



CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 2, Randomized, Observer-blind Study to Evaluate the Safety, Reactogenicity, and Immunogenicity in Relation to the Product Attributes of mRNA-1083 (SARS-CoV-2 and Influenza) Vaccine in Adults ≥ 50 to < 65 Years of Age

Protocol Number: mRNA-1083-P201

Compound: mRNA-1083

Brief Title: A clinical study to investigate the product attributes of mRNA-1083 (SARS-CoV-2 and influenza vaccine)

Study Phase: Phase 2

Sponsor Name: ModernaTX, Inc.

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Regulatory Agency Identifier Number(s): IND: 29324

Date: 04 Feb 2025

Sponsor Signatory:

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

Sponsor Signatory and Contact Information will be provided separately.

CONFIDENTIAL

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DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled “A Phase 2, Randomized, Observer-blind Study to Evaluate the Safety, Reactogenicity, and Immunogenicity in Relation to the Product Attributes of mRNA-1083 (SARS-CoV-2 and Influenza) Vaccine in Adults ≥ 50 to < 65 Years of Age” dated 04 Feb 2025 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 intervention only to participants under my personal supervision or the supervision of a Subinvestigator. I will not supply study intervention to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

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

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

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

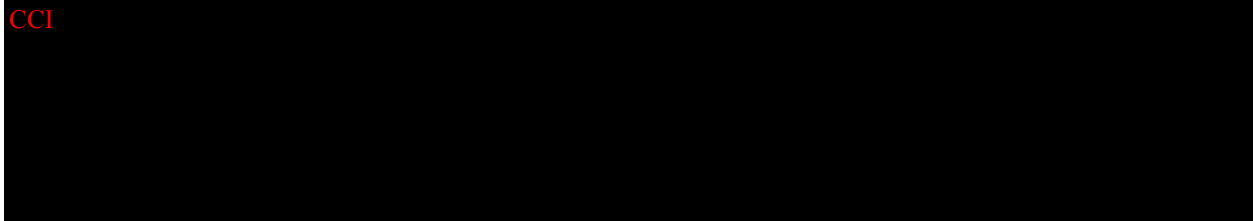
DOCUMENT HISTORY	
Document	Date
Amendment 1	04 Feb 2025
Original Protocol	10 May 2024

Amendment 1, 04 Feb 2025

This amendment is considered substantial.

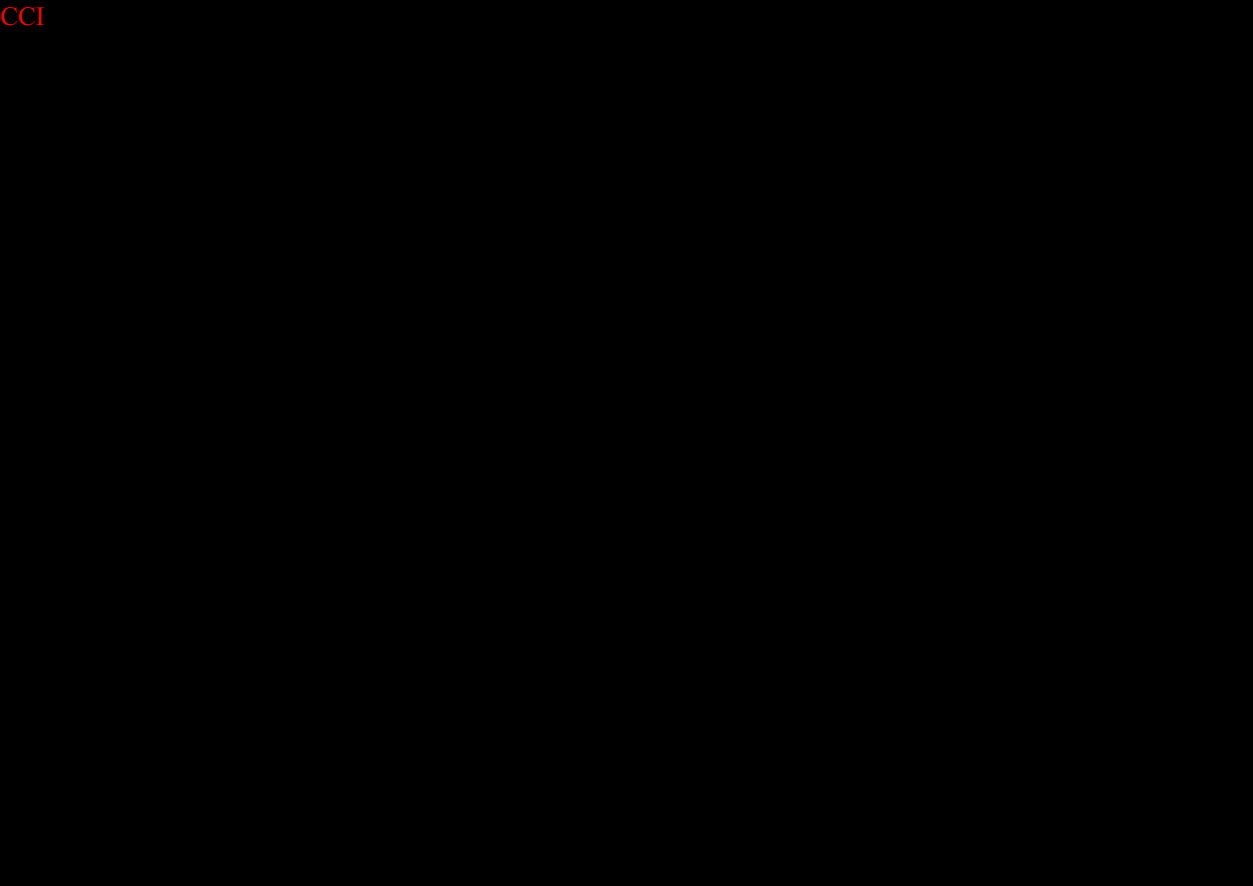
Main Rationale for the Amendment

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Summary of Major Changes in Protocol Amendment 1

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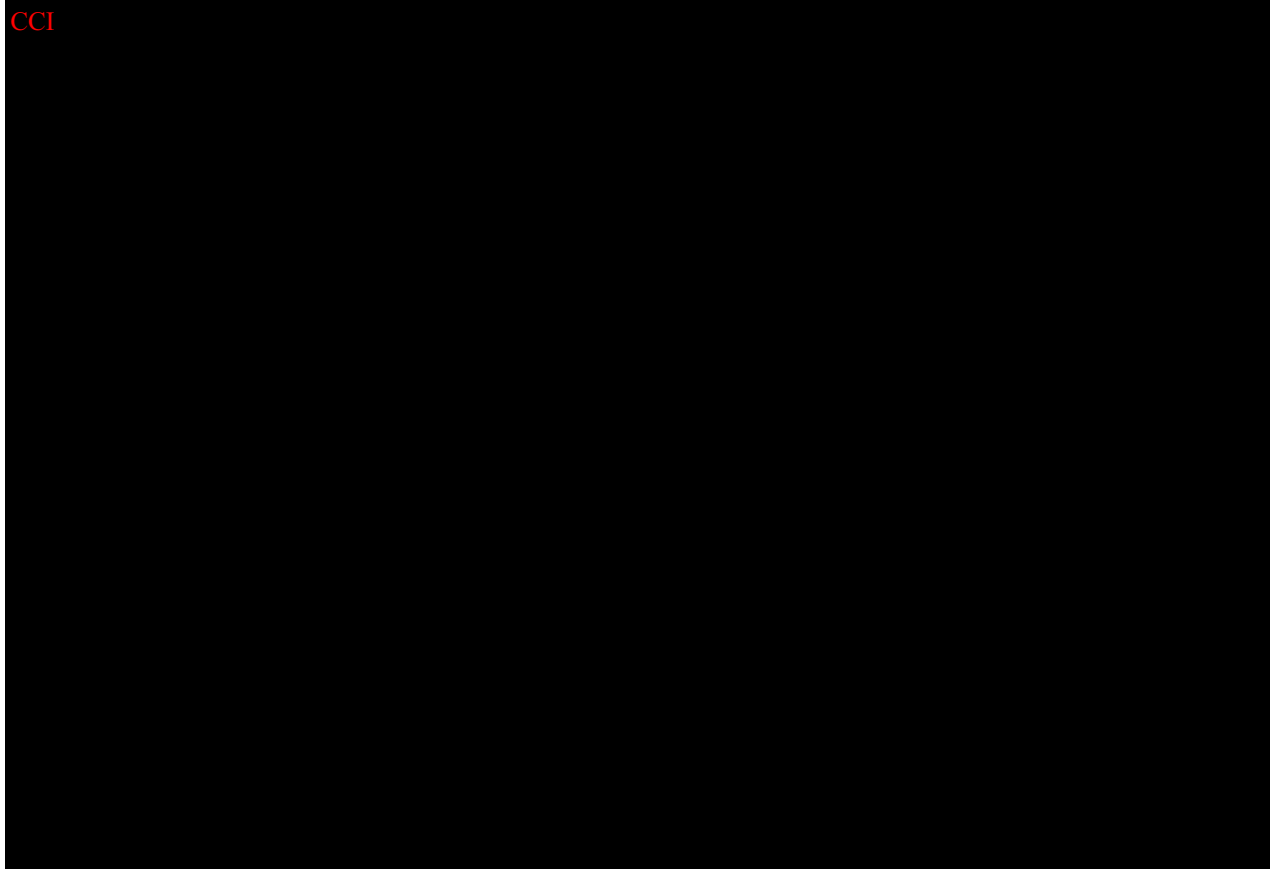


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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	clinical research organization
CSR	clinical study report
DHHS	Department of Health and Human Services
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EoS	end-of-study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
HCP	healthcare professional
HRT	hormonal replacement therapy
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	intramuscular(ly)
IND	investigational new drug

Abbreviation	Definition
IRB	institutional review board
IRT	interactive response technology
IST	internal safety team
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
NH	northern hemisphere
OTC	over-the-counter
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PI	Principal Investigator
POCBP	person of childbearing potential
PONCBP	person of nonchildbearing potential
PPIS	per-protocol immunogenicity set
PsVNA	pseudovirus neutralization assay
QTL	quality tolerance limit
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCR	seroconversion rate
SH	southern hemisphere
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SoA	schedule of activities
SRR	seroresponse rate
US	United States
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 2, Randomized, Observer-blind Study to Evaluate the Safety, Reactogenicity, and Immunogenicity in Relation to the Product Attributes of mRNA-1083 (SARS-CoV-2 and Influenza) Vaccine in Adults ≥ 50 to < 65 Years of Age

Brief Title:

A clinical study to investigate the product attributes of mRNA-1083 (SARS-CoV-2 and influenza vaccine)

Regulatory Agency Identifier Number(s):

Registry	ID
IND	29324

Rationale:

This Phase 2 study is designed to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of the mRNA-1083 multicomponent influenza and SARS-CoV-2 vaccine in adults ≥ 50 to < 65 years of age. This study is comprised of 2 parts, Parts 1 and 2. A 40- μ g dose of mRNA-1083 from 5 lots (Lots A, B, C, D, and E) representing product attributes reflecting a range of storage durations at 2°C to 8°C will be evaluated across both parts. This study will generate additional clinical experience with variability in product attributes to support product specifications. The specifics of the product attributes evaluated will be included in the CSR.

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, mRNA-1083 40 μ g was selected for adults aged ≥ 50 years to be further evaluated in the Phase 3 study ([NCT06097273](#)) and this Phase 2 study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.	GM value at Day 29 in antibody measured by HAI assay for influenza and by PsVNA for SARS-CoV-2.
To evaluate the safety and reactogenicity in relation to the product attributes of mRNA-1083.	- Solicited local and systemic ARs through 7 days after the study injection. - Unsolicited AEs through 28 days after the study injection. - MAAEs from Day 1 to Day 181 (Month 6) or EoS.

Objectives	Endpoints
	- AESIs from Day 1 to Day 181 (Month 6) or EoS. - SAEs from the time of informed consent to Day 181 (Month 6) or EoS. - AEs leading to discontinuation from study participation from Day 1 to Day 181 (Month 6) or EoS.
Secondary	
To further evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.	- GMFR at Day 29 relative to Day 1 in antibody measured by HAI assay for influenza and by PsVNA for SARS-CoV-2. - SCR at Day 29 in anti-HA antibody values measured by HAI assay for influenza. - SRR at Day 29 in nAb values measured by PsVNA for SARS-CoV-2.
Exploratory	
To evaluate the humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083 at all evaluable humoral immunogenicity timepoints.	- GM values and GMFR at all evaluable timepoints by HAI assay for influenza and by PsVNA for SARS-CoV-2. - SCR of influenza at all evaluable timepoints. - SRR of SARS-CoV-2 at all evaluable timepoints.
To further characterize immunogenicity in relation to the product attributes of mRNA-1083.	Frequency, levels, and specificities of immune responses, or other endpoints to be determined for the further characterization of immunogenicity.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GM = geometric mean; GMFR = geometric mean fold rise; HA = hemagglutination; HAI = hemagglutination inhibition; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate.

Overall Design Synopsis:

This study is a Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in adults ≥ 50 to < 65 years of age. This study is comprised of 2 parts. In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups (Lots A, B, C, and D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups (Lots A and E) in Part 2. All participants will receive a single IM injection of study intervention administered in a deltoid muscle on Day 1.

Brief Summary:

The purpose of this study is to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of mRNA-1083 vaccine when administered as a single IM injection in adults ≥ 50 to < 65 years of age.

Study details include:

- The study duration for each participant will be approximately 6 months from randomization.
- There will be up to 4 scheduled in-person visits (Screening Visit, Day 1, Day 29, and Day 181 [Month 6]/EoS Visit), unscheduled visits if required, and 2 safety telephone calls (Day 8 and Day 91 [Month 3]) as specified in the SoA.
- Participants will be instructed to complete eDiary entries daily for solicited ARs for 7 days (ie, the day of the study injection and 6 subsequent days).
- Collection of unsolicited AEs will be from the study intervention administration on Day 1 through Day 28 (ie, the day of study intervention administration and 27 subsequent days).
- Collection of AEs leading to discontinuation from study participation, unsolicited MAAEs, and unsolicited AESIs from the study intervention administration on Day 1 through Day 181 (Month 6) or EoS or discontinuation from the clinical study.
- Collection of SAEs will be from signing of the ICF through Day 181 (Month 6) or EoS.
- Blood samples will be collected from all participants for evaluation of humoral immunogenicity on Day 1 (prior to study intervention administration), Day 29, and Day 181 (Month 6) or EoS.

Number of Participants:

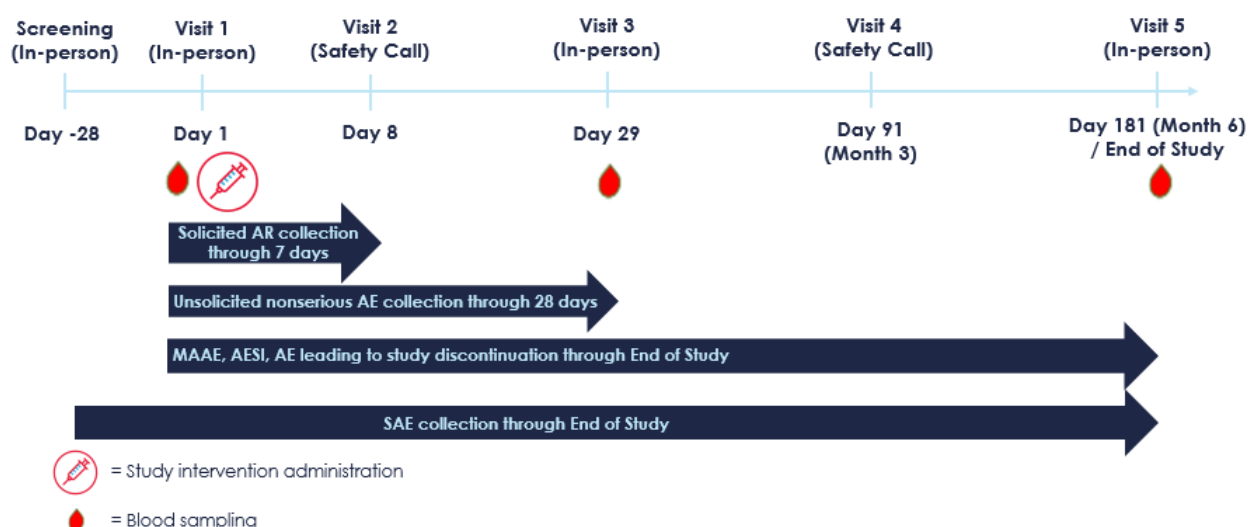
In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups (Lots A, B, C, and D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups (Lots A and E) in Part 2.

Study Groups and Duration:

- The study includes a Screening period (up to 28 days before Day 1), study intervention administration on Day 1 (Baseline), and a Follow-up period (through Day 181 [Month 6] after the study intervention). The study duration for each participant will be approximately 6 months.
- All participants will receive a single IM injection of study intervention administered in a deltoid muscle on Day 1.
- The study will comprise 4 study groups in Part 1 and 2 study groups in Part 2.

1.2. Schema

Figure 1: Study Schema



	Study Intervention Group	Vaccine Administered	Approximate Sample Size
Part 1			
	Group 1	mRNA-1083 40 µg: Lot A	150
	Group 2	mRNA-1083 40 µg: Lot B	150
	Group 3	mRNA-1083 40 µg: Lot C	150
	Group 4	mRNA-1083 40 µg: Lot D	150
Part 2			
	Group 5	mRNA-1083 40 µg: Lot A	150
	Group 6	mRNA-1083 40 µg: Lot E	150

Abbreviations: AE = adverse event; AR = adverse reaction; AESI = adverse event of special interest; MAAE= medically attended adverse event; SAE = serious adverse event.

1.3. Schedule of Activities

Table 1: Schedule of Activities (Part 1 and Part 2)

Visit Number	Screening	1	2	3	4	5	USV	Notes
Timepoint	Screening ^a	Day 1 (Baseline) ^a	Day 8	Day 29	Day 91/ Month 3	Day 181/ Month 6 (EoS) ^b	Up to Month 6/USV	1 month = 30 days
Window Allowance (Days)	Up to -28	N/A	-1 to +3	-7 to +3	±5	±14	N/A	
Type of Visit	C	C	SC	C	SC	C	C	
Informed consent, demographics, concomitant medications, medical history ^c	X							Refer to Section 10.1.4 and Section 6.9
Inclusion and exclusion criteria	X	X						Refer to Section 5.1 and Section 5.2
Full physical examination ^d	X							Refer to Section 8.2.1
Symptom directed physical examination ^d		X		X		X	X	Refer to Section 8.2.1
Injection site and corresponding draining lymph nodes assessment		X						Refer to Section 8.2.1
Vital sign measurements ^e	X	X						Refer to Section 8.2.2
Pregnancy testing ^f	X	X						Refer to Section 8.2.3
Randomization		X						Refer to Section 6.3
Blood collection for humoral immunogenicity ^g		X ^h		X		X		Refer to Section 8.8
Blood collection for SARS-CoV- 2 antibodies, nucleocapsid		X ^h						Refer to Section 8.8

Visit Number	Screening	1	2	3	4	5	USV	Notes
Timepoint	Screening ^a	Day 1 (Baseline) ^a	Day 8	Day 29	Day 91/ Month 3	Day 181/ Month 6 (EoS) ^b	Up to Month 6/USV	1 month = 30 days
Window Allowance (Days)	Up to -28	N/A	-1 to +3	-7 to +3	±5	±14	N/A	
Study injection (including 30-minute, postdosing observation period) ⁱ		X						Refer to Section 6.1
eDiary activation for recording solicited ARs (7 days) ^j		X						Refer to Section 8.2.5
Review of solicited AR eDiary			X					Refer to Section 8.2.5
Follow-up safety call ^k			X		X			Refer to Section 8.2.4
Recording of unsolicited AEs		X	X	X				Refer to Section 8.3
Recording of AESIs, MAAEs, AEs leading to discontinuation, and concomitant medications/procedures relevant to or for their treatment		X	X	X	X	X	X	Refer to Section 8.3.1.3 and Section 8.3.1.6
Recording of SAEs ^l and concomitant medications/procedures relevant to or for their treatment	X	X	X	X	X	X	X	Refer to Section 8.3.1.2
Recording of concomitant medications and nonstudy vaccinations ^m	X	X	X	X	X	X	X	Refer to Section 6.9.2
Study completion						X		

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = in-person visit; eDiary = electronic diary; EoS = end-of-study; FSH = follicle stimulating hormone; HCP = healthcare professional; IM = intramuscular; MAAE = medically attended adverse event; N/A = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety telephone call; SoA = schedule of activities; USV = unscheduled visit.

^a. Screening and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-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.
- c. Verbal history is acceptable.
- d. A full physical examination, including height and weight for calculation of body mass index, will be performed at the Screening Visit. If the participant reports symptoms, symptom-directed physical examinations will be performed at other clinic visits. Interim physical examinations will be performed at the discretion of the Investigator. Any clinically significant 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 may be collected at other clinical visits only in conjunction with a symptom-directed physical examination. For all vital sign measurements, participant must be seated for 5 minutes before any measurements are taken.
- f. For participants of childbearing potential, a point-of-care urine pregnancy test will be performed at the Screening Visit and before the IM injection on Day 1. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. The FSH level may be measured for participants of nonchildbearing potential at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
- g. Blood samples on Day 1, Day 29, and Day 181 (Month 6) will be collected in all participants. Serum from humoral immunogenicity samples will be stored for potential future use.
- h. All Baseline samples must be collected prior to the study intervention administration on Day 1.
- i. All participants will be randomized to receive a single IM injection of study intervention in a deltoid muscle.
- j. The eDiary will be activated and entries will be recorded by the participant at approximately 30 minutes after injection while at the clinic with instruction provided by study site staff. Study participants will continue to record in the eDiary after they leave the clinic preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection, for a total of 7 days.
- k. Trained study site staff will call all participants to collect information related to any AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation from study participation, information on concomitant medications/procedures associated with those events, and any nonstudy vaccinations.
- l. SAEs will be collected from the time of informed consent through Day 181 (Month 6) or EoS.
- m. All concomitant medications will be recorded through 28 days after injection. Additionally, nonstudy vaccinations and certain concomitant medications will be recorded through Day 181 (Month 6) or EoS.

2. INTRODUCTION

The Sponsor is developing LNP-encapsulated mRNA-based prophylactic multicomponent vaccines (also referred 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), which 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 substantial challenge to public health ([WHO 2023a](#)). 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. Due to the disappearance of B/Yamagata lineage from circulation, the WHO recently recommended that influenza vaccines for the upcoming 2024 SH influenza season use a trivalent formulation (2 influenza A antigens and B/Victoria antigen) rather than the previously recommended quadrivalent vaccine (2 influenza A antigens and 2 influenza B antigens) ([WHO 2024a](#), [WHO 2023b](#)).

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome. An outbreak of a novel coronavirus (later designated SARS-CoV-2, the causative agent of COVID-19) initially emerged in Wuhan, Hubei Province, and China in Dec 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020; widespread community transmission of SARS-CoV-2 has been reported in all WHO regions resulting in an estimated total of 775 million cases and 7 million deaths (as of 07 Apr 2024 [[WHO 2024b](#)]). Though the WHO announced the end of the COVID-19 pandemic on 5 May 2023 ([Bond and McNicholas, 2024](#)), COVID-19 still remains a major public health issue, impacting the health and wellbeing of many. In 2023 alone, surveillance data from the US estimated approximately 850,000 hospitalizations and 70,000 deaths due to COVID-19 with the majority of cases and deaths occurring among older individuals ([CDC 2024](#)).

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 virus and SARS-CoV-2 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 virus and SARS-CoV-2.

2.1. Study Rationale

This Phase 2 study is designed to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of the mRNA-1083 multicomponent influenza and SARS-CoV-2 vaccine in adults ≥ 50 to < 65 years of age. A 40- μg dose of mRNA-1083 from 5 lots (Lots A, B, C, D, and E) representing product attributes reflecting a range of storage durations at 2°C to 8°C will be evaluated. Part 1 will evaluate Lots A, B, C, and D. Part 2 will evaluate Lots A and E. This study will generate additional clinical experience with variability in product attributes to support product specifications. The specifics of the product attributes evaluated will be included in the CSR.

Multiple compositions and dose levels of mRNA-1083 were evaluated in a Phase 1/2 clinical study ([NCT05827926](#)) ([Section 4.3](#)). Based on Day 29 safety and immunogenicity data obtained during the Phase 1/2 study, mRNA-1083 40 μg was selected for adults aged ≥ 50 years to be further evaluated in the Phase 3 study ([NCT06097273](#)) and this Phase 2 study.

2.2. Background

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 2 study contains the 5 mRNAs being evaluated in the Phase 3 study ([NCT06097273](#)): 4 mRNAs encoding the surface glycoprotein HA of seasonal influenza virus strains recommended by the WHO for the NH 2023/2024 season and 1 mRNA encoding the linked N-terminal domain and receptor-binding domain subdomains of the SARS-CoV-2 spike glycoprotein of the fall/winter 2023-2024 recommended variant XBB.1.5.

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. Immediate systemic allergic 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 vaccine against 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 intervention administration.

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

As with other IM injections, the study interventions should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder

(such as hemophilia) because bleeding or bruising may occur following an IM administration in these individuals.

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

In postauthorization setting, there have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in adolescents and young males, within 7 to 14 days 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. Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis ([Gargano et al 2021](#)).

A completed IA of Part 1 of Study mRNA-1083-P101 ([NCT05827926](#)) study found that all 3 mRNA-1083 compositions and doses in the study were generally well tolerated. The majority of solicited ARs were Grade 1 or Grade 2 in severity, and most had an onset within 1 to 2 days of vaccination. In the mRNA-1083 study arms, participants ≥ 18 to <50 years old reported a higher frequency of solicited ARs than those in either the ≥ 50 to <65 or ≥ 65 to <80 year age groups. Overall, mRNA-1083 was observed to have an acceptable safety profile with no significant safety signals identified.

2.3.2. Benefit Assessment

The following benefits may accrue to participants:

- Participants will contribute to the development of a potentially efficacious combined vaccine against seasonal influenza virus and SARS-CoV-2.
- Participants will obtain information about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination and vital signs measurement).

2.3.3. Overall Benefit/Risk Conclusion

Considering the nonclinical data for the combined administration of mRNA-1010 and mRNA-1283 vaccines, the clinical safety and immunogenicity data for mRNA-1083, and supportive data from 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 anticipated risks.

3. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.	GM value at Day 29 in antibody measured by HAI assay for influenza and by PsVNA for SARS-CoV-2.
To evaluate the safety and reactogenicity in relation to the product attributes of mRNA-1083.	- Solicited local and systemic ARs through 7 days after the study injection. - Unsolicited AEs through 28 days after the study injection. - MAAEs from Day 1 to Day 181 (Month 6) or EoS. - AESIs from Day 1 to Day 181 (Month 6) or EoS. - SAEs from the time of informed consent to Day 181 (Month 6) or EoS. - AEs leading to discontinuation from study participation from Day 1 to Day 181 (Month 6) or EoS.
Secondary	
To further evaluate the Day 29 humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083.	- GMFR at Day 29 relative to Day 1 in antibody measured by HAI assay for influenza and by PsVNA for SARS-CoV-2. - SCR at Day 29 in anti-HA antibody values measured by HAI assay for influenza. - SRR at Day 29 in nAb values measured by PsVNA for SARS-CoV-2.
Exploratory	
To evaluate the humoral immune responses to vaccine-matched strains in relation to the product attributes of mRNA-1083 at all evaluable humoral immunogenicity timepoints.	- GM values and GMFR at all evaluable timepoints by HAI assay for influenza and by PsVNA for SARS-CoV-2. - SCR of influenza at all evaluable timepoints. - SRR of SARS-CoV-2 at all evaluable timepoints.
To further characterize immunogenicity in relation to the product attributes of mRNA-1083.	Frequency, levels, and specificities of immune responses, or other endpoints to be determined for the further characterization of immunogenicity.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction;
EoS = end-of-study; GM = geometric mean; GMFR = geometric mean fold rise; HA = hemagglutination;

HAI = hemagglutination inhibition; MAAE = medically attended adverse event; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay; SAE = serious adverse event; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity in relation to the product attributes of mRNA-1083 (SARS-CoV-2 and influenza) vaccine in adults ≥ 50 to < 65 years of age.

The study includes a Screening period (up to 28 days before Day 1), study intervention administration on Day 1 (Baseline), and a Follow-up period (through Day 181 [Month 6] after the study intervention). The study duration for each participant will be approximately 6 months.

The study will be comprised of 2 parts, Parts 1 and 2. In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups (Lots A, B, C, and D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups (Lots A and E) in Part 2. The study intervention groups are shown in [Table 3](#).

The study schema is included in [Section 1.2](#) and the SoA is presented in [Section 1.3](#).

Table 3: Study Intervention Groups

Group Name	Vaccine Administered	Approximate Sample Size	Dose (μg)
Part 1			
Group 1	mRNA-1083 Lot A	150	40
Group 2	mRNA-1083 Lot B	150	40
Group 3	mRNA-1083 Lot C	150	40
Group 4	mRNA-1083 Lot D	150	40
Part 2			
Group 5	mRNA-1083 Lot A	150	40
Group 6	mRNA-1083 Lot E	150	40

Abbreviation: mRNA = messenger ribonucleic acid.

Participants will have up to 4 scheduled in-person visits (Screening, Day 1, Day 29, and Day 181 [Month 6]), unscheduled visits if required, and 2 safety telephone calls (Day 8 and Day 91 [Month 3]). At the intervention visit on Day 1, participants will be instructed on how to document solicited ARs in the provided eDiary ([Section 8.2.5](#)). Solicited ARs, unsolicited AEs, MAAEs, AEs leading to withdrawal, AESIs, and SAEs will be collected per the SoA ([Section 1.3](#)). The study site staff will perform scheduled safety telephone calls to participants on Day 8 and Day 91 (Month 3) to collect AEs, MAAEs, AESIs, AEs leading to withdrawal, SAEs, information about concomitant medications/procedures associated with those events, and any nonstudy vaccinations.

Blood sample collection for humoral immunogenicity will occur on Day 1 (prior to study intervention administration), Day 29, and Day 181 (Month 6) or EoS in all study participants. The samples will be processed and analyzed per the Study Laboratory Manual of this study.

The study will include an IST ([Section 10.1.7.1](#)) and a CEAC ([Section 10.1.7.2](#)).

4.2. Scientific Rationale for Study Design

The study design and the collection of primary endpoint assessments are consistent with vaccine evaluation studies. The product attributes will differ in the lots (Lots A, B, C, D, and E) of the study intervention.

The rationale of the proposed study is summarized in [Section 2.1](#) and the rationale behind the dose level selection is described in [Section 4.3](#). The rationale for the sample size is further discussed under [Section 9.6](#).

4.2.1. Patient Input into Design

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

4.3. Justification for Dose

The Sponsor has been conducting Study 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. In this study, mRNA-1083 composition with a 5:1 total influenza RNA to SARS-CoV-2 RNA mass ratio was evaluated at the 15-µg, 30-µg, and 60-µg dose levels in participants aged ≥ 18 to < 65 years, and the 30-µg and 60-µg dose levels were evaluated in participants aged ≥ 65 to < 80 years. The Day 29 interim data from Study mRNA-1083-P101 demonstrated that all evaluated mRNA-1083 dose levels had an acceptable safety and reactogenicity profile in adults ≥ 50 years. However, the frequency and severity of solicited ARs increased with increasing dose levels. No consistent dose-dependent immune responses were observed in mRNA-1083 groups, although a trend toward higher postvaccination influenza A HAI GMTs and SARS-CoV-2 PsVNA titers was observed with the 60-µg dose level versus the 30-µg dose level in adults ≥ 50 years old. Therefore, to balance the reactogenicity and immunogenicity profile, to ensure an effective dose through the product shelf-life until expiry in both a clinical study and potential commercial use, considering the impact of manufacturing capability, storage conditions, and storage duration on mRNA-1083 product attributes, the 40-µg dose level of mRNA-1083 was selected for adults ≥ 50 years of age to be further evaluated in the Phase 3 study ([NCT06097273](#)) and this Phase 2 study.

4.4. End-of-study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA ([Section 1.3](#)).

5. STUDY POPULATION

Prospective approval of protocol deviations to below eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

1. Adults ≥ 50 to < 65 years of age at the time of signing the ICF.
2. Investigator assessment that the participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participants of nonchildbearing potential may be enrolled in the study.
Nonchildbearing potential is defined as postmenopausal or permanently sterilized as described in [Section 10.5](#). An FSH level may be measured at the discretion of the Investigator to confirm postmenopausal status.
4. Participants who could become pregnant:
 - A participant who could become pregnant is eligible to participate if not pregnant or breast/chestfeeding, and if using a contraceptive method that is highly effective (with a failure rate of $< 1\%$ per year), preferably with low user dependency, as described in [Section 10.5](#), for at least 90 days after the study intervention administration and if they agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the study intervention.
 - A POCBP must have a negative highly sensitive pregnancy test (urine) as required by local regulations at Screening and on Day 1, before the study intervention; see [Section 8.2.3](#).
 - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from study participation if the serum pregnancy result is positive.
 - Additional requirements for pregnancy testing during and after study intervention are located in [Section 8.2.3](#).
 - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.
5. Capable of giving signed informed consent, as described in [Section 10.1.4](#), which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
6. Have received an influenza vaccine in the previous season (since Sep 2023 for Part 1, since Sep 2024 for Part 2).

5.2. Exclusion Criteria

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

1. Acutely ill or febrile (temperature $\geq 38.0^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$]) within 72 hours prior to or at the Screening Visit or Day 1. See [Section 5.4](#) for additional guidance.
2. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable or may affect participant safety, assessment of study endpoints, assessment of immune response, or adherence to study procedures.

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

3. Reported diagnosis or condition that is associated with increased risk of severe influenza disease or complications, including individuals with chronic medical conditions (such as heart disease, chronic lung disease or asthma, chronic renal disease, hematologic conditions, chronic liver disease, diabetes, and neurological and neuromuscular conditions).
4. Undergone surgical procedures within 28 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.
5. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, asplenia, or recurrent severe infections.

Certain immune-mediated conditions that are stable and well-controlled (eg, Hashimoto thyroiditis) as well as those that do not require systemic immunosuppressants per [Exclusion Criteria 15](#) and [Exclusion Criteria 16](#) (eg, psoriasis or vitiligo), may be permitted at the discretion of the Investigator.
6. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid injection site areas).
7. History of anaphylaxis or severe hypersensitivity reaction requiring medical intervention after receipt of any of the following: mRNA vaccine or therapeutic; components of an mRNA vaccine or therapeutic; influenza vaccine; or components of an influenza vaccine, including egg protein.
8. History of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
9. Diagnosis of malignancy within the previous 5 years (excluding nonmelanoma skin cancer).
10. Any medical, psychiatric, or occupational condition, including a 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.

11. History of myocarditis, pericarditis, or myopericarditis, within 90 days prior to the Screening Visit. Participants who have not returned to baseline after their convalescent period will also be excluded.
12. History of Guillain-Barre syndrome after any influenza vaccine.
13. History of SARS-CoV-2 infection within 90 days prior to Day 1.
14. Tested positive for influenza by local health authority-approved testing methods within 150 days prior to Day 1.
15. Received corticosteroids at ≥ 10 mg/day of prednisone or equivalent for >14 days in total within 90 days prior to Day 1 or is anticipating the need for corticosteroids at any time during the study.

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

Inhaled, nasal, and topical steroids are allowed.
16. Received systemic immunosuppressive treatment, including long-acting biological therapies that affect immune responses (eg, infliximab), within 180 days prior to Day 1 or plans to do so during the study.
17. Received or plans to receive any vaccine authorized or approved by a local health agency within 28 days prior to Day 1 or plans to do so within 28 days post study injection.
18. Received a licensed seasonal influenza vaccine within 150 days prior to Day 1.
19. Received a licensed/authorized SARS-CoV-2 vaccine within 90 days prior to Day 1.
20. Received any investigational influenza vaccine, investigational COVID-19 vaccine, or investigational combination vaccine for influenza and COVID-19 within 12 months prior to Day 1. Participants from mRNA-1083-P201 Part 1 will also be excluded from Part 2.
21. Treated with antiviral therapies for influenza (eg, Tamiflu[®]) within 150 days prior to Day 1.
22. Treated with any other non-influenza antiviral therapies (including antivirals for treating individuals with human immunodeficiency virus 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 post study injection.
23. Has received systemic immunoglobulins or blood products within 90 days prior to Day 1 or plans to receive them during the study.
24. Has participated in an investigation clinical study within 90 days prior to Day 1 based on the medical history interview or plans to do so while participating in this study. Participants may continue in prior interventional study follow-up activities if it does not involve further investigational treatment and/or procedures that may affect safety

and/or other study endpoints, and study participation does not result in a breach of either study protocol.

Note: Interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary.

25. Had close contact with someone with laboratory-confirmed influenza infection or with someone who has been treated with antiviral therapies for influenza (eg, Tamiflu) within 5 days prior to Day 1.
26. Has had close contact to someone with COVID-19 as defined by the CDC within 10 days prior to Day 1.
27. Has donated ≥ 450 mL of blood products within 28 days prior to Day 1 or plans to donate blood products within 28 days post study injection.
28. Is 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

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention due to not meeting the criteria for study participation. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes dates of informed consent, demography, screen failure details, eligibility criteria, and any SAE.

Screen failure individuals may be rescreened one time within the 28-day screening window to determine if they will be eligible upon rescreening. Rescreened participants should be assigned a new participant number, but all participant numbers assigned to the same individual should be linked within IRT to avoid the ongoing duplications of participants.

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Body temperature (preferred route is oral) must be measured on the dosing visit before study intervention administration. The following events constitute criteria for delay of study intervention, and, if any of these events occur at the time scheduled for dosing, the participant may receive the study intervention 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 7.2](#)):

- Acute moderate or severe infection with or without fever at the time of dosing.
- Fever, defined as body temperature $\geq 38.0^{\circ}\text{C}/\geq 100.4^{\circ}\text{F}$ at the time of dosing.

Participants with a fever of $\geq 38.0^{\circ}\text{C}/\geq 100.4^{\circ}\text{F}$ will be contacted within the time window acceptable for participation and re-evaluated for eligibility. Participants who have been afebrile for at least 72 hours can be re-evaluated for administration of study intervention.

5.5. 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.

The mRNA-1083 used in this study targets the influenza strains recommended for the NH 2023/2024 season and the SARS-CoV-2 variant recommended for fall/winter 2023/2024. Thus, participants should be encouraged to receive the influenza and SARS-CoV-2 vaccines recommended for 2024/2025 season (Part 1) and 2025/2026 season (Part 2) after the Day 29 Visit, as directed by the package insert of the respective vaccines or as recommended by their HCP.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

All participants will receive a single IM injection of study intervention administered in a deltoid muscle on Day 1. The study interventions to be used in this clinical study are shown in [Table 4](#). The mRNA-1083 lots are formulated in a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

Table 4: Study Intervention(s) Administered

Group Name	Vaccine Administered	Dose (µg)
Part 1		
Group 1	mRNA-1083 Lot A ^a	40
Group 2	mRNA-1083 Lot B ^a	40
Group 3	mRNA-1083 Lot C ^a	40
Group 4	mRNA-1083 Lot D ^a	40
Part 2		
Group 5	mRNA-1083 Lot A ^a	40
Group 6	mRNA-1083 Lot E ^a	40

Abbreviation: mRNA = messenger ribonucleic acid.

^a. Lot numbers will be assigned and reflected on the label.

Study Intervention Packaging and Labeling

The study intervention used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of Sponsor or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH Guidance for Industry, GCP guidelines, guidelines for Quality System Regulations, and applicable regulations. For further direction, refer to the Pharmacy Manual.

6.2. Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized study site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the Pharmacy Manual, with access limited to the Investigator and authorized study site staff.

4. The Investigator or designee is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information on preparation, handling, storage, and accountability is in the Pharmacy Manual.

6.3. Assignment to Study Intervention

In Part 1, approximately 600 participants will be randomized (in equal allocation ratio) into 4 study groups to receive a single injection of mRNA-1083 (Lot A, Lot B, Lot C, or Lot D). Upon completion of Part 1, approximately 300 participants will be randomized (in equal allocation ratio) into 2 study groups to receive a single injection of mRNA-1083 (Lots A or E) in Part 2. Randomization will be performed using an IRT.

6.4. Blinding

The study intervention assignment, including the injection site and the corresponding vaccine administered, will be concealed by having the delegated unblinded study personnel prepare the study intervention in a secure location that is not accessible or visible to other study site staff. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded study site personnel involved in the conduct of the clinical study unless this information is necessary in the case of an emergency. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection. Only delegated unblinded medically qualified study site staff will conduct the injection procedure. They will not be involved in assessments of any study endpoints. Once the injection is completed, only the blinded study site staff will perform further assessments and interact with the participant. Access to the randomization code will be strictly controlled at the pharmacy.

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

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 an independent unblinded statistical team at specified timepoint(s) for analysis as outlined in [Section 9.1](#).

Unblinding:

This is a blinded study in which the Investigators are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a

determination. If the Investigator decides that unblinding is warranted, the Investigator may contact the Sponsor to discuss the situation prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment for the participant. If a participant's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

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

6.5. Study Intervention Compliance

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 interventions as planned.

6.7. Continued Access to Study Intervention After the EoS

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

6.8. Treatment of Overdose

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

For this study, any dose of mRNA-1083 greater than the participant's assigned dose ([Section 6.1](#)) will be considered an overdose.

However, in the event of an overdose, the Investigator/treating physician should:

- Provide or arrange for medical or supportive care as needed.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose.
- All instances of overdose must be reported by the Investigator to the Sponsor within 24 hours and reported to the IRB/IEC per local guidelines, as applicable.
- Any AEs associated with the overdose of the study intervention must be reported as a nonserious AE, unless other serious criteria are met ([Section 8.3.1.2](#)).

Dose deviations will be tracked as protocol deviations.

6.9. Prior and Concomitant Therapy

6.9.1. Prior Medications

Any medication or vaccine (including OTC or prescription medicines, blood products, and recreational drugs) that the participant is receiving within the period starting 28 days before the Screening Visit to the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

In addition, the following will be collected:

- Use of facial injections or dermal fillers at any time before study.
- Any seasonal influenza vaccine administered since Sep 2023.
- Any investigational influenza vaccine administered within 365 days of Day 1.
- Any authorized or investigational COVID-19 vaccine at any time before study injection.

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

6.9.2. 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 (Month 6) 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 (Month 6) or EoS.
- Any concomitant medications used to prevent or treat either COVID-19 or influenza through Day 181 (Month 6) or EoS.
- Antiviral and antiretroviral medications through Day 181 (Month 6) or EoS.
- Any concomitant medications relevant to or for the treatment of a MAAE and AESI from Day 1 through Day 181 (Month 6) or EoS.

- Any concomitant medications relevant to or for the treatment of an SAE from signing the ICF through Day 181 (Month 6) 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.

6.9.3. Prohibited Therapy

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PPIS analysis. Analysis sets are described in [Section 9.3](#).

- Any investigational or nonregistered product (drug or vaccine) other than the study intervention used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 10 mg/day or the 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.
- Immunoglobulins or long-acting biological therapies that affect immune responses (eg, infliximab) or any blood products administered during the clinical study period.
- A vaccine not foreseen by the study protocol administered during the period from 28 days before through 28 days after the study intervention.
- 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 10.1.11](#).

7.1. Discontinuation of Study Intervention

Not applicable as participants will only receive 1 study injection.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). If a participant chooses to withdraw from the study, the Investigator (or designee) should document the reason for withdrawal in EDC if the participant provides one.
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an EoS Visit should be conducted, as shown in the SoA ([Section 1.3](#)). See the EoS Visit in the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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.
- A participant who withdraws from the study will not be replaced.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

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

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

- Adverse event.
- Solicited adverse reaction/reactogenicity.
- Death.
- Lost to follow-up.
- Physician decision.
- Pregnancy.
- Protocol deviation.
- Study terminated by Sponsor.
- Withdrawal of consent.
- Randomized by mistake.
- 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.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit. If contact is made, the participant should be counseled on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
 - 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.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- A participant should be not considered lost to follow-up until the last expected study visit for the individual participant and completion of due diligence.
- Site personnel, or an independent third party, will attempt to collect the status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.
- If due diligence, as described above, has been completed and the participant continues to be unreachable, the participant will be considered lost to follow-up.

7.4. Pause Rules

Not applicable.

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 ([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:

- Study procedures and their timing are summarized in the SoA ([Section 1.3](#)). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- 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.
- Procedures conducted as part of the participant’s routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- 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, to support enabling all participants in the ability to adhere with the clinical study requirements.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Demographic information relating to the participant’s sex, age, ethnicity, and race will be recorded at Screening in EDC.
- Medical history of each participant will be collected and recorded in EDC.

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. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA ([Section 1.3](#)). Immunogenicity assessments are in [Section 8.8](#).

8.2. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant according to the SoA ([Section 1.3](#)):

- Solicited local and systemic ARs that occur during the 7 days following study intervention administration (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily by the participant using eDiaries.
- Unsolicited AEs (ie, AEs that are not included in the protocol-defined solicited ARs) observed or reported during the 28 days following study intervention administration (ie, the day of study intervention administration and 27 subsequent days).
- AEs leading to discontinuation from study participation, MAAEs, and AESIs will be collected from the study intervention administration on Day 1 through Day 181 (Month 6) or EoS or discontinuation from the clinical study.
- SAEs will be collected from the signing of the ICF until Day 181 (Month 6) or EoS or discontinuation from the study. Of note, SAEs collected during the period from signing of the ICF and before the study intervention on Day 1 will not be included in the summary analyses.
- Details of all pregnancies in participants will be collected after the start of study intervention and until the end of their participation in the clinical study. All pregnancies must be followed to determine the outcome; however, pregnancy-related data received after the end of the clinical study may not be collected in the clinical database.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and nonstudy vaccinations.

8.2.1. Physical Examinations

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

- 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 during postinjection study visits should be reported as an AE.
- Investigators should pay special attention to clinical signs/symptoms related to previous serious illnesses.
- On the day of study intervention administration, before administration, the arm(s) receiving the injection(s) should be examined and the associated lymph node(s) should be evaluated, and any abnormalities should be documented.

8.2.2. Vital Signs

Vital signs will be measured at the timepoints indicated in the SoA ([Section 1.3](#)), in a sitting position. 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. On the day of study intervention administration, vital sign measurements will be collected once before and at least 30 minutes after study intervention. If Baseline vital signs are clinically concerning, the participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection. Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination.

Febrile participants on study intervention days (fever is defined as a body temperature $\geq 38.0^{\circ}\text{C}/\geq 100.4^{\circ}\text{F}$) may be rescheduled within the relevant window periods. Criteria for delay of study intervention are provided in [Section 5.4](#). Afebrile participants with minor illnesses may be injected at the discretion of the Investigator. If fever is clinically concerning, participant should not be dosed.

An abnormal vital sign measurement following study intervention administration should be assessed to determine if clinically significant and therefore 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.

8.2.3. 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 ([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 on Day 1. At the discretion of the Investigator or if required by local regulatory requirements, a pregnancy test either via blood or point-of-care urine can be performed at any other time. Further details on reporting and follow-up of pregnancy are provided in [Section 8.3.9](#).

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 10.5](#) for details).

8.2.4. 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 ([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/procedures 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. A safety telephone call may trigger an unscheduled visit.

8.2.5. Use of Electronic Diaries

At the time of consent, the participants must confirm they will be willing to complete an eDiary (for 7-day reactogenicity) using either an application downloaded to their personal device 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 the only source document allowed for solicited local or systemic ARs (including body temperature measurements).

Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided with an eDiary device. Participants will be instructed to complete eDiary entries as per the SoA ([Section 1.3](#)).

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), the eDiary will be activated and participants will be trained and will 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 8.3.1.4](#)). 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. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

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

The definitions of solicited ARs, AEs, SAEs, AESIs, and MAAEs are provided in [Section 8.3.1](#). The time period and frequency for collecting safety information are provided in [Section 8.3.2](#). The method of detecting AEs and SAEs is provided in [Section 8.3.3](#). The method of recording AEs and SAEs is described in [Section 8.3.4](#). The assessment of intensity and causality is provided in [Section 8.3.5](#). The follow-up of AEs and SAEs is described in [Section 8.3.6](#). The reporting of SAEs/AESIs is described in [Section 8.3.7](#). Regulatory reporting requirements for SAEs are provided in [Section 8.3.8](#). Pregnancy reporting is provided in [Section 8.3.9](#).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, of special interest, considered related to the study intervention or study procedures, or that caused the participant to discontinue the clinical study (see [Section 7](#)). This includes events reported by the participant.

AEs related to pregnancies, as described in [Section 8.3.9](#), and AEs as a result of medication errors, including overdose, as described in [Section 6.8](#), are subject to AE collection/reporting rules.

8.3.1. Safety Events

AEs are defined in [Section 8.3.1.1](#). SAEs are defined in [Section 8.3.1.2](#). AESIs are defined in [Section 8.3.1.3](#). Solicited ARs are defined in [Section 8.3.1.4](#). MAAEs are defined in [Section 8.3.1.6](#).

8.3.1.1. Definition of Adverse Event

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

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Unsolicited AEs ([Section 8.3.1.5](#)) 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 not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- 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).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.3.1.2. Definition of Serious Adverse Event

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

a. Results in death.

- 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.

b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

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

d. Results in persistent or significant disability/incapacity

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

e. Congenital anomaly or birth defect

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

f. 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 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.

8.3.1.3. Adverse Event of Special Interest

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

Investigator to the Sponsor 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 10.2.1](#)).
- Refer to [Section 10.3](#) (Appendix 3) for a list of AESIs pertinent to this study.
- Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in [Section 8.3.7](#).

8.3.1.3.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as AESIs and reported as an SAE (refer to [Section 8.3.7](#) for reporting of SAEs/AESIs), based on 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. 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/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition ([Rüggeberg et al 2007](#)).

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

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving 2 or more organ systems, as follows:
 - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, 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, rhinorrhea.

- **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting.

8.3.1.3.2. Myocarditis and/or Pericarditis

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

The Investigator's medical judgment must be applied when assessing participants reporting symptoms concerning for myocarditis and/or pericarditis contained within the CDC case definition. Diagnostic evaluation (eg, ECG, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition ([Table 8](#)) should promptly be obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be considered in those with positive test results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated. The Investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis and/or pericarditis will be continued to be followed in the study for safety as per the protocol.

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 all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical studies per the CEAC charter, to determine if they meet CDC criteria for "probable" or "confirmed" events and make recommendations to the Sponsor ([Gargano et al 2021](#)). The CDC Working Case Definitions are provided in [Section 10.4](#) (Appendix 4) as guidance and the CEAC is described in [Section 10.1.7.2](#).

8.3.1.4. Solicited Adverse Reactions

Solicited ARs (reactogenicity events) are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with study intervention administration. The eDiary will solicit daily participant reporting of ARs using a structured checklist ([Section 8.2.5](#)). Participants will record such occurrences in the eDiary on the day of study intervention and 6 subsequent days, for a total of 7 days.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in [Table 5](#). All solicited ARs (local and systemic) will be considered causally related to study intervention.

If a participant reports that a solicited AR occurred during the solicited period but was not recorded in the eDiary, the event should be recorded in EDC only if it meets serious criteria, was medically attended, or resulted in discontinuation of the participant from the study.

Any missed eDiary timepoint and reason should be recorded in the EDC.

eDiary clarifications are expected to be recorded in EDC when there is an error in the participant entry or when the PI has a different assessment.

If a participant reports a solicited AR in the eDiary, and the solicited AR continues beyond 7 days after dosing, the participant should notify the site to provide an end date. The site should follow-up with the participant until resolution of the event or EoS. Solicited ARs ongoing at the time of EoS can be documented as ongoing.

If the participant reports an event consistent with reactogenicity that started after the solicited period (ie, after Day 7), it should not be recorded as reactogenicity, but as an AE in EDC.

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

- Solicited local or systemic AR that results in a visit to an HCP (MAAE; [Section 8.3.1.6](#)).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (reactogenicity event leading to discontinuation from study participation).
- Solicited local or systemic AR lasting beyond 7 days postintervention.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.
- Solicited local or systemic AR assessed by the Investigator as unrelated to the vaccine, but related to another diagnosis (eg, viral infection), are to be reported as an unsolicited AE reflecting the final diagnosis.

Assessment of Severity

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials ([DHHS 2007](#)) has been modified to categorize local and systemic reactogenicity events (solicited ARs) observed during this study. The intensity grading scale for solicited ARs used in this study is presented in [Table 5](#).

Table 5: Adult and Adolescent Solicited Adverse Reactions and Grades

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

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Injection site swelling/induration (hardness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5 cm	51-100 mm/ 5.1-10 cm	>100 mm/ >10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life- threatening)
Fever (oral)	<38.0°C <100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0- 40.0°C 102.1- 104.0°F	> 40.0°C > 104.0°F

Abbreviation: EDC = electronic data capture.

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

8.3.1.5. 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 an HCP). 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.

8.3.1.6. Medically Attended Adverse Event

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 an HCP external to the study site (eg, emergency room, 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.

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

- Solicited ARs will be collected from Day 1 through Day 7 (the day of injection and the following 6 days).
- All unsolicited AEs will be collected from the study intervention administration on Day 1 through Day 28 postinjection.

- All AEs leading to discontinuation from study participation, AESIs, and MAAEs will be collected from the study intervention administration on Day 1 through Day 181 (Month 6) or EoS Visit at the timepoints specified in the SoA ([Section 1.3](#)).
- All SAEs will be collected from the signing of the ICF until Day 181 (Month 6) or EoS at the timepoints specified in the SoA ([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, as indicated in [Section 8.3.7](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, 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 intervention or study participation, the Investigator must promptly notify the Sponsor.

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

8.3.3. Method of Detecting AEs and SAEs

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.

8.3.4. 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 lost to follow-up, as defined in [Section 7.3](#).

All unsolicited AEs, including SAEs, reported or observed during the clinical study will be recorded on the AE page of the eCRF.

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 ([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 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 designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.3.5. Assessment of Intensity and Causality

Assessment of Intensity

The intensity of an AR or AE refers to the extent to which it affects the participant's daily activities. Specific criteria for local and systemic reactogenicity events are presented in [Section 8.3.1.4](#).

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

- **Mild:**
These events do not interfere with the participant's usual activities of daily living.

- **Moderate:**
These events cause some interference with the participant's usual activities of daily living and require limited or no medical intervention.
- **Severe:**
These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study site staff (or delegate) should elicit from the participant, the impact of AEs on the participant's activities of daily living and should document it appropriately in the participant's source documentation. Changes in the 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. 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.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and occurrence of each AE/SAE and document this in the medical notes. The Investigator will use clinical judgment to determine the relationship.

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

8.3.6. Follow-up of AEs and SAEs

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

participant is lost to follow-up (as defined in [Section 7.3](#)). All contacts, or contact attempts, concerning follow-up of AEs/SAEs should be recorded in the participant's source documentation. Further information on follow-up procedures is provided below:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or 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 HCPs.
- 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 (if available).

8.3.7. Reporting of SAEs/AESIs

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 benefit/risk assessment of a study injection under clinical investigation are met.

Any AE considered serious by the Investigator or that meets SAE criteria ([Section 8.3.1.2](#)) 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 or AESI from a study participant or receives updated data on a previously reported SAE or AESI after the electronic data collection tool 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.

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.

8.3.8. Regulatory Reporting Requirements for SAEs

- Prompt notification within 24 hours by the Investigator to the Sponsor of an SAE, is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators. 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, if appropriate according to local requirements.
- 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.

8.3.9. Pregnancy

- Any participants who become pregnant at any time during the study should remain in the 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's pregnancy. See [Section 8.3.7](#).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to [Section 8.3.7](#)).
- 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.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.3.7](#). While the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this clinical study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this clinical study.

8.6. Future Genetics Research

Future genetic research is not evaluated in this clinical study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity

Planned timepoints for all immunogenicity assessments are provided in the SoA ([Section 1.3](#)).
The following analytes will be measured:

- Influenza: Serum antibody level as measured by the HAI assay.
- SARS-CoV-2: Serum nAb titers as measured by PsVNA.

8.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of the statistical analyses will be provided in the SAP, which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to the primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH 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.

9.1. Blinding and Responsibility for Analyses

This is an observer-blind clinical study. The Investigator, study site staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until the end of the study, with the following exceptions to facilitate IA and safety monitoring:

- An independent unblinded statistical and programming team will perform the preplanned IA ([Section 9.7.1](#)). Sponsor team members will be prespecified to be unblinded to the IA 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 Data Blinding Plan.
- The IST will review unblinded safety data provided by the independent unblinded statistician to safeguard the interests of clinical study participants and to help ensure the integrity of the clinical study. The IST will review unblinded statistical outputs for ad hoc safety reviews during the study as requested by the study Medical Monitor and study team. [Section 10.1.7](#) provides additional information on IST and safety review.

9.2. Statistical Hypothesis

This study does not have formal statistical hypothesis testing planned for the study objectives (safety, reactogenicity, and immunogenicity). Descriptive analysis will be conducted for safety and immunogenicity endpoints.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined in [Table 6](#).

Table 6: Population for Analysis

Analysis Sets	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 immunogenicity blood sample collection schedule for both Baseline and Day 29 assessments 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 study intervention group corresponding to what they actually 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; PPIS = per-protocol immunogenicity set.

- a. The PPIS will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.
- 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 study intervention group corresponding to what they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before the first database lock and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

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

9.4.1. Immunogenicity Analyses

Immunogenicity analyses will be based on the PPIS. There is no hypothesis testing planned for the immunogenicity objectives, and immunogenicity analyses will be descriptive.

The primary endpoints include the GM value of anti-HA antibody and SARS-CoV-2 nAb at Day 29. The GM value at Day 29 will be estimated using an analysis of covariance model on the log-transformed antibody values at Day 29, with the study intervention group as the fixed variable and log-transformed baseline values as a covariate. For each study intervention group, the geometric least square mean and its corresponding 95% CI in a log-transformed scale estimated from the model will be back transformed to obtain estimates of GM value and its 95% CI in the original scale.

The observed GM values at each evaluable timepoint with corresponding 95% CI will also be provided for each study intervention group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for

presentation. The following descriptive statistics will also be provided for antibody values at each timepoint: the number of participants (n), median, minimum, and maximum.

The GMFR of antibody values at Day 29 and subsequent timepoint relative to baseline with corresponding 95% CI will be provided for each study intervention group. The GMFR 95% CI will be calculated based on the t-distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will be also provided for fold rise at each timepoint: the number of participants (n), median, minimum, and maximum.

The SCR and SRR with corresponding 95% CI (using the Clopper-Pearson method) will be summarized at each Postbaseline timepoint for each study intervention group. Seroconversion of antibodies for an influenza strain at participant level is defined as a postvaccination value $\geq 1:40$ if baseline is $< 1:10$ or a ≥ 4 -fold rise in postvaccination value if baseline is $\geq 1:10$. Seroresponse of SARS-CoV-2 antibodies at participant level is defined as a postvaccination value $\geq 4 \times \text{LLOQ}$ if baseline is $< \text{LLOQ}$, or a ≥ 4 -fold rise in postvaccination value if baseline is $\geq \text{LLOQ}$.

9.4.2. Safety Analyses

All safety analyses are descriptive in nature and will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by study group.

Safety and reactogenicity will include solicited ARs (local and systemic ARs), unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, AEs leading to discontinuation from study participation, vital sign measurements, and physical examination findings.

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

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

The number of events of unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to discontinuation from study participation will be reported in summary tables accordingly using descriptive statistics. Pregnancy outcomes will also be summarized.

More details for safety analyses will be described in the SAP.

9.4.3. Exploratory Analyses

In case any analysis of exploratory endpoints is performed, details will be described in the SAP.

9.4.4. Subgroup Analyses

Subgroup analyses for selected immunogenicity and safety endpoints may be performed using the same methods as described in [Section 9.4.1](#) and [Section 9.4.2](#), respectively. Immunogenicity and safety analyses may be assessed in the following subgroups:

- Sex (Female, Male)
- Race
- Ethnicity
- Number of prior doses of COVID-19 vaccines (only for SARS-CoV-2 related immunogenicity analyses)

9.5. Multiplicity

No multiplicity adjustment will be needed for either within each of the IA and final analyses or between the IA and the final analysis because there will not be formal statistical hypothesis testing planned for the study objectives (safety, reactogenicity, and immunogenicity).

9.6. Sample Size Determination

Approximately 600 participants and 300 participants will be randomized in Part 1 and Part 2 of this study, respectively. With approximately 150 participants randomized into each study intervention group, there is approximately 90% probability of observing at least 1 participant in each study intervention group reporting an AE if the true rate of AEs is 1.5%.

9.7. Planned Analyses

9.7.1. Interim Analyses

For each study part, an interim analysis of immunogenicity and/or safety may be performed after participants who receive the study vaccine have completed the Day 29 assessment.

9.7.2. Final Analysis

For each study part, the final analysis will be performed after all participants have completed all planned study procedures or discontinued from the study. Results of the final analysis will be presented in a CSR. Details about all study analyses will be provided in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
 - Applicable ICH GCP guidelines.
 - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 Annex 1, Section D, No. 17, letter 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 PI 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

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

10.1.4. Informed Consent Process

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

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

10.1.5. 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. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.7. Committees Structure

10.1.7.1. Internal Safety Team

Safety monitoring for this clinical study will include the blinded study team members, inclusive of at a minimum, the Sponsor's Medical Monitor, Sponsor's Safety Physician and a CRO Medical Monitor and an unblinded IST. The IST is comprised of the Sponsor's physicians, who will not otherwise be involved in the conduct of the clinical study. The study team will conduct ongoing blinded safety reviews during the clinical study and will be responsible for notifying the IST of potential safety signal events. Ad hoc IST reviews may occur as outlined in the IST charter.

10.1.7.2. Cardiac Event Adjudication Committee

An independent CEAC of medically qualified external experts, including cardiologists, will review reported 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, pericarditis, or myopericarditis will be referred to the Sponsor, who will then determine if additional action is needed. The CEAC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the charter.

10.1.8. Dissemination of Clinical Study Data

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

10.1.9. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the Source Data Agreements and the Clinical Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11. Study and Site Start and Closure

First Act of Recruitment

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

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

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

10.1.12. Publication Policy

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

10.2. Appendix 2: Safety Appendix

10.2.1. SAE Reports

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

10.2.2. Pregnancy Forms

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

10.3. Appendix 3: Adverse Events of Special Interest

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

Table 7 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 infection.

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

Table 7: Adverse Events of Special Interest (COVID-19 Vaccines)

Medical Concept	Additional Notes
Anosmia, Ageusia	- New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology. <u>DOES NOT INCLUDE</u> anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies.
Subacute Thyroiditis	<u>Acute</u> inflammatory disease of the thyroid (immune-mediated or idiopathic). <u>DOES NOT INCLUDE</u> new onset of chronic thyroiditis.
Acute Pancreatitis	New onset of pancreatitis <u>in the absence of a clear, alternate etiology</u>, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	Any event of appendicitis.
Rhabdomyolysis	New onset of rhabdomyolysis <u>in the absence of a clear, alternate etiology</u>, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute Respiratory Distress Syndrome (ARDS)	- New onset of ARDS/respiratory failure due to acute inflammatory lung injury. <u>DOES NOT INCLUDE</u> nonspecific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload.
Coagulation Disorders	New onset of thrombosis, thromboembolic event, or nontraumatic hemorrhage/bleeding disorder (eg, stroke, deep vein thrombosis [DVT], pulmonary embolism, disseminated intravascular coagulation [DIC], etc.).
Acute Cardiovascular Injury	- New onset of <u>clinically confirmed</u>, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia confirmed by ECG (eg, atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. <u>DOES NOT INCLUDE</u> transient sinus tachycardia/bradycardia, nonspecific symptoms such as palpitations, racing heart, heart

Medical Concept	Additional Notes
	fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute Kidney Injury	- New onset of acute kidney injury or acute renal failure <u>in the absence of a clear, alternate etiology</u>, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc; - Increase in serum creatinine by ≥ 0.3 mg/dl (or ≥ 26.5 μmol/L) within 48 hours; OR - Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days.
Acute Liver Injury	- New onset <u>in the absence of a clear, alternate etiology</u>, such as trauma, tumor, hepatotoxic medications/substances, etc; >3-fold elevation above the upper normal limit for ALT or AST; OR >2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP.
Dermatologic Findings	- Chilblain-like lesions. - Single organ cutaneous vasculitis. - Erythema multiforme. - Bullous rashes. - Severe cutaneous adverse reactions, such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions.
Systemic Inflammatory Syndromes	- Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C). - Kawasaki's disease. - Hemophagocytic lymphohistiocytosis (HLH).
Thrombocytopenia	- Platelet count $< 150 \times 10^9/L$ (thrombocytopenia). - New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome.
Acute Aseptic Arthritis	- Clinical syndrome characterized by <u>acute onset</u> of signs and symptoms of joint inflammation <u>without recent trauma</u> 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 PCR. <u>DOES NOT INCLUDE</u> new onset of chronic arthritic conditions.
New Onset of or Worsening of Neurologic Disease	- Immune-mediated neurological disorders. - Guillain-Barre Syndrome. - Acute disseminated encephalomyelitis (ADEM).

Medical Concept	Additional Notes
	• Peripheral facial nerve palsy (Bell's palsy). • Transverse myelitis. • Encephalitis/encephalomyelitis. • Aseptic meningitis. • Seizures/convulsions/epilepsy. • Narcolepsy/hypersomnia.
Anaphylaxis	• Anaphylaxis <u>associated with study intervention administration.</u>
Other Syndromes	• Fibromyalgia. • Postural orthostatic tachycardia syndrome. • Chronic fatigue syndrome. • Myalgic encephalomyelitis. • Post viral fatigue syndrome. • Myasthenia gravis. • Capillary leak syndrome (new diagnosis or flare up in participants with prior history of capillary leak syndrome).

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; COVID-19 = Coronavirus disease 2019; ECG = electrocardiogram; GGT = Gamma-glutamyl transferase; HELLP = hemolysis, elevated liver enzymes, low platelet count; PCR = polymerase chain reaction.

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

Table 8: Case Definitions of Probably and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
	Probably Case	Confirmed Case
Acute myocarditis	Presence of ≥ 1 new or worsening of the following clinical symptoms ^a : - Chest pain, pressure, or discomfort - Dyspnea, shortness of breath, or pain with breathing - Palpitations - Syncope	Presence of ≥ 1 new or worsening of the following clinical symptoms ^a : - Chest pain, pressure, or discomfort - Dyspnea, shortness of breath, or pain with breathing - Palpitations - Syncope
	AND	AND
	≥ 1 new finding of: - troponin level above upper limit of normal (any type of troponin) - abnormal ECG or rhythm monitoring findings consistent with myocarditis^c - abnormal cardiac function or wall motion abnormalities on echocardiogram - cMRI findings consistent with myocarditis^{d¶}	≥ 1 new finding of: - Histopathologic confirmation of myocarditis^b - cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	AND	AND
	No other identifiable cause of the symptoms and findings	No other identifiable cause of the symptoms and findings
Acute pericarditis^e	Presence of ≥ 2 new or worsening of the following clinical features: - acute chest pain^f. - pericardial rub on exam. - new ST-elevation or PR-depression on ECG. - new or worsening pericardial effusion on echocardiogram or magnetic resonance imaging.	
Myopericarditis	This term may be used for participants who meet criteria for both myocarditis and pericarditis.	

Abbreviations: AV = atrioventricular; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram.

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

- a. Participants who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
- b. Using the Dallas criteria ([Aretz et al 1987](#)). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
- c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least 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.
<https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal> icon
- e. <http://academic.oup.com/eurheartj/article/36/42/2921/2293375external> icon.
- 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.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Person of Childbearing Potential (POCBP)

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

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

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

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

Person of Nonchildbearing Potential (PONCBP)

Participants in the following categories are considered PONCBP:

1. Premenopausal participant with permanent infertility due to one of the following:
 - a. Documented hysterectomy.
 - b. Documented bilateral salpingectomy.

- c. Documented bilateral oophorectomy.
- d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

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

2. Postmenopausal participant

- a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
 - Participants on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods^b That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)^c • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) <i>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.</i> 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
• 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

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from reproductive sexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. External condom and internal condom 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.

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