	X	
eDiary collection of EQ-5D-5L[n]		Baseline (preinjection) thereafter daily Day 2 through Day 7 postinjection					
eDiary collection of WPAI: General Health V2.0[o]		X	X				
Recording of unsolicited AEs		X	X	X			
Recording of MAAEs		X	X	X	X	X	
Recording of SAEs[p], AESIs, and AEs leading to discontinuation and any concomitant medications relevant to or for the treatment of the events	X[p]	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[q]	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; eDiary = electronic diary; EFS = Edmonton Frail Scale; EoS = end of study; EQ-5D-5L = EuroQoL 5-dimension 5-levels; FSH = follicle-stimulating hormone; ICF = informed consent form; IM = intramuscular; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety (phone) call; SCRN = Screening; USV = unscheduled visit; WPAI:GH = Work Productivity and Activity Impairment Questionnaire: General Health.

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 if within the 42-day Screening window.

b. EoS is defined as completion of the last visit of the last participant in the clinical study or last scheduled procedure as shown in the SoA for the last participant in the clinical study globally. If a participant discontinues from the clinical study, an EoS visit should be conducted if possible (see Section 7.1).

c. Verbal history is acceptable.

d. A full physical examination, including height and weight, will be performed at the Screening Visit; symptom-directed physical examinations may be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant findings identified by an HCP during postinjection study visits should be reported as an AE.

e. Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs will only be collected at Screening and on the day of injection (Day 1), once before and at least 30 minutes after injection. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination.
f. A point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM 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. The FSH level may be measured for participants of nonchildbearing potential at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
g. All participants will be randomized to receive 2 IM injections, 1 in each deltoid muscle.
h. Assessment of EFS will only be performed for participants ≥65 years of age (Cohort A).
i. Humoral immunogenicity samples on Day 1 and Day 29 will be collected in all participants in Cohort A and Cohort B. Samples for humoral immunogenicity on Day 181 will be collected and analyzed for at least 800 participants of each cohort. These participants will require a clinic visit on Day 181. Plasma and serum from humoral immunogenicity samples will be stored for potential future use.
j. Transcriptomic and genomic samples will be part of the optional biomarker assessment once consented by the study participant. All blood samples must be collected prior to receipt of injection on Day 1.
k. An NP swab specimen(s) for assessment of pathogens, including influenza virus and SARS-CoV-2, will be collected before injection on Day 1.
l. The eDiary activation and entries will be recorded by the participant at approximately 30 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, on the day of injection and for 6 days following injection, for a total of 7 days.
m. Trained study staff will call all participants to collect information related to any AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation, information on concomitant medications associated with those events, and any nonstudy vaccinations.
n. The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). All participants will receive eDiary prompts to complete the EQ-5D-5L daily starting at Day 1 (Baseline) through 7 days after study injection. For Day 1 (Baseline), participants should complete the EQ-5D-5L questionnaire prior to administration of the study injection.
o. Cohort B only. At Baseline, the WPAI questionnaire is to be completed prior to administration of the study injection.
p. SAEs will be collected from the time of informed consent through Day 181 (Month 6) or EoS.
q. All concomitant medications will be recorded through 28 days after injection. Additionally, nonstudy injections and certain concomitant medications will be recorded through Day 181 or EoS.

2. INTRODUCTION

ModernaTX, Inc. (the Sponsor) is developing LNP-encapsulated 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 (A/H1N1, A/H3N2, B/Victoria, B/Yamagata) and SARS-CoV-2 (Omicron XBB.1.5) and is intended to prevent disease associated with these viruses.

Seasonal influenza viruses are estimated by the WHO to cause 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths each year resulting in a severe challenge to public health (WHO 2023). Influenza epidemics occur each year and follow a seasonal circulation pattern with increased cases during the winter months in the NH and SH (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 2023a). Influenza vaccines based on mRNA technology could provide several benefits compared with current vaccines, including the ability to respond to strain changes more quickly, avoidance of mutations that may be acquired during vaccine production in eggs or cell culture, stronger immune responses, as well as improved protection in older adults (Rockman et al 2020).

CoVs 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. SARS-CoV-2, a novel CoV and 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 still considers it a significant global health threat, even after declaring an end to the public health emergency in May 2023, with more than 767 million confirmed cases and 6.9 million deaths as of 5 Jun 2023 (WHO 2023a). Even with more than 13.3 billion doses of vaccine administered to prevent COVID-19 infections as of 6 Jun 2023, more than 219,0000 new cases have been reported in the previous 7 days globally and significant variability in disease burden exists across different regions of the world (WHO 2023a). On 11 September 2023, the FDA approved an updated Spikevax to include the currently recommended 2023-2024 SARS-CoV-2 variant, XBB.1.5 (FDA news release, 2023).

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.

2.1. Study Rationale

The Sponsor is developing mRNA-1083, an LNP-encapsulated mRNA-based prophylactic combination vaccine encoding influenza and SARS-CoV-2 antigens. The mRNA-1083 being evaluated in this Phase 3 study contains 5 mRNAs: 4 mRNAs encoding surface glycoprotein HA of seasonal influenza virus strains and 1 mRNA encoding the linked NTD-RBD subdomains of the SARS-CoV-2 spike glycoprotein. 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 3 study aims to evaluate the safety, reactogenicity, and immunogenicity of the mRNA-1083 multi-component influenza and SARS-CoV-2 vaccine for adults aged 50 and older. Multiple compositions and dose levels were evaluated in a Phase 1/2 clinical study (NCT05827926). Based on Day 29 safety and immunogenicity data obtained during the Phase 1/2 study, (40 µg) mRNA-1083 was selected for adults aged ≥50 years to be further evaluated in this Phase 3 study.

2.2. Background

The Sponsor is using its mRNA-based platform to develop a custom-manufactured LNP-encapsulated, mRNA-based vaccine against diseases caused by influenza virus types A and B and SARS-CoV-2. The mRNA vaccines included in this clinical study are described below.

mRNA-1083

mRNA-1083 is an LNP-encapsulated, mRNA-based, prophylactic, multi-component vaccine encoding antigens from influenza viruses and SARS-CoV-2. The mRNA-1083 being evaluated in this Phase 3 study contains 5 mRNAs: 4 mRNAs that encode membrane-bound HA of the 4 different influenza strains recommended by the WHO for the NH 2023/2024 season CCI [redacted] and 1 mRNA that 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 encoded NTD and RBD subdomains are linked together with a short flexible linker, and a transmembrane domain anchors the expressed protein to the cell membrane. CCI [redacted] The strains of influenza and SARS-CoV-2 variant represented in mRNA-1083 are the same as those in the licensed influenza and SARS-CoV-2 comparators for the 2023-2024 season. mRNA-1083 has previously been evaluated in a Phase 1/2 clinical study (NCT05827926).

COVID-19 Vaccine, mRNA, Spikevax, 2023-2024 Formula

The COVID-19 Vaccine, mRNA, Spikevax 2023-2024 Formula (Monovalent XBB.1.5 Omicron subvariant), henceforth referred to as Spikevax, is an mRNA vaccine for the prevention of COVID-19 in adults ≥18 years of age. COVID-19 is caused by SARS-CoV-2. The vaccine

contains 1 mRNA that encodes the full-length SARS-CoV-2 prefusion-stabilized spike glycoprotein of the fall/winter 2023-2024-recommended variant XBB.1.5.

Fluzone HD and Fluarix

Fluzone HD and Fluarix are both seasonal, 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 for the NH 2023/2024 influenza season.

Fluarix is a standard-dose vaccine that is approved for adults ≥18 years of age.

Fluzone HD is a high-dose vaccine, containing an increased amount of antigen 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.

2.3. 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 IB.

2.3.1. 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 2002). Since the authorization of the Sponsor's mRNA-1273 Spikevax vaccine for COVID-19, the US CDC estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precautionary measure, all participants will remain under observation at the clinic for at least 30 minutes after study injection.

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 injections 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 ARs are expected after IM study injection. 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 injection, 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 injection have been observed in early phase clinical studies with similar mRNA-based study injections. 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 post-authorization 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 after the second or subsequent doses of the vaccine. These are typically mild cases and individuals tend to recover within a short time following conservative treatment. HCPs and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

In a completed Phase 3 study of the mRNA-1273 injection for COVID-19 in 30,420 healthy adults (mRNA-1273-P301 [NCT04470427]), the most frequently reported ARs after any dose of study injection 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. ARs from clinical studies and post-authorization experience with mRNA-1273 occurring in ≥1% of recipients include injection site rash, injection site urticaria, rash, and delayed injection site reactions.

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.

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 100 µg) and in mRNA-1283-201 (dose levels up to 10 µg) revealed no significant safety concerns. The safety and reactogenicity profiles of mRNA-1283 (2.5, 5, and 10 µg) and mRNA-1283.11 (5 and 10 µg) were overall similar to mRNA-1273 (50 µg).

Data from mRNA-1010-P101 (NCT04956575) (Phase 1/2 and Phase 2 NH study portions, doses tested ranged from 25 to 200 µg of mRNA-1010) showed no significant safety concerns regarding mRNA-1010. Additionally, there are 3 ongoing Phase 3 studies with more than 15,000 participants exposed to 50 µg of mRNA-1010 (mRNA-1010-P301 [NCT05415462], mRNA-1010-P302 [NCT05566639], and mRNA-1010-P303 [NCT05827978]). Interim analyses from all three studies have showed no significant safety concerns regarding mRNA-1010.

The Day 29 interim analysis of mRNA-1083-P101 (NCT05827926), which evaluated multiple compositions and dose levels of mRNA-1083, showed no safety concerns and participants ≥50 years tolerated mRNA-1083 well with the majority of adverse reactions mild to moderate in severity. CCI [redacted]

mRNA-1083 may or may not offer protection against seasonal influenza and/or COVID-19.

Further details are provided in the current IB.

2.3.2. 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.

- The clinical study will contribute to the development of a potentially efficacious vaccine against seasonal influenza virus and SARS-CoV-2 together as a single injection.

2.3.3. 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.

Considering the nonclinical data for the combined administration of mRNA-1010 and mRNA-1283 vaccines and the clinical safety and immunogenicity data for mRNA-1083, mRNA-1010, mRNA-1283, mRNA-1273, 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. Cohort A (≥65 years of age)

Table 2: Objectives and Endpoints for Cohort A

Objectives	Endpoints
Primary	
• To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the safety and reactogenicity of study injections across treatment arms.	• Solicited local and systemic ARs through 7 days after study injection. • Unsolicited AEs through 28 days after study injection. • MAAEs from Day 1 through Day 181 (Month 6) or EoS. • AESIs from Day 1 through Day 181 (Month 6) or EoS. • SAEs from the time of informed consent through Day 181 (Month 6) or EoS. • AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.

Objectives	Endpoints
Secondary	
• To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza. • GM level at Day 29 by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.	• GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.
• To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.	• GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza in a subset of participants.
Exploratory (may be performed)	
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 to vaccine-mismatched strains for influenza and SARS-CoV-2 across treatment arms.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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
• To characterize other health outcomes during the first 7 days after study injections.	• Describe EQ-5D-5L health questionnaire utility score through 7 days after study injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reactions; COVID-19 = coronavirus disease 2019; EoS = End of Study; EQ-5D-5L = EuroQol 5-dimension 5-level; GM = geometric mean; GMFR = geometric mean fold rise; HAI = hemagglutination inhibition; HA = hemagglutinin; LLOQ = lower limit of quantification; MAAE = medically attended AE; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

3.2. Cohort B (≥50 to <65 years)

Table 3: Objectives and Endpoints for Cohort B

Objectives	Endpoints
Primary	
• To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the safety and reactogenicity of study injections across treatment arms.	• Solicited local and systemic ARs through 7 days after each study injection. • Unsolicited AEs through 28 days after each study injection. • MAAEs from Day 1 through Day 181 (Month 6) or EoS. • AESIs from Day 1 through Day 181 (Month 6) or EoS. • SAEs from the time of informed consent through Day 181 (Month 6) or EoS. • AEs leading to discontinuation from Day 1 through Day 181 (Month 6) or EoS.
Secondary	
• To further evaluate the humoral immune response of mRNA-1083 for superiority	• GM level at Day 29 by HAI assay for influenza.

Objectives	Endpoints
relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.	• GM level at Day 29 by PsVNA for SARS-CoV-2. • Influenza: Percentage of participants with seroconversion, defined as a Day 29 post-injection level ≥1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay. • SARS-CoV-2: Percentage of participants with seroresponse, defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4 × LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at Day 29.	• GMFR at Day 29 compared with Day 1 by HAI assay for influenza and by PsVNA for SARS-CoV-2.
• To evaluate the humoral immune responses for influenza across treatment arms at Day 29 using the microneutralization assay.	• GM level at Day 29 and GMFR at Day 29 compared with Day 1 by microneutralization assay for influenza in a subset of participants.
Exploratory (may be performed)	
• To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across treatment arms at all evaluable humoral immunogenicity time points.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 to vaccine-mismatched strains for influenza and SARS-CoV-2 across treatment arms.	• GM level and GMFR at all evaluable time points compared with Day 1 by HAI for influenza and by 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 characterize other health outcomes during the first 7 days after study injections.	• Describe EQ-5D-5L health questionnaire utility score through 7 days after study injection. • Describe WPAI:GH V2.0 impairment percentages for absenteeism, presenteeism, work productivity loss, and activity

Objectives	Endpoints
	impairment through 7 days after study injection.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reactions; COVID-19 = coronavirus disease 2019; EoS = End of Study; EQ-5D-5L = EuroQol 5-dimension 5-level; GM = geometric mean; GMFR = geometric mean fold rise; HAI = hemagglutination inhibition; HA = hemagglutinin; LLOQ = lower limit of quantification; MAAE = medically attended AE; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WPAI:GH = Work Productivity and Activity Impairment: General Health.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 3, randomized, stratified, observer-blind, active-control study conducted in 2 age-group substudies (Cohort A and Cohort B) and will evaluate the following:

- Cohort A will evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 40 µg as compared with co-administered active licensed comparator vaccines, Fluzone HD and Spikevax, in healthy adults ≥65 years of age. Randomization will be stratified by age groups (65 to <75 years and ≥75 years of age where at least 10% of participants are ≥75 years of age) and the influenza vaccine status in the most recent influenza season (received or not received since September 2022).
- Cohort B will evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 40 µg as compared with co-administered active licensed comparator vaccines, Fluarix and Spikevax, in healthy adults 50 to <65 years of age. Randomization will be stratified by the influenza vaccine status in the most recent influenza season (received or not received since September 2022).

The study intervention and dose level for each cohort age substudy is based on the results of the mRNA-1083-P101 (NCT05827926) Day 29 Interim Analyses. The overall sample size for the Phase 3 study will be approximately 8000 participants. The participants will be randomized 1:1 in 2 study groups per Table 4 and Table 5.

- In the Cohort A substudy (65 years and older), approximately 4000 participants will be randomized (in a 1:1 ratio) into the investigational vaccine and control arms, and stratified by age groups (65 to <75 years and ≥75 years of age; where at least 10% of participants are ≥75 years of age) and influenza vaccine status in the most recent influenza season (received or not received since September 2022).
- In the Cohort B substudy (50 to <65 years), approximately 4000 participants will be randomized (in a 1:1 ratio) into the investigational vaccine and control arms, and stratified by influenza vaccine status in the most recent influenza season (received or not received since September 2022).

Table 4: Randomized Groups for Cohort A Substudy (greater than or equal to 65 years of age)

Group #	Group Name	Sample Size
1	mRNA-1083 + Placebo	2000
2	Fluzone HD + Spikevax	2000
	Total Sample Size	**4000**

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

Table 5: Randomized Groups for Cohort B Substudy (greater than or equal to 50 to less than 65 years of age)

Group #	Group Name	Sample Size
1	mRNA-1083 + Placebo	2000
2	Fluarix + Spikevax	2000
	Total Sample Size	**4000**

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

4.2. Scientific Rationale for Study Design

This study is designed to show noninferior immunogenicity of mRNA-1083 as compared with Fluarix and Spikevax in healthy adults 50 to <65 years of age or Fluzone HD and Spikevax in healthy adults 65 years of age or greater.

In this observer-blind study, participants, clinic staff involved in participant assessment, and Sponsor personnel (or its designees) will be blinded to participant vaccine allocation. A limited number of Sponsor and/or CRO personnel will be unblinded to conduct safety data analyses for the DSMB safety data reviews (as described in the DSMB charter) and perform the primary analysis. Unblinded study personnel, who will not participate in any other aspect of the study, will perform study intervention accountability, dose preparation, and study intervention administration.

The NP swab specimen(s) for assessment of pathogens, including influenza virus and SARS-CoV-2, will be collected prior to study injection on Day 1 (see Section 8.3.4).

4.2.1. Participant Input into Design

Participants were not involved in the design of this clinical study.

4.3. Justification for Dose

The Sponsor has been conducting mRNA-1083-P101 (NCT05827926), a Phase 1/2 randomized, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of multiple mRNA-1083 compositions and dose levels compared with active-control vaccines for both seasonal influenza and COVID-19.

The Day 29 interim analysis from mRNA-1083-P101 demonstrated that the mRNA-1083 composition with CCI [redacted] did not reveal any significant safety concerns and showed an acceptable reactogenicity profile. This mRNA-1083 vaccine was tested at 15 µg, 30 µg, and 60 µg in participants ages ≥50 to <65 years old and 30 µg and 60 µg in participants ≥50 to <65 years old. Although the majority of solicited adverse reactions at the 60-µg dose were mild to moderate in severity, the reactogenicity of the mRNA-1083 vaccine did increase with dose level. At the 30 µg level in adults aged 50 to <80 years, the majority of solicited adverse reactions were Grade 1 or 2 in severity, with <5% of solicited adverse reaction reported as Grade 3 and no Grade 4 reactions reported. A favorable immunogenicity profile was seen with the 30 µg 1083 dose, Day 29 influenza and SARS-CoV-2 antibody GMRs were greater than 1 relative to licensed comparator vaccines mRNA-1273 (≥50 to <80 years old), Fluzone HD (≥65 to <80 years old), and Fluarix (≥50 to <65 years old), for all

influenza strains and SARS-CoV-2 variants in the vaccine. Together these mRNA-1083-P101 interim data support that 30 µg mRNA-1083 CCI [redacted] has a favorable safety, reactogenicity and immunogenicity profile in adults 50 to <80 years.

CCI [redacted] an mRNA-1083 40 µg dose was selected for the mRNA-1083-P301 study in adults ≥50 years of age, based on the results of the mRNA-1083-P101 study. While the 40 µg dose was not tested in the mRNA-1083-P101 trial, the safety and reactogenicity profile of mRNA-1083 40 µg is expected to be similar to the 30 µg dose, and doses up to 60 µg were tested and tolerated.

4.4. End-of-Study Definition

A participant is considered to have completed the clinical study once they have completed all periods of the clinical study including the last scheduled procedure as shown in the SoA, Section 1.3.

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

4.5. Safety Oversight

4.5.1. Drug Safety Monitoring Board

Safety monitoring for this study will include blinded safety reviews by the study team during the study and an unblinded DSMB. The DSMB will be composed of independent members with relevant therapeutic and/or biostatistical expertise to allow for the ongoing review of safety data from this study population. Throughout the study, the DSMB will conduct reviews of related SAEs at regular intervals, as outlined by the DSMB charter. Enrollment will be ongoing during the reviews of these SAES, if the study team has not identified any safety concern. Additional ad hoc DSMB safety data reviews may occur as outlined by the DSMB charter.

4.5.2. Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for “probable” or “confirmed” events, (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis or pericarditis will be referred to the Sponsor, who will then determine if additional action is needed. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Healthy adults either ≥65 years of age (Cohort A) or 50 to <65 years of age (Cohort B) at the time of consent (Screening Visit).

Type of Participant and Disease Characteristics

2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures, and according to the Investigator's assessment, is in good general health.

Sex and Contraceptive/Barrier Requirements

3. Participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized as described in Section 10.4. An FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
4. Participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
   - Has a negative pregnancy test at the Screening Visit and on the day of vaccine administration.
   - Has practiced adequate contraception, as described in Section 10.4, or has 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 10.4, through 3 months following vaccine administration. Adequate contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label.

Informed Consent

5. Capable of giving signed informed consent, as described in Section 10.1.4, for participation in this study, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol, including all evaluations and procedures as specified in this protocol.

Other Inclusion Criteria

6. 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 ≥90 days prior to Day 1.

5.2. Exclusion Criteria

Participants are excluded from this clinical study 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 42-day Screening window and will retain their initially assigned participant number.
2. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable, or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring changes in management or medication ≤60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
    - Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, if they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune modifying treatments), at the discretion of the Investigator.
3. Participants who have undergone surgical procedures within 14 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study injection are also excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency (eg, HIV), immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Certain immune-mediated conditions that are stable and well-controlled (eg, alopecia areata, Hashimoto thyroiditis, type 1 diabetes mellitus, gout, primary ovarian insufficiency) as well as those that do not require systemic immunosuppressants per Exclusion Criterion 14 (eg, asthma, psoriasis, or vitiligo), are permitted at the discretion of the Investigator.
5. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
6. 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.
7. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
8. Diagnosis of malignancy within the previous 2 years (excluding nonmelanoma skin cancer).

9. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
10. Has a history of myocarditis or pericarditis or myopericarditis within 90 days prior to the Screening Visit. Participants who have not returned to Baseline clinical status after their convalescent period will also be excluded.
11. Has a history of Guillain-Barre syndrome.
12. Has a known history of SARS-CoV-2 infection within ≤90 days prior to Day 1.
13. Tested positive for influenza by local health authority-approved testing methods ≤150 days prior to Day 1.

Prior/Concomitant Therapy

14. Participant has received systemic immunosuppressants for >14 days in total within 180 days prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled nasal and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study injection.
15. Received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study injections or plans to receive a vaccine authorized or approved by a local health agency within 28 days after the study injections.
16. Received a seasonal influenza vaccine ≤150 days prior to Day 1.
17. Treated with antiviral therapies for influenza (eg, Tamiflu®) within 150 days prior to Day 1.
18. 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 injection.
19. 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 study.

Prior/Concurrent Clinical Study Experience

20. Participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so within 28 days after study injection. 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

21. Unaware whether they received an influenza vaccine ≤150 days prior to the Screening Visit.
22. 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.
23. Participated in any investigational seasonal influenza vaccine study within 12 months prior to Day 1.
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. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
26. 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. 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 study (screen failure) may be rescreened one time.

5.4. Lifestyle Restrictions

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

Participants in the clinical study 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.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study injections are all pre-specified, 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 study conduct. Experimental refers to mRNA-1083 vaccines and placebo administered in this study. Fluzone HD, Fluarix, and Spikevax are vaccine comparators.

6.1. Study Intervention(s) Administered

Study interventions are summarized in Table 6. The specific study arms and interventions for Cohort A and Cohort B substudies are described in Table 7 and Table 8.

Table 6: Cohort A and B - Interventions Administered

Intervention	mRNA-1083	Placebo	Fluzone HD	Fluarix	Spikevax
Intervention Name	mRNA-1083 (NH 2023/2024) (40 µg)	Placebo	Fluzone high dose quadrivalent vaccine	Fluarix quadrivalent	COVID-19 vaccine, mRNA, Spikevax, 2023-2024 formula
Intervention description	mRNA-1083 is formulated in an LNP dispersion in Tris buffer containing sucrose and acetate. This IMP will be provided in 2R Schott vials, will have all required labeling per regulations, and will be supplied to the pharmacy in an unblinded manner	0.9% sodium chloride - commercially available material	Commercially available formulation	Commercially available formulation	Commercially available formulation
Dosage Form	Suspension for injection	Suspension for injection	Suspension for injection (pre-filled syringe)	Suspension for injection (pre-filled syringe)	Suspension
Route of Administration	IM	IM	IM	IM	IM

Abbreviation: HD = high dose; IM = intramuscular(ly); IMP: investigational medicinal product; mRNA = messenger ribonucleic acid

Table 7: Cohort A Substudy - Arms and Interventions Administered

Substudy Title	**Cohort A Substudy (≥65 years of age): n=4000**	
Arm Title	mRNA-1083 + Placebo n=2000	Fluzone HD + Spikevax n=2000
Arm Type	Experimental	Active Comparator
Arm Description	Participants will receive mRNA-1083 (40 µg) and Placebo, administered as 2 IM injections, 1 in each deltoid muscle on Day 1.	Participants will receive Fluzone HD and Spikevax administered as 2 IM injections, 1 in each deltoid muscle on Day 1.

Abbreviation: HD = high dose; IM = intramuscular(ly); mRNA = messenger ribonucleic acid

Table 8: Cohort B Substudy - Arms and Interventions Administered

Substudy Title	**Cohort B Substudy (50 to <65 years of age): n=4000**	
Arm Title	mRNA-1083 + Placebo n=2000	Fluarix +Spikevax n=2000
Arm Type	Experimental	Active Comparator
Arm Description	Participants will receive mRNA-1083 (40 µg) and Placebo, administered as 2 IM injections, 1 in each deltoid muscle on Day 1.	Participants will receive Fluarix and Spikevax, administered as 2 IM injections, 1 in each deltoid muscle on Day 1.

Abbreviation: HD = high dose; IM = intramuscular(ly); mRNA = messenger ribonucleic acid

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 injections received, and any discrepancies are reported and resolved before use of the study injection.
- Only participants enrolled in the study may receive study injection, and only authorized site staff may supply, prepare, or administer study injection.
- All study injections 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.
- The Investigator is responsible for study intervention accountability including maintaining accurate records in a study intervention accountability log of receipt of all study intervention, site study intervention inventory, study intervention dispensing, study intervention injections, and return to the Sponsor or alternative disposition of

used and unused study intervention vials. A site monitor will review the inventory and accountability log during site visits and at the completion of the clinical study.

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

6.3. Assignment to Study Intervention

Randomization will be performed using an IRT.

6.4. Blinding and Masking of Study Intervention

The treatment assignment, including the injection site and the corresponding injection administered, will be concealed by having the unblinded pharmacy personnel prepare the study injection 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.

If the Investigator decides that unblinding is warranted, the Investigator may, at the Investigator's discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. The Sponsor recommends that the blind only be broken if knowledge of the vaccine assignment will affect that participant's clinical management. If a participant's intervention assignment is unblinded by the Investigator, the Sponsor must be notified within 24 hours of this occurrence. 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 final CSR.

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the clinical study, 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 injections will be administered by qualified and trained study personnel to ensure that all doses administered comply with those planned. Study injection will be recorded in the 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 injections as planned.

6.7. Criteria for Temporarily Delaying Administration of Study Intervention

Participants with a fever ≥38.0°C (100.4°F) 72 hours prior to or at the Screening Visit may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.

Body temperature (oral preferred) must be measured before study injection. The following events constitute criteria for delay of study injection, 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 (Section 1.3) or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7.1):

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

If the participant does not have an infection or fever as outlined above but the Investigator determines that the participant's health on the day of dosing temporarily precludes study injection, the visit should be rescheduled within the allowed interval for that visit.

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

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

6.9. Treatment of Overdose

As study injection is to be administered by a 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 EDC.
- Document the quantity of the excess dose in IRT.

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

6.10. Prior and Concomitant Therapy

6.10.1. Prior Medications

Information about prior medications (including any prescription or OTC medications, vaccines, or blood products) taken within the period starting 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) must be recorded in the eCRF.

In addition, the following will be collected:

- Use of facial injections or dermal fillers at any time before study.
- Any seasonal influenza vaccine administered during or since September 2022.
- Any investigational influenza vaccine administered within 365 days of Day 1.
- Any authorized or investigational COVID-19 vaccine at any time before study injection.

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 nonstudy vaccinations received:

- All nonstudy vaccinations administered within the period starting 28 days before the study injection and through Day 181 or EoS.
- All concomitant medications taken through 28 days after study injection. 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 study period after study injection through Day 181 or EoS.
- Any concomitant medications used to prevent or treat either COVID-19 or influenza through EoS.
- Antiviral and antiretroviral medications through Day 181 or EoS.
- Any concomitant medications relevant to or for the treatment of an MAAE from Day 1 through Day 181 or EoS.
- Any concomitant medications relevant to or for the treatment of an SAE or AESI from Day 1 through Day 181 or 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 study but may determine a participant's evaluability in the PPIS analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study injections used during the clinical study period.
- Immunosuppressants administered chronically (more than 14 days in total) during the clinical study period. For corticosteroids, ≥10 mg/day of prednisone or equivalent is

not permitted. Intra-articular and epidural steroids are not allowed within 28 days before and/or after study injection. 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 study period.
- Antiviral and antiretroviral medications during the clinical study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.13.

7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw consent and withdraw from the clinical study at any time, for any reason (or without providing any reason).

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

The Investigator will request that the participant complete all study procedures pending at the time of withdrawal.

At the time of discontinuing from the study, if possible, an EoS visit should be conducted (see the SoA in Section 1.3 for data to be collected).

Participants who withdraw or are withdrawn from the clinical study will not be replaced.

If a participant desires to withdraw from the clinical study 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.

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

- AE/SAE
- Solicited AR/reactogenicity
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by participant
- Noncompliance with study intervention
- Other

Participants who withdraw from the clinical study 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 study as a result of an AE, SAE, or solicited AR until resolution or stabilization of the event.

If a participant withdraws from the clinical study, 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 10.1.8).

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

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).

7.2. Lost to Follow-up

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

A participant should be not considered LTFU until due diligence has been completed. 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 study.
  - Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
  - 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 study.

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 in Section 1.3. A participant can also be seen for an unscheduled visit at any time during the clinical study, at the discretion of the Investigator. Reasons for an unscheduled visit may include, but are not limited to, reactogenicity issues 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 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 in Section 1.3. 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 study.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- 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 may be performed on the same day. Additionally, the Screening Visit assessments may be performed over multiple visits if within the 42-day Screening window.

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

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

8.1. Demography

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

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

8.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected in all participants at planned timepoints per the SoA in Section 1.3.

The following analytes will be measured:

- Influenza: Serum antibody levels as measured by HAI assay and, in a subset of participants, serum nAb levels as measured by microneutralization assay.
- SARS-CoV-2: Serum nAb levels as measured by PsVNA assay by enzyme-linked immunosorbent assay or multiplex assay specific to the SARS-CoV-2 proteins.

Samples for humoral immunogenicity on Day 181 will be collected and analyzed for at least 800 participants of each cohort. These participants will require a clinic visit on Day 181. Plasma and serum from humoral immunogenicity samples will be stored for potential future use.

8.3. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant according to the SoA in Section 1.3:

- Solicited local and systemic ARs that occur during the 7 days following study injections (ie, the day of injections and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Local solicited ARs will be recorded separately for each injection site.
- Unsolicited AEs observed or reported during the 28 days following study injections (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through EoS or discontinuation from the study.
- MAAEs from Day 1 (postinjection) through Day 181 (Month 6) or EoS or discontinuation from the study.
- SAEs from the time of informed consent through Day 181 (Month 6) or EoS or discontinuation from the study.
- AESIs from Day 1 through Day 181 (Month 6) or EoS or discontinuation from the study.
- Details of all pregnancies in participants will be collected after the start of study injection and until the end of their participation in the study. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after study completion may not be collected in the clinical database.
- Vital sign measurements.
- Physical examination findings.

- Concomitant medications and nonstudy vaccinations.

The incidence and severity of the above events will be monitored by the blinded study team members. Planned timepoints for the safety assessments are provided in the SoA in Section 1.3.

8.3.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system and extremities. Height and weight will also be measured and recorded. At Screening, the body mass index 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 both injection arms 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.

8.3.2. Vital Signs

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 in Section 1.3. On the day of study injection, vital sign measurements will be collected once before and at least 30 minutes after study injection. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

Following study injection, any abnormal vital sign measurement should be assessed by the Investigator to determine if it meets AE reporting criteria per protocol 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 study injection. Criteria for delay of study injection are provided in Section 6.7. If fever is clinically concerning, participant should not be dosed. Participants who are afebrile with minor illnesses may receive the study injection 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.

8.3.3. Safety Laboratory Assessments

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1/2 study mRNA-1083-P101 in adults.

8.3.4. Respiratory Viral Infection Assessment

All participants will provide NP 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.

8.3.5. Pregnancy Testing

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

Planned timepoints for pregnancy testing are provided in the SoA in Section 1.3.

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 10.4 for details).

Additional pregnancy testing during the clinical study may also be performed if required by local regulatory requirements. Further details on reporting and follow-up of pregnancy are provided in Section 8.4.5 and Section 10.4.

8.3.6. Safety Telephone Calls

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 in Section 1.3. 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.

8.3.7. Electronic Diaries

At the time of consent, the 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. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities. The eDiary will be a source document allowed for solicited systemic or local ARs (including body temperature measurements). An eDiary will also be used to complete PRO questionnaires Section 8.10).

Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided with an eDiary device. Participants will be instructed to complete eDiary entries as per the SoA (Section 1.3). 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 (injection 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. Participants will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) side as the injection arm(s) during the 7 days after study injection.

On Day 1 (injection day), participants will activate their eDiary and record data into the eDiary starting approximately 30 minutes postinjection 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 injection and for 6 days following study injection, for a total of 7 days.

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

- Solicited local and systemic ARs (Section 8.4.6). 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 eDiary data with participants during the Day 8 safety telephone call.

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

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

The 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 injection or study procedures, or that caused the participant to discontinue the clinical study.

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 10.3.3.

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

- All unsolicited AEs will be collected from the day of study injection through 28 days postinjection.
- All AEs leading to study discontinuation and AESIs will be collected from the start of study injection until Day 181 or EoS visit at the timepoints specified in the SoA in Section 1.3.
- All MAAE will be collected from Day 1 through Day 181 (Months 6) or EoS after study injection at the timepoints specified in the SoA in Section 1.3.
- All SAEs will be collected from the signing of the informed consent until Day 181 or EoS visit at the timepoints specified in the SoA in Section 1.3.

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 found on the form.

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 study and the Investigator considers the event to be reasonably related to the study injection or study participation, the Investigator must promptly notify the Sponsor.

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.

The Investigator is responsible for documenting AEs regardless of study arm or suspected causal relationship to study injection. 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 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 OTC 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.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All 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 7.2). 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 injection 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 injection under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators. For example, for reports that are required to be submitted to the European Union, Individual Case Safety Reports, will be submitted via the EudraVigilance Clinical Trial Module Gateway.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC according to local requirements, if appropriate.
- For expedited reporting purposes, the expectedness of SAEs will be assessed against the injection the participant received. AE terms not listed as expected events in the IB for the study intervention will be considered unexpected.

8.4.5. Pregnancy

- Any participant who reports a pregnancy after receiving study injection should remain in the clinical study and complete all study visits as scheduled.
- Details of all pregnancies detected or reported in participants during the period after administration of study injection through the EoS Visit, must be reported to the Sponsor using the Pregnancy Report Form.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the participant pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (refer to Section 10.3).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 10.3.2).
- Any poststudy pregnancy-related SAE considered reasonably related to the study injection by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

8.4.6. Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 8.3.7). Participants will record such occurrences in the eDiary on the day of study injection and 6 subsequent days, for a total of 7 days.

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.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Section 10.5 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.

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 8.4.8)
- Solicited local or systemic AR leading to the participant withdrawing from the clinical study or the participant being withdrawn from the clinical study by the Investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days postinjection.
- 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.

8.4.7. Unsolicited Adverse Event

An unsolicited AE 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).

- 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.

8.4.8. 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) 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.
- All MAAEs will be collected from Day 1 through Day 181 (Month 6) or EoS.

8.4.9. 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.

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

- 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 (Section 10.3.4).
- AESI for this protocol are listed in Section 10.6.
- Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in Section 10.3.4 (Reporting of SAEs).

8.4.9.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study injection 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 10.3.4. 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.

8.4.9.2. 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 10.7) and 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 study 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 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.

8.5. Pharmacokinetics

PK parameters are not evaluated in this clinical study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this clinical study.

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 study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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, RT-PCR of NP 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 in Section 1.3 and as detailed in the laboratory manual provided separately to sites.

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. Medical Resource Utilization and Health Economics

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

8.10. Patient Reported Outcomes

8.10.1. EQ-5D-5L

The 5-level EQ-5D version (EQ-5D-5L) consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions.

The EQ-VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

All participants will receive eDiary prompts to complete the EQ-5D-5L daily starting at Day 1 (Baseline) through the 7 days after study injection. For Day 1 (Baseline), participants should complete the EQ-5D-5L questionnaire prior to the administration of the study injection.

8.10.2. Edmonton Frail Score

The EFS score ranges from zero to 17 points. Severe Frailty is defined as a score of 12 to 17 possible points; apparent vulnerability is a score of 6 to 11 points; and non-frail is a score of 5 or less points.

For Cohort A, EFS will be collected at Baseline (Day 1), participants should complete the EFS questionnaire prior to the administration of the study injection.

8.10.3. Work Productivity and Activity Impairment: General Health (WPAI:GH) V2.0

For Cohort B participants the WPAI:GH will be collected using the eDiary on Day 1 (Baseline) and Day 8. For Day 1 (Baseline), participants should complete the WPAI:GH questionnaire prior to the administration of the study injection.

9. STATISTICAL CONSIDERATIONS

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

9.1. Blinding and Responsibility for Analyses

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

- An independent unblinded statistical and programming team will perform the planned primary analyses (Section 9.6). Selected 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 details will be included in the Study Blinding Plan.
- Per the DSMB charter, the DSMB 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 study. Section 4.5 provides additional information on DSMB and safety review.

9.2. Statistical Hypotheses

This clinical study consists of 2 separate substudies: 1 for Cohort A (65 years or greater) and 1 for Cohort B (≥50 to <65 years of age). Each of the 2 independent substudies has its own separate hypotheses and statistical analyses, and its own multiplicity control for overall Type I error rate (2-sided alpha of 5%) for the co-primary endpoints within the substudy. Each of the 2 substudies has the co-primary immunogenicity endpoints as described below.

Hypotheses in Cohort A Sub-study (≥65 Years)

Five Co-primary Endpoints Based on GM Level at Day 29

The null hypothesis H^1_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and 1 SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza or PsVNA for SARS-CoV-2, is inferior compared with that in participants who received Fluzone HD + Spikevax. Five coprimary immunogenicity endpoints based on GM level at Day 29 will be tested for noninferiority of mRNA-1083 + Placebo vs. active comparator at a two-sided 0.025 level.

The NI in GM level in participants who received mRNA-1083 (40 µg) + Placebo compared with that of participants who received Fluzone HD + Spikevax will be demonstrated by the lower

bound of the two-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a NIM of 1.5. The GMR is defined as the ratio of the GM level of HAI or PsVNA in those participants receiving mRNA-1083 (40 µg) + Placebo versus the GM level of those participants receiving Fluzone HD + Spikevax.

Five Co-primary Endpoints Based on Influenza SCR or SARS-CoV-2 SRR at Day 29

The null hypothesis H^2_0: for each of the 4 influenza strains (2 A strains: H1N1, N3N2 and 2 B strains: Victoria, Yamagata) and the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) or SRR using PsVNA (for SARS-CoV-2), is inferior compared with that in participants who received Licensed Fluzone HD + Spikevax. The NI in SCR or SRR in participants who received mRNA-1083 (40 µg) + Placebo compared with that of participants who received Fluzone HD + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the SCR or SRR difference at Day 29 ruling out -10% (lower bound >-10%) using a NIM of 10%.

For influenza, the SCR at Day 29 is defined as the proportion of participants with either a preinjection HAI level <1:10 and a postinjection HAI level ≥1:40, or a preinjection HAI level ≥1:10 and a minimum 4-fold rise in postinjection HAI antibody level. The SCR difference Day 29 is defined as the difference between the SCR at Day 29 among those participants receiving mRNA-1083 (40 µg) + Placebo and the SCR at Day 29 among those participants receiving Fluzone HD + Spikevax.

For SARS-CoV-2, the SRR at Day 29 is defined as the proportion of participants with either GMFR in nAb levels of ≥4-fold postinjection compared with Day 1 in those with Baseline level ≥LLOQ, or postinjection level ≥4×LLOQ if Baseline level is <LLOQ. The SRR difference at Day 29 is defined as the difference between the SRR at Day 29 among those participants receiving mRNA-1083 (40 µg) + Placebo and the SRR at Day 29 among those participants receiving Fluzone HD + Spikevax.

The success criteria of non-inferiority for GM level are met if H^1_0 is rejected at two-sided 0.025 level on the 5 coprimary endpoints for GM level. Similarly, the success criteria for SCR or SRR are met if H^2_0 is rejected at two-sided 0.025 level on the 5 coprimary endpoints for SCR or SRR.

Secondary Endpoints

If the noninferiority success criteria of the coprimary endpoints for GM level are met, the following hypotheses will be tested sequentially to support secondary objectives (See Figure 2):

The null hypothesis H^3_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza, is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1) for all 4 influenza strains. It will be tested at a two-sided α_1=5% level if noninferiority is demonstrated for GM level (H^1_0 rejected) and SCR or SRR (H^2_0 rejected); and at a two-sided α_1=2.5% level if non-inferiority is only demonstrated for GM level (H^1_0 rejected).

If the superiority success criteria for GM levels at Day 29 using HAI assay for influenza are met (H^3_0 rejected), the null hypothesis H^4_0 will be tested: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using PsVNA is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator, will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1). The same level α_1 will be passed to test hypothesis H^4_0.

If the superiority success criteria for GM levels at Day 29 using PsVNA assay for SARS-CoV-2 are met (H^4_0 rejected) and noninferiority success criteria for SCR or SRR are met (H^2_0 rejected), the hypothesis H^5_0 will be tested. The null hypothesis H^5_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in SCR in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SCR difference ruling out 0% (lower bound >0%) for all 4 influenza strains.

If the superiority success criteria for SCR at Day 29 using HAI assay for influenza are met (H^5_0 rejected), the hypothesis H^6_0 will be tested. The null hypothesis H^6_0: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by Day 29 SRR using PsVNA (for SARS-CoV-2) is not superior to that in participants who received Fluzone HD + Spikevax. The superiority in SRR in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SRR difference ruling out 0% (lower bound >0%).

Hypotheses in Cohort B Sub-study (≥50 to <65 years)

Five Co-primary Endpoints Based on GM Level at Day 29

The null hypothesis H^1_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and 1 SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response in participants who received mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza or PsVNA for SARS-CoV-2, is inferior compared with that in participants who received Fluarix + Spikevax. Five coprimary immunogenicity endpoints based on GM level at Day 29 will be tested for noninferiority of mRNA-1083 + Placebo vs. active comparator at a two-sided 0.025 level.

The NI in GM level in participants who received mRNA-1083 (40 µg) + Placebo compared with that of participants who received Fluarix + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a NIM of 1.5. The GMR is defined as the ratio of the GM level of HAI or PsVNA in those participants receiving mRNA-1083 (40 µg) + Placebo versus the GM level of those receiving Fluarix + Spikevax.

Five Co-primary Endpoints Based on Influenza SCR or SARS-CoV-2 SRR at Day 29

The null hypothesis H^2_0 for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) and the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response in participants who received mRNA-1083 (40 µg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) or SRR using PsVNA (for SARS-CoV-2), is inferior compared with that in participants who received Fluarix + Spikevax. The NI in SCR or SRR in those participants who received mRNA-1083 (40 µg) + Placebo compared with that of those who received Fluarix + Spikevax will be demonstrated by the lower bound of the two-sided 97.5% CI of the SCR or SRR difference at Day 29 ruling out -10% (lower bound >-10%) using a NIM of 10%.

For influenza, the SCR at Day 29 is defined as the proportion of participants with either a preinjection HAI level <1:10 and a postinjection HAI level ≥1:40, or a preinjection HAI level ≥1:10 and a minimum 4-fold rise in postinjection HAI antibody level. The SCR difference Day 29 is defined as the difference between the SCR at Day 29 among those participants receiving mRNA-1083 (40 µg) + Placebo and the SCR at Day 29 among those receiving Fluarix + Spikevax.

For SARS-CoV-2, the SRR at Day 29 is defined as the proportion of participants with either a GMFR in nAb levels of ≥4-fold postinjection compared with Day 1 in those with Baseline level ≥LLOQ or postinjection level ≥4×LLOQ if Baseline level is <LLOQ. The SRR difference at Day 29 is defined as the difference between the SRR at Day 29 among those participants receiving mRNA-1083 (40 µg) + Placebo and the SRR at Day 29 among those receiving Fluarix + Spikevax.

The success criteria of non-inferiority for GM level are met if H^1_0 is rejected at two-sided 0.025 level on the 5 coprimary endpoints for GM level. Similarly, the success criteria for SCR or SRR are met if H^2_0 is rejected at two-sided 0.025 level on the 5 coprimary endpoints for SCR or SRR.

Secondary Endpoints

If the noninferiority success criteria of the coprimary endpoints for GM level are met, the following hypotheses will be tested sequentially to support secondary objectives (See Figure 2):

The null hypothesis H^3_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using HAI assay for influenza, is not superior to that in participants who received Fluarix + Spikevax. The superiority in GM level in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1) for all 4 influenza strains. It will be tested at a two-sided α_1=5% level if noninferiority is demonstrated for GM level (H^1_0 rejected) and SCR or SRR (H^2_0 rejected); and at a two-sided α_1=2.5% level if non-inferiority is only demonstrated for GM level (H^1_0 rejected).

If the superiority success criteria for GM levels at Day 29 using HAI assay for influenza are met (H^3_0 rejected), the null hypothesis H^4_0 will be tested: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by GM level at Day 29 using PsVNA is not superior to that in participants who received Fluarix + Spikevax. The superiority in GM level in participants who received

mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the (100%- α_1) CI of the GMR ruling out 1 (lower bound >1). The same level α_1 will be passed to test hypothesis H^4_0.

If the superiority success criteria for GM levels at Day 29 using PsVNA assay for SARS-CoV-2 are met (H^4_0 rejected), and noninferiority success criteria for SCR or SRR are met (H^2_0 rejected), the hypothesis H^5_0 will be tested. The null hypothesis H^5_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2 and 2 B strains: Victoria, Yamagata) , the immunogenicity response to mRNA1083 (40 µg) + Placebo, as measured by Day 29 SCR using HAI assay (for influenza strains) is not superior to that in participants who received Fluarix HD + Spikevax. The superiority in SCR in participants who received mRNA1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SCR difference ruling out 0% (lower bound >0%) for all the 4 influenza strains.

If the superiority success criteria for SCR at Day 29 using HAI assay for influenza are met (H^5_0 rejected), the hypothesis H^6_0 will be tested. The null hypothesis H^6_0: for the SARS-CoV-2 strain (Omicron XBB.1.5), the immunogenicity response to mRNA-1083 (40 µg) + Placebo, as measured by Day 29 SRR using PsVNA (for SARS-CoV-2) is not superior to that in participants who received Fluarix + Spikevax. The superiority in SRR in participants who received mRNA-1083 (40 µg) + Placebo compared to that of participants who received active comparator will be demonstrated by the lower bound of the 95% CI of the SRR difference ruling out 0% (lower bound >0%).

9.3. Sample Size Determination

With a total of 4000 participants for each cohort, approximately 2000 participants in Cohort A and 2000 participants in Cohort B (a total of 4000) will be exposed to study vaccine in the mRNA-1083 (40 µg) + Placebo group. This will have approximately over 95% probability to observe at least 1 participant with an AE given a true 0.1% AE rate.

A subset of participants will be randomly selected from the FAS of Cohort A and B, respectively, to be tested by microneutralization assay according to the secondary objective (Section 3). Details of the sampling strategy will be documented in the SAP.

9.3.1. Cohort A Substudy (greater than or equal to 65 years of age)

All 4000 participants in Cohort A who meet the PPIS criteria will be included in the PPIS for immunogenicity objectives. With approximately 2000 participants (including the assumed approximate 15% drop-outs) receiving mRNA-1083 (40 µg) + Placebo, and 2000 receiving Fluzone HD + Spikevax, this will provide at least 95% overall power to demonstrate NI across the five co-primary immunogenicity endpoints for GM level at Day 29 between mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2sided alpha of 0.025, approximately 15% dropout rate, true GMR of 0.85 (SD of antibody level in natural logarithm being 1.5) and a NIM of 1.5 for GMR in all the 4 influenza strains and 1 SARSCoV2 strain.

The study has at least 95% overall power to demonstrate NI across the 5 coprimary immunogenicity endpoints for SCR or SRR between mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power

evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop-out rate, an underlying SCR or SRR of 68% in the mRNA-1083 (40 µg) + Placebo group and an SCR or SRR of 70% in Fluzone HD + Spikevax group (with a true SCR or SRR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza A strains and 1 SARS-CoV-2 strain, and assumes an underlying SCR of 58% in the mRNA-1083 (40 µg) + Placebo group and a SCR of 60% in Fluzone HD + Spikevax group (with a true SCR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza B strains.

9.3.2. Cohort B Substudy (greater than or equal to 50 to less than 65 years of age)

All 4000 participants in Cohort B who meet the PPIS criteria will be included in the PPIS (in 1:1 ratio, including the assumed approximate 15% drop-outs; approximately 2000 participants receiving mRNA-1083 [40 µg] + Placebo, and 2000 receiving Fluarix + Spikevax). This will provide at least 95% overall power to demonstrate NI across the five co-primary immunogenicity endpoints for GM level at Day 29 between mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop-out rate, true GMR of 0.85 (SD of antibody level in natural logarithm being 1.5) and a NIM of 1.5 for GMR in all the 4 influenza strains and 1 SARS-CoV-2 strain.

The study has at least 95% overall power to demonstrate NI across the 5 coprimary immunogenicity endpoints for SCR or SRR between mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax in all the 4 influenza strains and 1 SARS-CoV-2 strain. The power evaluation assumes a 2-sided alpha of 0.025, approximately 15% drop-out rate, an underlying SCR or SRR of 68% in the mRNA-1083 (40 µg) + Placebo group and an SRR/SCR of 70% in Fluarix + Spikevax group (with a true SCR or SRR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza A strains and 1 SARS-CoV-2 strain, and assumes an underlying SCR of 58% in the mRNA-1083 (40 µg) + Placebo group and a SCR of 60% in Fluarix + Spikevax group (with a true SCR difference being -2%) and a NIM of 10% for the rate difference in the 2 influenza B strains.

9.4. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Table 9: Populations for Analyses in Cohort A and Cohort B Substudies, Respectively

Analysis Set	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.
FAS	The FAS consists of all participants who are randomly assigned and receive the study intervention. Participants will be analyzed according to the group to which they were randomized.
PPIS[a]	The PPIS consists of all participants in the FAS who comply with the timing of immunogenicity blood sample collections to have both Baseline and Day 29 assessments, have negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and have no major protocol deviations or conditions/medications that affect the immune response.

Analysis Set	Description
PPIS for MN	The PPIS for MN consists of a subset of participants randomly sampled from the FAS to be tested for MN, who comply with the timing of immunogenicity blood sample collections to have both Baseline and Day 29 assessments, have negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and have no major protocol deviations or conditions/medications that affect the immune response.
Safety Set[b]	The Safety Set consists of all participants who are randomly assigned and receive the study intervention. Participants will be included in the treatment group corresponding to what they received.
Solicited Safety Set[c]	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; MN = microneutralization assay; PPIS = Per Protocol Immunogenicity Set; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Each of Cohort A and Cohort B will have its separate set of analysis populations defined as above that will be applied in separate statistical analysis planned in each of the 2 cohorts, respectively.

a. The PPIS will be used as the primary analysis set for analyses of immunogenicity in Cohort A or Cohort B unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.

b. The Safety Set will be used for all analyses of safety, except for the solicited ARs.

c. 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 study will be separately planned and performed on the data collected in Cohort A and B substudies, respectively.

The SAP will be developed and finalized before the primary analysis of Cohort A and B substudies (whichever will come earlier) and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

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

9.5.1. Immunogenicity Analyses

Cohort A for Adults ≥65 Years of Age

The primary analysis population of immunogenicity will be the PPIS in Cohort A for adults aged 65 years or greater, unless otherwise specified. The primary objective of Cohort A is to evaluate the immunogenicity response between the participants receiving mRNA-1083 (40 µg) + Placebo and those receiving Fluzone HD + Spikevax among adults ≥65 years of age.

Immune responses for influenza, as measured by GM level and SCR at Day 29 by HAI assay in the group of mRNA-1083 (40 µg) + Placebo, will be compared with those in the participants receiving Fluzone HD + Spikevax for all 4 influenza strains.

Immune responses for SARS-CoV-2, as measured by GM level and SRR at Day 29 by PsVNA in the group of mRNA-1083 (40 µg) + Placebo, will be compared with those participants receiving Fluzone HD + Spikevax for the matched strain.

An ANCOVA model will be carried out including the log-transformed HAI or PsVNA levels at Day 29 as the dependent variable, the treatment group as the fixed variable, log transformed Baseline HAI or PsVNA levels as a fixed covariate, adjusting for the stratification factors, that is, the age group (65 to <75 years of age versus 75 years of age or older) and the influenza vaccine status in the most recent influenza season (received or not received since Sep 2022). The GLSM and its corresponding 2-sided 95% CI in log-transformed scale estimated from the ANCOVA model will be back-transformed to the original scale to obtain an estimate of the GM level. GMR will be estimated by the ratio of GLSM and the corresponding 2-sided and 95% CI and 97.5% CI to assess the immune response difference between the group of mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax. For each strain of influenza and SARS-CoV-2, the NI of GM level will be considered demonstrated between the group of mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax if the lower bound of the 2-sided 97.5% CI of the GMR is >0.667 based on the prespecified NIM of 1.5.

The number and percentage of participants with either seroconversion (for influenza) or seroresponse (for SARS-CoV-2) postvaccination at Day 29 will be provided along with the two-sided 95% CI of SCR or SRR, estimated using the Clopper-Pearson method. The difference in either SCR or SRR between the group of mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax, along with its 95% CI and 97.5% CI estimated using the Miettinen-Nurminen's method will be provided to assess the immune response difference. For each strain of influenza and SARS-CoV-2, the NI of SCR or SRR will be considered demonstrated between the group of mRNA-1083 (40 µg) + Placebo and Fluzone HD + Spikevax if the lower bound of the 2-sided 97.5% CI of the SCR or SRR difference is >-10% based on the prespecified NIM of 10%.

After the primary NI hypothesis testing has been performed for GMR and SCR or SRR difference, the secondary superiority hypothesis testing will be performed sequentially following the procedure specified in Figure 2. For the other descriptive secondary and exploratory endpoints, GM level of HAI, microneutralization assay, or PsVNA with corresponding 95% CI will be provided at each timepoint. GMFR of HAI, microneutralization assay, or PsVNA with corresponding 95% CI at each post-Baseline timepoint over pre-injection Baseline at Day 1 will be provided. A subset of PPIS (approximately 800 participants) may be used for exploratory endpoints involving immunogenicity analysis at Day 181. Descriptive summary statistics including median, minimum, and maximum will also be provided.

Cohort B for Adults 50 to <65 Years of Age

The primary analysis population of immunogenicity will be the PPIS in Cohort B for adults aged ≥50 to <65 years, unless otherwise specified. The primary objective of Cohort B is to evaluate the immunogenicity response between the participants receiving between mRNA-1083 (40 µg) + Placebo and those receiving Fluarix + Spikevax among the adults 50 to <65 years of age.

Immune responses for influenza, as measured by GM level and SCR at Day 29 by HAI assay in the group of mRNA-1083 (40 µg) + Placebo, will be compared with those in the participants receiving Fluarix + Spikevax for all 4 influenza strains.

Immune responses for SARS-CoV-2, as measured by GM level and SRR at Day 29 by PsVNA in the group of mRNA-1083 (40 µg) + Placebo, will be compared with those participants receiving Fluarix + Spikevax for the matched strain.

An ANCOVA model will be carried out including the log-transformed HAI or PsVNA levels at Day 29 as the dependent variable, the treatment group as the fixed variable, log transformed Baseline HAI or PsVNA levels as a fixed covariate, adjusting for the stratification factor, the influenza vaccine status in the most recent influenza season (received or not received since September 2022). The GLSM and its corresponding 2-sided 95% CI in log-transformed scale estimated from the ANCOVA model will be back-transformed to the original scale to obtain an estimate of the GM level. GMR will be estimated by the ratio of GLSM and the corresponding 2-sided 95% CI and 97.5% CI to assess the immune response difference between the group of mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax. For each strain of influenza and SARS-CoV-2, the NI of GM level will be considered demonstrated between the group of mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax if the lower bound of the 2-sided 97.5% CI of the GMR is >0.667 based on the prespecified NIM of 1.5.

The number and percentage of participants with either seroconversion (for influenza) or seroresponse (for SARS-CoV-2) postvaccination at Day 29 will be provided along with the two-sided 95% CI of SCR or SRR, estimated using the Clopper-Pearson method. The difference in either SCR or SRR between the group of mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax, along with its 95% CI and 97.5% CI estimated using the Miettinen-Nurminen's method will be provided to assess the immune response difference. For each strain of influenza and SARS-CoV-2, the NI of SCR or SRR will be considered demonstrated between the group of mRNA-1083 (40 µg) + Placebo and Fluarix + Spikevax if the lower bound of the 2-sided 97.5% CI of the SCR or SRR difference is >-10% based on the prespecified NIM of 10%.

After the primary NI hypothesis testing has been performed for GMR and SCR or SRR difference, the secondary superiority hypothesis testing will be performed sequentially following the procedure specified in Figure 2. For the other descriptive secondary and exploratory endpoints, GM level of HAI, microneutralization assay, or PsVNA with corresponding 95% CI will be provided at each timepoint. GMFR of HAI, microneutralization assay, or PsVNA levels with corresponding 95% CI at each post-Baseline timepoint over pre-injection Baseline at Day 1 will be provided. A subset of PPIS (approximately 800 participants) may be used for exploratory endpoints involving immunogenicity analysis at Day 181. Descriptive summary statistics including median, minimum, and maximum will also be provided.

9.5.2. Efficacy Analyses

No efficacy analyses will be performed for either Cohort A or B.

9.5.3. Safety Analyses

The safety analyses will be separately performed by Cohort A and B, respectively.

All safety analyses will be based on the Safety Set of each cohort, except summaries of solicited ARs, which will be based on the Solicited Safety Set of each cohort. 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 postinjection follow-up will be summarized. A two-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR. Solicited ARs and grades are defined in Section 10.5.

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 MedDRA and presented by MedDRA system organ class and preferred term.

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

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.

The analysis strategy for safety parameters is presented in Table 10. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

Table 10: 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)	✓	NA	✓
Any unsolicited AE	✓	✓	NA
Any unsolicited treatment-related AE	✓	✓	NA
Any SAE	✓	✓	NA
Any treatment-related SAE	✓	✓	NA
Any unsolicited AESI	✓	✓	NA
Any unsolicited treatment-related AESI	✓	✓	NA
Any unsolicited MAAE	✓	✓	NA
Any unsolicited treatment-related MAAE	✓	✓	NA
Any unsolicited severe AE	✓	✓	NA
Any unsolicited treatment-related severe AE	✓	✓	NA
Any unsolicited AE leading to withdrawal from study participation	✓	✓	NA

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; NA = not applicable; 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 will be described in the SAP.

9.6. Planned Analyses

The statistical analyses in this clinical study will be separately planned and performed on the data collected in the 2 substudies Cohorts A and B, respectively, with each substudy independently having its own hypotheses, statistical analyses, and multiplicity control.

The SAP will be developed and finalized before the primary analyses. The SAP will describe the pre-planned 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.

9.6.1. Cohort A Substudy (greater than or equal to 65 years)

The primary analysis of safety, reactogenicity, and immunogenicity for Cohort A substudy will occur when all the Cohort A participants have completed the Day 29 visit.

9.6.2. Cohort B Substudy (greater than or equal to 50 to less than 65 years)

The primary analysis of safety, reactogenicity, and immunogenicity for Cohort B substudy will occur when all the Cohort B participants have completed the Day 29 visit.

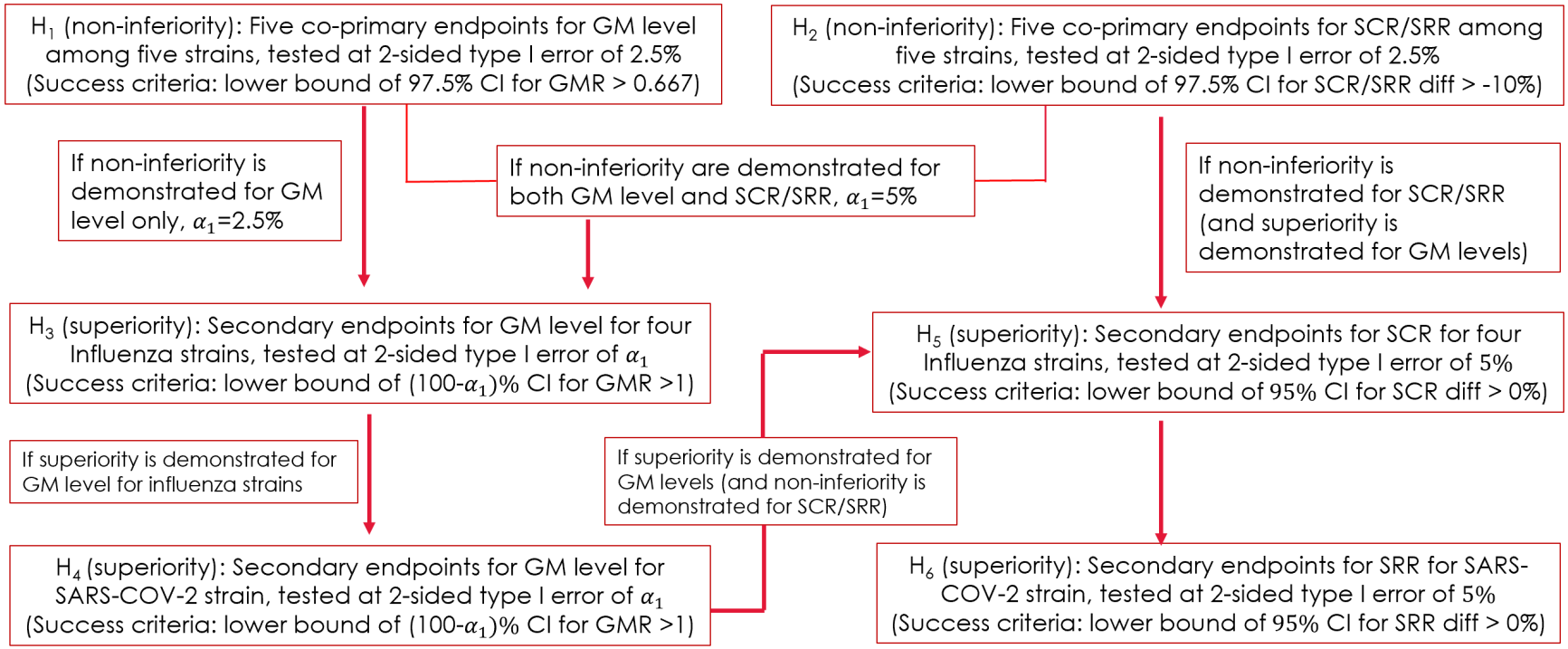
9.6.3. Multiplicity

No multiplicity adjustment will be needed between the Cohort A and B substudies.

For Cohort A, a 2-sided alpha of 0.05 will be fully spent, as shown in the testing sequence for coprimary and secondary endpoints in Figure 2.

Similarly for Cohort B, a 2-sided alpha of 0.05 will be fully spent, as shown in the testing sequence for coprimary and secondary endpoints in Figure 2.

Figure 2: Hypotheses testing sequence for coprimary and secondary endpoints



Abbreviations: CI = confidence interval; GM = geometric mean; H = Hypothesis; SCR = seroconversion rate, SRR = seroresponse rate.

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the clinical study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the clinical study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the clinical study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. 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 study. The Investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory authorities to inspect the study injection storage area, study injection stocks, study injection 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 study, 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 study.

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

10.1.4. Informed Consent Process

The ICF(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 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 study, 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 their representative will explain the nature of the clinical study to the participant and answer all questions regarding the clinical study.

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

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

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

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

The participant must be made aware of and give consent to direct access to 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 rescreening occurs within 28 days from the previous ICF signature date.

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

10.1.5. Recruitment Strategy

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

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

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

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

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

The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.8. 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 study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity 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.

10.1.9. Dissemination of Clinical Study Data

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

10.1.10. 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, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring); methods; responsibilities; and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this clinical study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the clinical study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this clinical study must be retained by the Investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the

discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be 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 study 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 study by reviewing the data obtained and procedural aspects. These inspections may include onsite inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

10.1.11. Data Collection and Management

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

This clinical study 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.

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

10.1.12. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents are filed at the Investigator's site.

The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.13. Study and Site Start and Closure

First Act of Recruitment

The start-of-study is defined as the date of the first site activated.

The first act of recruitment is the first participant signing first informed consent in line with first participant first visit and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study injection development.

For site termination:

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

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

10.1.14. Publication Policy

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 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 study 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 injection decision or response evaluation, the results must be recorded.
- Investigators must document their review of each laboratory safety report.

Table 11: Protocol-required Clinical Laboratory Tests

Laboratory Tests	Parameters
Pregnancy Testing	• Highly sensitive urine hCG pregnancy test (as needed for participants of childbearing potential)[a]
Other Screening Tests	• FSH (as needed in participants of nonchildbearing potential only)[b]

Abbreviations: FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; IEC = independent ethics committee; IRB = institutional review board

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

b. 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.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study injection even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study injection or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Unsolicited AEs (Section 8.4.7) are 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).

Events <u>not</u> Meeting the AE 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 is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

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

- **Results in death**
  A death that occurs during the clinical study or that comes to the attention of the Investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to study injection.
- **Is life threatening**
  The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

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

- **Results in persistent or significant disability/incapacity**
  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Medically important event**
  Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

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

10.3.3.1. AE and SAE Recording

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 7.2.

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

All SAEs reported or observed during the clinical study will be recorded on the AE page of the eCRF. All SAEs will be collected from signing of the ICF until EoS visit at the timepoints specified in the SoA in Section 1.3.

Information to be collected includes type of event, time of onset, Investigator-specified assessment of severity and relationship to study injection, 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.

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

10.3.3.2. 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 study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.4.6.

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.

10.3.3.3. Assessment of Causality

The Investigator is obligated to assess the relationship between study injection and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

- **Not related:** There is not a reasonable possibility of a relationship to the study injection. Participant did not receive the study injection OR temporal sequence of the AE onset relative to administration of the study injection is not reasonable OR the AE is more likely explained by another cause than the study injection.
- **Related:** There is a reasonable possibility of a relationship to the study injection. There is evidence of exposure to the study injection. The temporal sequence of the AE onset relative to the administration of the study injection is reasonable. The AE is more likely explained by the study injection than by another cause.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or its designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AESIs (as defined in Section 8.4.9) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.2).

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

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

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 number on the form. Initial notification via email does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.

Regulatory reporting requirements for SAEs are described in Section 8.4.4.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Definitions:

Participant of Childbearing Potential

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

Participant of Non-Childbearing Potential

2. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - The FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
   - Participants on HRT and whose menopausal status is in doubt will be required to use one of the contraception methods described below, if they wish to continue their HRT during the clinical study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
3. Permanent sterilization methods (for the purpose of this clinical study) include:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.
   - Documented bilateral tubal ligation.
4. 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 injection, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• 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 reproductive sexual intercourse during the entire period of risk associated with the study injection. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• External or internal condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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.

10.5. Appendix 5: 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 poststudy injection 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.

10.6. Appendix 6: Adverse Events of Special Interest

The table below 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, per protocol, even when they occur during/following COVID-19 infection.

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

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.
ARDS	• New onset of /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 non-traumatic hemorrhage/bleeding disorder (eg, stroke, deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, etc.)
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.

Medical Concept	Additional Notes
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 in the absence of a clear, alternate etiology, 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 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
Thrombocytopenia	• Platelet count $<150 \times 10^9$/L (thrombocytopenia) • New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or hemolysis, elevated liver enzymes and low platelet count (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

Medical Concept	Additional Notes
New onset, or worsening, of the following neurological diseases	• Immune-mediated neurological disorders • Guillain-Barre Syndrome • Acute disseminated encephalomyelitis • Peripheral facial nerve palsy (Bell's palsy) • Transverse myelitis • Encephalitis/encephalomyelitis • Aseptic meningitis • Seizures/convulsions/epilepsy • Narcolepsy/hypersomnia
Anaphylaxis	• Anaphylaxis associated with study injection as defined per protocol • Follow reporting procedures in Section 8.4.9.1
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome • Myalgic encephalomyelitis • Postviral fatigue syndrome • Myasthenia gravis • Capillary leak syndrome (new diagnosis or flare up in participants with prior history of capillary leak syndrome)

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 study is presented in Table 12.

Table 12: 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] 1. chest pain, pressure, or discomfort 2. dyspnea, shortness of breath, or pain with breathing 3. palpitations 4. syncope	Presence of ≥1 new or worsening of the following clinical symptoms:[a] 1. chest pain, pressure, or discomfort 2. dyspnea, shortness of breath, or pain with breathing 3. palpitations 4. syncope
	OR	**OR**
	Infants and children aged <12 years might instead have ≥2 of the following symptoms: 1. irritability 2. vomiting 3. poor feeding 4. tachypnea 5. lethargy	Infants and children aged <12 years might instead have ≥2 of the following symptoms: 1. irritability 2. vomiting 3. poor feeding 4. tachypnea 5. lethargy
	AND	**AND**
	≥1 new finding of 1. troponin level above upper limit of normal (any type of troponin) 2. abnormal ECG or EKG or rhythm monitoring findings consistent with myocarditis[c] 3. abnormal cardiac function or wall motion abnormalities on echocardiogram 4. cMRI findings consistent with myocarditis[d]	≥1 new finding of 1. Histopathologic confirmation of myocarditis[b] 2. cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	AND	**AND**
	1. No other identifiable cause of the symptoms and findings	1. No other identifiable cause of the symptoms and findings

Condition	Definition
Acute pericarditis[e]	Presence of ≥2 new or worsening of the following clinical features: 1. acute chest pain[f] 2. pericardial rub on exam 3. new ST-elevation or PR-depression on ECG 4. 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 Centers 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).

11. REFERENCES

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias B, Bogaert J, et al. ESC Scientific Document Group, 2015 ESC guidelines for the diagnosis and management of pericardial disease: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). Eur Heart J. 2015;36(42):2921-64.

Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol. 1987;18(6):619-24.

Centers for Disease Control and Prevention (CDC) [Internet]. Atlanta: Symptoms of COVID-19. [updated 2022 Oct 26; cited 2023 Jun 6]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.

Centers for Disease Control and Prevention (CDC) [Internet]. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). [updated 2023 Jan 3; cited 2023 June 5]. Available from: https://www.cdc.gov/mis/mis-c/hcp_cstecdc/.

Centers for Disease Control and Prevention (CDC) [Internet]. Seasonal Influenza. [updated 2023a Jun 2; cited 2023 Jun 6]. Available from: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). [Internet]. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007. [cited 2023 Jun 6]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Food and Drug Administration (US). [Internet]. News Release. FDA Takes Action on Updated mRNA COVID-19 Vaccines to Better Protect Against Currently Circulating Variants. September 2023 [cited 2023 Sep 19]. Available from: https://www.fda.gov/news-events/press-announcements/fda-takes-action-updated-mrna-covid-19-vaccines-better-protect-against-currently-circulating.

Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Col Cardio. 2018;72(24):3158-76.

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

Kurosky SK, Davis KL, Krishnarajah G. Effect of combination vaccines on completion and compliance of childhood vaccinations in the United States. Hum Vaccin Immunother. 2017;13(11):2494-502.

Monto AS, Petrie JG, Cross RT, Johnson E, Liu M, Zhong W, et al. Antibody to influenza virus neuraminidase: an independent correlate of protection. J Infect Dis. 2015;212(8):1191-99.

Riedel S, Hobden JA, Miller S, Morse SA, Mietzner TA, Detrick B, et al. Jawetz, Melnick & Adelberg's Medical Microbiology. 28th ed. New York: McGraw-Hill Education; 2019. Chapter 39, Orthomyxoviruses (Influenza Viruses); p. 581-94.

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

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

Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US – December 14, 2020 – January 18, 2021. JAMA. 2021;325(11):1101-2.

World Health Organization (WHO). Influenza (Seasonal). [Internet]. [updated 2023 Jan 12; cited 2023 Jun 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

World Health Organization (WHO). Coronovirus (COVID-19) Dashboard [Internet]. 2023a Jun 5 [cited 2023 Jun 5]. Available from: https://covid19.who.int/.

Zent O, Arras Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations – a post marketing surveillance review. Eur J Pediatr. 2002;161(1):21-5.