CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety and immunogenicity of heptavalent mRNA-1975 (SR1-7) and monovalent mRNA-1982 (SR1) in parallel against Lyme disease in healthy participants 18 through 70 years of age
Protocol Number:	mRNA-1975/1982-P101
Amendment Number:	4
Date of Amendment 4	08 Apr 2025
Date of Amendment 3:	18 Nov 2024
Date of Amendment 2:	16 Apr 2024
Date of Amendment 1:	08 Jun 2023
Date of Original Protocol:	14 Apr 2023
Compound:	mRNA-1975 and mRNA-1982
Brief Title:	A Phase 1/2 study to evaluate the safety and immunogenicity of mRNA-1975 and mRNA-1982 against Lyme disease in participants 18 through 70 years of age
Study Phase:	1/2
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	325 Binney Street Cambridge, MA 02142
Regulatory Agency Identifier Number(s):	IND 29494
Date:	08 Apr 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

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

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety and immunogenicity of heptavalent mRNA-1975 (SR1-7) and monovalent mRNA-1982 (SR1) in parallel against Lyme disease in healthy participants 18 through 70 years of age" dated 08 Apr 2025 and the most recent version of the mRNA-1975/1982 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 ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) GCP Guidance, and all applicable local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB/IEC approval except to eliminate an immediate risk to participants.

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

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

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	08 Apr 2025
Amendment 3	18 Nov 2024
Amendment 2	16 Apr 2024
Amendment 1	08 Jun 2023
Original Protocol	14 Apr 2023

Amendment 4 (08 Apr 2025)

This amendment is considered to be nonsubstantial because it does not impact the design or methodology of the study.

Overall Rationale for the Amendment:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AV	atrioventricular
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards for the Reporting of Trials
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DHHS	Department of Health and Human Services
DVBD	Division of Vector-Borne Diseases
eCCG	eCRF Completion Guidelines
ECG or EKG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EM	erythema migrans

Abbreviation	Definition
EoS	end-of-study
EU	Europe
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMP	Good Manufacturing Practice
GMT	geometric mean titer
hCG	human chorionic gonadotropin
HCP	health care professional
HELLP	hemolysis, elevated liver enzymes, low platelet count
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular(ly)
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IST	internal safety team
LAM	lactational amenorrhea method
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle

Abbreviation	Definition
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MTTT	Modified Two-Tiered Testing for Lyme serology screening
NA	not applicable
OspA	outer surface protein A
PCR	polymerase chain reaction Polymerase Chain Reaction
PD	post dose
POCBP	participant of childbearing potential
PONCBP	participant of nonchildbearing potential
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBA	serum bactericidal activity
SCR	seroconversion rate
SoA	schedule of activities
SR	serotype
STTT	Standard Two-Tiered Testing for Lyme serology screening
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
USV	unscheduled visit
WBC	white blood cell
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety and immunogenicity of heptavalent mRNA-1975 (SR1-7) and monovalent mRNA-1982 (SR1) in parallel against Lyme disease in healthy participants 18 through 70 years of age.

Brief Title:

A Phase 1/2 study to evaluate the safety and immunogenicity of mRNA-1975 and mRNA-1982 against Lyme disease in participants 18 through 70 years of age.

Regulatory Agency Identifier Number(s):

IND 29494

Rationale:

The incidence of Lyme disease, caused by *Borrelia* bacteria, continues to rise as the geographic spread of the tick vectors has increased in recent years. According to the CDC, there are approximately 30,000 reported cases of Lyme disease per year in the US (Schwartz et al 2017). The incidence of Lyme disease in the United States has approximately doubled since 1991, from 3.74 cases per 100,000 to 7.95 cases per 100,000 in 2014 (Climate Change Indicators in the United States, 2016). Annual incidence rates utilizing US health insurance claims databases are 6 to 8 times higher and show evidence of increasing diagnoses over time. For example, in US MarketScan data from 2010–2018, the rate of Lyme disease diagnoses increased 20% in high-incidence states and 48% in low-incidence states and nearly doubled (89%) in neighboring states (Schwartz et al 2021). There are an estimated 85,000 cases of Lyme diagnosed each year in Europe (Stone et al 2017) and the highest incidence occurs in central Europe, particularly in Germany, Austria, Slovenia, and the coastal regions of Sweden. A systematic review found evidence of increasing incidence in Western Europe (Vandekerckhove et al 2021) and country-specific studies from Europe have also reported increases in Lyme disease incidence rates (Sajanti et al 2017).

The emergence of new species causing Lyme disease, such as *B. mayonii* in North America, may contribute to an increase in the number of reported cases. Increases in Lyme disease cases have been reported in Canada and the South and Midwest of the US (Canada, 2023). Based on surveillance data in Canada, the number of reported cases of Lyme disease increased from 144 in 2009 to 3,147 in 2021. Factors driving the increase in Lyme cases in North America, Europe, and Asia include climate change, host and reservoir expansion, and improved monitoring, detection, and reporting of Lyme disease (Stone et al 2017). There is no approved vaccine available to prevent Lyme disease. *Borrelia* infection is sometimes not diagnosed until later in disease, resulting in significant clinical morbidity and cardiac, neurological, and joint complications, posing a healthcare financial burden. Preventive strategies against Lyme disease have been largely unsuccessful, evident with the increasing number of reported cases annually; thus, an effective preventive vaccine against Lyme disease is a medical priority and an unmet need.

This study will evaluate 2 IMPs, mRNA-1975 and mRNA-1982, designed as 3-dose prophylactic vaccines against *Borrelia* infection by eliciting anti-OspA antibody responses, which had been

shown to block the transmission of *Borrelia* spirochetes from the bite of an infected tick and prevent Lyme disease. mRNA-1975 encodes for 7 different serotype OspA for 4 major *Borrelia* species causing disease in the US and Europe: *B. burgdorferi* (SR1), *afzelii* (SR2), *bavariensis* (SR4), and *garinii* (SR3, 5-7). In comparison, mRNA-1982 encodes for OspA from SR1 that is specific for *B. burgdorferi*, the dominant species circulating in the US that causes Lyme disease.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1975 and mRNA-1982.	• Solicited local and systemic ARs through 7 days after each study injection. • Unsolicited AEs through 28 days after each study injection. • MAAEs from Day 1 to 6 months after last study injection. • AESIs from Day 1 to EoS. • SAEs from Day 1 to EoS. • AEs leading to discontinuation of study injection or study participation from Day 1 to EoS. • Safety laboratory abnormalities through 7 days after each study injection.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1975 and mRNA-1982 at Days 1, 29, 85, and 197.	• GMC of anti-OspA binding IgG antibodies measured by ELISA or a similar method at Days 1, 29, 85, and 197. • GMFR of anti-OspA binding IgG Ab concentration at Days 29, 85, and 197 compared to Day 1 (Baseline).
Exploratory	
CCI [redacted]	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; Ig = immunoglobulin; MAAE = medically attended adverse event; OspA = outer surface protein A; SAE = serious adverse event; SBA = serum bactericidal activity.

Overall Design Synopsis:

The purpose of this Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study is to evaluate the safety and immunogenicity against Lyme disease in parallel of heptavalent mRNA-1975 and monovalent mRNA-1982 in healthy adult participants aged 18 through 70 years.

In this clinical study, mRNA-1975 and mRNA-1982, which have been developed as prophylactic vaccines to block the transmission of *Borrelia* spirochetes from the bite of an infected tick, will be investigated in healthy adult participants to evaluate safety and immunogenicity. A group of participants receiving placebo will also be enrolled.

A total of 800 healthy adult participants will be enrolled, comprised of 100 participants randomized equally into each dose group, including a placebo group (Table 1). All participants will receive a 3-dose series of the assigned study injection or placebo. (Figure 1).

Table 1: Randomized Dose Groups

Product	Dose	Schedule	Sample Size
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
Placebo (saline)	NA	3 doses (0, 2, and 6 months)	100

Abbreviations: mRNA = messenger ribonucleic acid; NA = not applicable.

Enrollment Procedure:

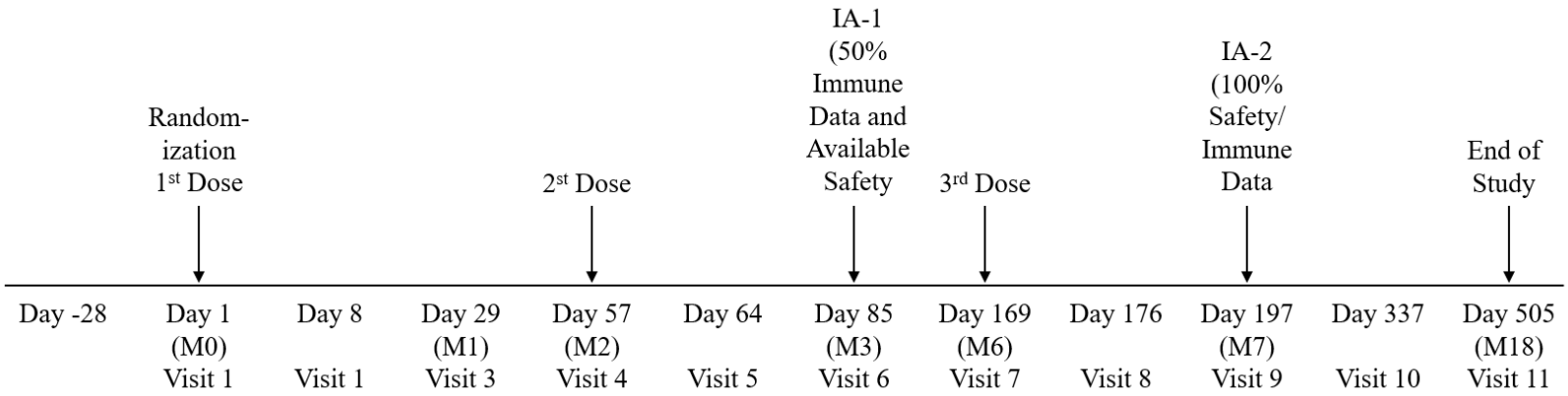
As shown in Figure 2, study enrollment will begin with an initial sentinel cohort consisting of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 4 participants randomized to placebo (N = approximately 34 total). Study enrollment will then pause for an independent IST review of unsolicited AEs through Day 8 focused on AEs potentially concerning for myocarditis/pericarditis. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, enrollment will resume with a second sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for a second focused IST review of unsolicited AEs reported in the study overall through Day 8 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, study enrollment will resume with a third and final sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for

a third focused IST review of all available safety data for the study overall through Day 8 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified in the third scheduled IST review, dose expansion with enrollment of the remaining 90 participants in each of the dose groups will proceed in parallel.

Similarly, administration of Dose 2 (Day 57) will begin with the initial sentinel cohort. Administration of Dose 2 will then pause for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of the initial sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the second sentinel cohort. Administration of Dose 2 will then pause again for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the third and final sentinel cohort. Administration of Dose 2 will then pause again for an IST review of all available safety data for the study overall through Day 64 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified, administration of Dose 2 to the remaining 90 participants in each of the dose groups will proceed in parallel.

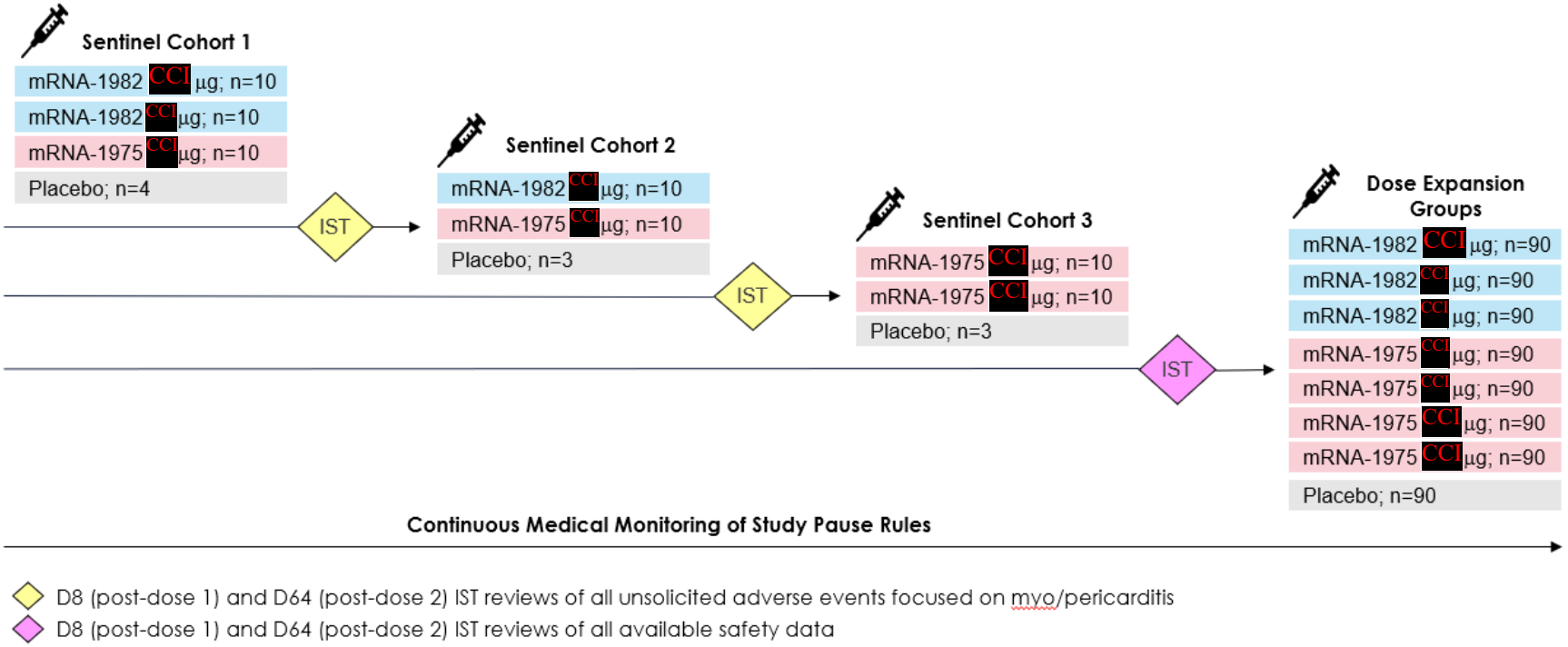
1.2. Schema

Figure 1: Study Schema



Abbreviations: IA = interim analysis; M = month.

Figure 2: Sentinel Cohort Dose Escalation and IST Reviews for Dose 1 and Dose 2



Abbreviations: µg = microgram(s); D = day; IST = internal safety team; mRNA = messenger ribonucleic acid; n = number of participants.

1.3. Schedule of Activities

Table 2: Schedule of Activities

Visit Number	Screening[a]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11[b]	USV[c]
Month Timepoint	-	M0	-	M1	M2	-	M3	M6	-	M7	M12	M18	-
Time Period	Up to 28 days before Day 1	Day 1	Day 8	Day 29	Day 57	Day 64	Day 85	Day 169	Day 176	Day 197	Day 337	Day 505/ EoS	-
Days Since Most Recent Injection[d]	NA	0	7	28	0	7	28	0	7	28	168	336	-
Window Allowance (Days)	-28	NA	±2	+5	±5	±2	±3	±5	±2	±3	±14	-30, +14	-
Type if Visit	-	C	C	C	C	C	C	C	C	C	C	C	C
ICF, demographics, concomitant medications, medical history	X	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion and exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	-	-
Vital signs[e]	X	X	-	-	X	-	-	X	-	-	-	-	-
Height, weight, and BMI	X	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination (required)[f]	X	X	-	-	X	-	-	X	-	-	-	-	X
Physical examination (optional)[f]	-	-	X	X	-	X	X	-	X	X	X	X	-
Safety laboratory tests[g, h]	X	-	X	-	X	X	-	X	X	-	-	-	-
Immunogenicity testing[h]	-	X	-	X	X	-	X	X	-	X	X	X	-
Lyme serodiagnostic testing[h]	X	-	-	-	-	-	X	X	-	-	X	X	X[c]
Pregnancy test[i]	X	X	-	-	X	-	-	X	-	-	-	-	-
12-lead ECG[j]	X	-	-	-	-	-	-	-	-	-	-	-	-
CCI													
Randomization	-	X	-	-	-	-	-	-	-	-	-	-	-
Study injection (including 60-minute postdosing observation period)	-	X	-	-	X	-	-	X	-	-	-	-	-
Participant eDiary recording of solicited local and systemic ARs (7 days)[l]	-	X (Days 1-7)	-	-	X (Days 57-63)	-	-	X (Days 169-175)	-	-	-	-	-
Unsolicited AEs (28 days)[m]	-	X (Days 1-28)		-	X (Days 57-84)		-	X (Days 169-196)		-	-	-	-

Visit Number	**Screening[a]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11[b]**	**USV[c]**
Month Timepoint	**-**	**M0**	**-**	**M1**	**M2**	**-**	**M3**	**M6**	**-**	**M7**	**M12**	**M18**	**-**
Time Period	**Up to 28 days before Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 64**	**Day 85**	**Day 169**	**Day 176**	**Day 197**	**Day 337**	**Day 505/ EoS**	**-**
Days Since Most Recent Injection[d]	**NA**	**0**	**7**	**28**	**0**	**7**	**28**	**0**	**7**	**28**	**168**	**336**	**-**
Window Allowance (Days)	**-28**	**NA**	**±2**	**+5**	**±5**	**±2**	**±3**	**±5**	**±2**	**±3**	**±14**	**-30, +14**	**-**
Type if Visit	**-**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
Review of eDiary	-	-	X	-	-	X	-	-	X	-	-	-	-
Recording of all MAAEs[n]	-	X	X	X	X	X	X	X	X	X	X	-	X[n]
Recording of all AESIs and AEs leading to study discontinuation of IMP or withdrawal[o]	-	X	X	X	X	X	X	X	X	X	X	X	X
Recording of all SAEs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations[p]	-	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; BMI = body mass index; C = in-clinic safety visit; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; EDC = electronic data capture; eDiary = electronic diary; EoS = end-of-study; FSH = follicle-stimulating hormone; ICF = informed consent form; IMP = investigational medicinal product; M = month; MAAE = medically attended adverse event; MTTT = Modified Two-Tiered Testing for Lyme serology screening; NA = not applicable; PCR = polymerase chain reaction; SAE = serious adverse event; STTT = Standard Two-Tiered Testing for Lyme serology screening; USV = Unscheduled Visit; V = visit.

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

b. This visit will be the EoS for all enrolled participants.

c. Participants may experience AEs that necessitate a USV. Participants with signs or symptoms potentially consistent with Lyme disease (see Section 8.6) should undergo a USV that includes an evaluation for Lyme disease, to include at minimum a review of symptomology, focused physical examination, MTTT serology, CCI [redacted]. Collection tubes for MTTT serology CCI [redacted] will be stored and used specifically for unscheduled visits. The immune response to the study vaccine may cause a false positive result on MTTT serology; consequently, when indicated per IDSA guidelines (IDSA 2020), Lyme serology evaluation of participants who present with symptoms clinically concerning for Lyme disease should include a commercially available STTT, consisting of a first step Lyme antibody screening serology with reflex to second step Western blot, to inform diagnostic or treatment decisions. Other diagnostic tests (eg, ECG) may be performed at the discretion of the Investigator. Since Lyme disease symptoms may overlap with symptoms of influenza and COVID-19, nasopharyngeal swab testing for multiplex PCR testing may also be performed. USV for evaluation of AEs not potentially consistent with Lyme disease should not include Lyme serodiagnostic testing or CCI [redacted]

d. All visits should be scheduled based on the date of the most recent injection.

e. Vital sign measurements: Systolic and diastolic blood pressure, pulse, and oral temperature. The preferred route of temperature assessment is oral. Vital signs will only be collected at Screening and on the days of study injection, once before and at least 60 minutes after injection. Vital signs will be collected at other clinical visits at the discretion of the Investigator.

f. Physical examination: A complete physical examination must be performed at Screening. On the day of study intervention but before administration, a focused physical exam of the arm receiving the injection and associated lymph node(s) must be performed and documented, at a minimum. At all other (nondosing) visits, interim complete or focused physical examinations can be performed, as needed at the discretion of the Investigator. Any clinically significant finding identified by a healthcare professional during study visits through 6 months after the last study injection should be reported as a MAAE.

g. Safety laboratory tests include white blood cell count, platelets, hemoglobin, ALT, AST, creatinine, alkaline phosphatase, and total bilirubin (see Section 10.2, Appendix 2). Screening labs should be collected prior to randomization, any time up to 28 days before Day 1. Please refer to the laboratory manual for further instructions.

h. Any blood samples collected on the days of study injection (Day 1, Day 57, Day 169) must be collected prior to participant receipt of study injection.

i. Point-of-care urine pregnancy test will be performed at the Screening Visit and before the study intervention dose on Day 1, Day 57, and Day 169. 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 at the Screening Visit as necessary and at the discretion of the Investigator to confirm postmenopausal status.

j. A Baseline 12-lead ECG will be obtained, after 10 minutes of supine rest, at the Screening Visit. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis/pericarditis occurs within the conduct of the study. The ECG output should be filed in the participant's binder, and the Investigator will not be expected to document an ECG reading. Central reading of the ECG will not be performed. Clinically significant abnormal ECG findings, if incidentally observed by the Investigator, may contribute to Investigator's assessment of eligibility, at their discretion.

k. CCI [redacted]

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

m. Unsolicited AEs will be collected during the 28 days following each injection (ie, the days of study injection [Day 1, Day 57, Day 169] and 27 subsequent days following each study injection).

n. MAAEs are recorded through 6 months after the last study injection.

o. All SAEs and AESIs will be reported by the Investigator or designee to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system.

p. All concomitant medication will be collected during the period of unsolicited AE collection from Screening through 28 days post last dose, and in association with treatment of MAAE, AESI, SAE outside of the period of collecting of unsolicited AEs (from Screening through 28 days post last dose).

2. INTRODUCTION

2.1. Study Rationale

The incidence of Lyme disease, caused by *Borrelia* bacteria, continues to rise as the geographic spread of the tick vectors has increased in recent years. There is no approved vaccine available to prevent Lyme disease in humans. *Borrelia* infection is sometimes not diagnosed until later in the disease, resulting in significant clinical morbidity and cardiac, neurological, and joint complications, posing a healthcare financial burden. Preventive strategies against Lyme disease have been largely unsuccessful, evident with the increasing number of reported cases annually; thus, an effective preventive vaccine against Lyme disease is a medical priority and an unmet medical need.

2.2. Background

The Sponsor is developing mRNA-1975 and mRNA-1982, LNP-encapsulated, mRNA-based vaccines, for the prevention of Lyme disease.

Lyme disease, also known as Lyme *borreliosis*, is caused by spirochete bacteria known collectively as *B. burgdorferi* sensu lato and transmitted by the bite of an infected tick. The incidence of Lyme disease continues to rise as the geographic spread of tick vectors has increased in recent years. Lyme disease is the most common tick-borne infection in the US, Europe, and Asia. A systematic review and meta-analysis found the global *B. burgdorferi* infection seroprevalence was 14.5% (95% CI 12.8% to 16.3%), indicating a substantial global burden (Dong et al 2022). In the US, a single *Borrelia* species, *B. burgdorferi* (also known as *B. burgdorferi* sensu stricto), is responsible for most infections, while multiple *Borrelia* species spread infection in Europe and Asia (Marques et al 2021). From 1996 to 2015 there was observed expansion of the geographic range of *I. scapularis*, the main Lyme disease vector in the US (Eisen et al 2016). Based on current trends in the epidemiology of Lyme disease and spread of the vector exacerbated by increases in the vector populations due to global warming (Wikel 2018), incidence of Lyme disease is expected to continue to increase globally over time with continued spread to new areas (Stone et al 2017).

In comparison to the US, multiple *Borrelia* species spread infection in Europe and Asia (Marques et al 2021). There is greater heterogeneity among European Lyme diseases, with different SRs of OspA commonly found for each species. A recent systematic review of 21 countries in Europe found that the dominant genospecies reported was *B. afzelii*, (48.1%), followed by *B. garinii* (24.6%), *B. burgdorferi* sensu stricto (11.9%), and *B. valaisiana* (10.8%) (Hansford et al 2022). Additionally, *B. miyamotoi* is considered an emerging pathogen, found in several countries, but with a much lower prevalence (1.5%). Other genospecies detected included *B. spielmanii* (3.0%), *B. lusitaniae* (1.2%), and *B. bavariensis* (0.4%). *B. afzelii* genospecies is dominant in Europe while *B. garinii* is found to be the dominant genospecies in England.

In 2019 there were approximately 35,000 cases of confirmed and probable Lyme disease reported to the CDC, of which 95% were reported from just 14 states all concentrated in the Northeast, mid-Atlantic, and upper Midwest states following the distribution of Ixodes scapularis ticks (Kugeler et al 2015). Case numbers of Lyme disease are difficult to access accurately and likely are underestimated. While reported cases from state and local health departments to the CDC have identified approximately 30,000 cases per year in the US (Schwartz et al 2017),

corresponding to an estimated annual incidence rate of 12 cases per 100,000 population, studies using US health insurance claims data have estimated Lyme disease incidence ranging from 329,000 (Nelson et al 2015) to 476,000 cases per year (Kugeler et al 2021).

Lyme disease is also the most common tick-borne disease in Europe, steadily increasing to more than 360,000 reported cases between 1990 and 2010 (WHO 2014). Central Europe has the highest reported incidence. Notable countries included Poland, reporting as high as 54.3 cases per 100,000 in 2019 (Zbrzeźniak 2021), and Germany, reporting 26 cases per 100,000 in 2015 (Enkelmann et al 2018). Analysis of Swiss data collected by mandatory surveillance systems between 2008 and 2011 reported a yearly incidence rate of 131 cases per 100,000 (Altpeter et al 2013). An extensive literature documenting the epidemiology of Lyme disease in the Netherlands reported a yearly increase in Lyme disease until 2014, after which it plateaued at 140 cases per 100,000 (Hofhuis et al 2016). The estimated incidence rate in Western Europe is 22 cases per 100,000 person years (Sykes and Makiello, 2017), with evidence of an increasing number of infections in many geographic areas.

Lyme disease exhibits a bi-modal age distribution, with the highest incidence rates in children under 15 years old and older adults (Schwartz et al 2017; Kugeler et al 2022). In many studies, such as in the UK and Germany, bi-modal peaks in the incidence of Lyme disease are observed with the highest rates in 5- to 10-year-old children and older-middle to older aged adults. (Tulloch et al 2019; Enkelmann et al 2018). Lyme disease is a multisystem inflammatory disease that can present early as an EM rash and/or as a febrile illness with subsequent polymorphic clinical manifestations. Late presentations, which can occur when early disease is not diagnosed or treated, can include significant joint, neurologic, or cardiac sequelae (Robinson et al 2015).

The bacterial OspA is a major surface protein expressed by the *Borrelia* spirochete within the midguts of unfed ticks before transmission. Antigen expression is down regulated on the spirochete as the tick is taking a blood meal and spirochetes are transmitted to the human host (Schwan et al 1995; de Silva et al 1996; Montgomery et al 1996). Antibodies elicited against OspA can neutralize spirochetes within the tick before transmission (Fikrig et al 1992; Shih et al 1995) or in the host (Fikrig et al 1992). In animal and human studies, antibody responses against OspA have been correlated with protection against *B. burgdorferi* infection (Barbour et al 1984; Steere et al 1998). Thus, OspA antigen was the primary component in a previously licensed human vaccine against Lyme disease (LYMErix®), which provided up to 76% protection against Lyme disease in a Phase 3 clinical study and was available in the US from 1998 to 2002 (Steere et al 1998). Similar efficacy was observed in a Phase 3 study conducted with a different OspA-based vaccine, ImmuLyme®, which elicited up to 92% protection against Lyme disease (Sigal et al 1998).

Borrelia spirochetes evade natural immune clearance using mechanisms of antigenic variation that result in ineffective antibody responses against the bacterial infection, and antibody response to OspA during or after natural infection is often not detected. Thus, diagnostic tests rely on detection of IgG and IgM against a wide array of other *Borrelia* antigens.

There is no approved vaccine available to prevent Lyme disease. While Lyme disease can be treated successfully with antibiotic therapy, it often is not diagnosed until later in the disease course, resulting in significant clinical morbidity with cardiac, neurological, and joint complications, and healthcare burden. Preventive strategies against Lyme disease targeting tick and environmental controls have been largely unsuccessful as evidenced by the increasing

number of annual reported cases; therefore, an effective preventive vaccine against Lyme disease is a medical priority and an unmet need.

mRNA-1975 and mRNA-1982 have been developed as prophylactic vaccine candidates with an intended mechanism of action to block the transmission of *Borrelia* spirochetes to the human host from the bite of an infected tick. mRNA-1975 (heptavalent vaccine candidate) is designed to elicit antibodies against 7 SRs of OspA antigen expressed across the 4 major *Borrelia* species causing disease in the US and Europe (*B. burgdorferi* [SR1], *afzelii* [SR2], *bavariensis* [SR4], and *garinii* [SR3, 5-7]), CCI [redacted]. In contrast, mRNA-1982 (monovalent vaccine candidate) is designed to be specific for *B. burgdorferi*, the dominant species circulating in the US, CCI [redacted] (SR1).

2.3. Benefit/Risk Assessment

2.3.1. Potential Benefits of Study Participation

The following benefits may accrue to participants who will receive the mRNA-1975 or mRNA-1982 study intervention:

- Participants who receive the mRNA-1975 or mRNA-1982 may or may not directly benefit from study injection as the efficacy of the mRNA-1975 or mRNA-1982 has yet to be established. Those randomized to the placebo group will not have direct benefit.
- Participants will be contributing to the process of developing new potentially prophylactic and therapeutic measures in areas of unmet medical need.
- The study may contribute to the development of a vaccine against Lyme disease.

2.3.2. Risks from Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). Since the authorization of the Sponsor's mRNA-1273 vaccine for COVID-19, the US CDC estimate of the rate of anaphylaxis based on reporting in the Vaccine Adverse Event Reporting System is approximately 2.5 cases/million doses administered (Shimabukuro et al 2021). As a precaution, all participants will remain under observation at the study site for at least 60 minutes after injection.

Vasovagal syncope (fainting) can occur before or after any study injection, 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.

IM injection with mRNA vaccines manufactured by the Sponsor CCI [redacted] has commonly resulted in transient and self-limited local inflammatory reactions. These typically include pain, erythema (redness), or swelling/induration (hardness) at the injection site and/or ipsilateral underarm swelling/tenderness, mostly mild to moderate in severity and usually occurring within 24 hours of injection. Most of these reactions are Grade 1 or 2 in severity and resolve within 3 to 4 days of

onset. The most commonly reported systemic reactions include headache, myalgia, arthralgia, fatigue, chills, fever, vomiting, and/or nausea. In most cases, these reactions resolve spontaneously within several days (Baden et al 2021). Clinical laboratory abnormalities after injection have been observed in early Phase clinical studies with mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward Baseline (Day 1) values over time.

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 (including rest, nonsteroidal anti-inflammatory drugs, and/or colchicine). Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021) The risk of myocarditis or pericarditis after administration of non-COVID-19 mRNA vaccines is unknown (Section 8.4.5.2).

The study includes evaluation of Lyme serology by a protocol-specified central laboratory modified two-tiered test (MTTT). Preliminary data suggest that the immune response to the study vaccine OspA antigen may cause vaccine-induced positive Tier 2 test. Instructions for follow-up in such cases are provided in Section 8.6.

2.3.3. Overall Benefit/Risk Conclusion

The proposed Phase 1/2 clinical study evaluates mRNA-1975, at 4 dose levels CCI [redacted] µg, and mRNA-1982 at 3 dose levels, CCI [redacted] µg, administered at Months 0, 2, and 6 (Days 1, 57, and 169), in healthy participants aged 18 through 70 years of age.

Safety will be monitored throughout the study as described in Section 8.3.

Considering the favorable nonclinical data to date with mRNA-1975 and mRNA-1982, the Sponsor's experience with mRNA-1273 and other mRNA vaccine candidates, oversight by an IST, and the medical need for an approved vaccine against *Borrelia* infection to prevent Lyme disease, the Sponsor considers the potential benefits of participation to justify the risks.

3. OBJECTIVES AND ENDPOINTS

In Table 3, the objectives and endpoints are described and defined, respectively.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of mRNA-1975 and mRNA-1982.	• Solicited local and systemic ARs through 7 days after each study injection. • Unsolicited AEs through 28 days after each study injection. • MAAEs from Day 1 to 6 months after last study injection. • AESIs from Day 1 to EoS. • SAEs from Day 1 to EoS. • AEs leading to discontinuation of study injection or study participation from Day 1 to EoS. • Safety laboratory abnormalities through 7 days after each study injection.
Secondary	
• To evaluate the humoral immunogenicity of mRNA-1975 and mRNA-1982 at Days 1, 29, 85, and 197.	• GMC of anti-OspA binding IgG antibodies measured by ELISA or a similar method at Days 1, 29, 85, and 197. • GMFR of anti-OspA binding IgG Ab concentration at Days 29, 85, and 197 compared to Day 1 (Baseline).
Exploratory	
CCI [redacted]	

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; Ig = immunoglobulin; MAAE = medically attended adverse event; OspA = outer surface protein A; SAE = serious adverse event; SBA = serum bactericidal activity.

4. STUDY DESIGN

4.1. Overall Design

4.1.1. General Design

This is a Phase 1/2, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity in parallel of 1) mRNA-1975, containing SR1-7 antigens specific for the 4 major *Borrelia* species causing disease in US and Europe (*B. burgdorferi* (SR1), *afzelii* (SR2), *bavariensis* (SR4) and *garinii* (SR3, 5-7)) and, 2) mRNA-1982, containing SR1 antigen specific for *B. burgdorferi*, among healthy participants 18 through 70 years of age. The purpose of this mRNA-1975/1982-P101 study is to generate appropriate safety and immunogenicity data to enable selection of a mRNA IMP and dose for further clinical development.

A total of 800 healthy participants will be enrolled. Those with a history of past treated Lyme infection will represent no more than 20% of all participants. Randomization in the dose expansion groups will be stratified by with or without history of past treated Lyme infection (confirmed by Lyme seropositivity at Screening).

Approximately 100 participants will be randomized equally into each of the 8 groups (Table 4) consisting of 4 dose groups for mRNA-1975, 3 dose groups for mRNA-1982, and 1 saline placebo group.

Table 4: Randomized Dose Groups

Product	Dose	Schedule	Sample Size
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1975	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
mRNA-1982	CCI µg	3 doses (0, 2, and 6 months)	100
Placebo (saline)	NA	3 doses (0, 2, and 6 months)	100

Abbreviations: mRNA = messenger ribonucleic acid; NA = not applicable.

A total of 2 IAs are planned for this study. For details refer to Section 9.6.

4.1.2. Enrollment Procedure

As shown in Figure 2, study enrollment will begin with an initial sentinel cohort consisting of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 4 participants randomized to placebo (N = approximately 34 total). Study enrollment will then pause for an independent IST review of unsolicited AEs through Day 8 focused on AEs potentially concerning for myocarditis/pericarditis. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, enrollment will resume with a second

sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for a second focused IST review of unsolicited AEs reported in the study overall through Day 8 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, study enrollment will resume with a third and final sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for a third focused IST review of all available safety data for the study overall through Day 8 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified in the third scheduled IST review, dose expansion with enrollment of the remaining 90 participants in each of the dose groups will proceed in parallel.

Similarly, administration of Dose 2 (Day 57) will begin with the initial sentinel cohort. Administration of Dose 2 will then pause for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of the initial sentinel cohort. If no AEs concerning myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the second sentinel cohort. Administration of Dose 2 will then pause again for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of follow-up for the second sentinel cohort. If no AEs concerning myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the third and final sentinel cohort. Administration of Dose 2 will then pause again for an IST review of all available safety data for the study overall through Day 64 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified, administration of Dose 2 to the remaining 90 participants in each of the dose groups will proceed in parallel.

4.2. Scientific Rationale for Study Design

The mRNA-1975/1982-P101 study will provide data on the overall safety, reactogenicity and immunogenicity in participants 18 through 70 years of age to enable the selection of an IMP at an appropriate dose level for the initiation of a Phase 3 adult efficacy program. In the absence of clearly defined correlates of protection for Lyme disease with anti-OspA antibodies, the placebo will be used for descriptive comparisons of safety and immunogenicity.

Participants with no prior history of Lyme infection or past treated Lyme infection (no more than 20% of total participants) will be enrolled. In the dose expansion groups, Baseline seropositive and seronegative participants stratified across treatment groups. To determine whether each participant has had past treated Lyme infection, the CDC recommended MTTT algorithms for Lyme disease will be utilized at Screening (CDC 2019a, CDC 2019b). Participants who have past Lyme infection with reported or documented treatment will be eligible for enrollment, as past natural infection does not protect against repeated infection. The safety and immunogenicity data in both populations will allow evaluation of differences, if any, in IMP-elicited responses between participants who have never been infected with *Borrelia* compared to those who had been previously infected and treated. There will be interval scheduled serological testing with MTTT for Lyme disease throughout the study.CCI

CCI [redacted]

4.3. Justification for Dose

No clinical studies of mRNA-1975 or mRNA-1982 have been conducted to date. mRNA-1982, which contains CCI mRNA encoding serotype 1 OspA of *B. burgdorferi,* will be studied at 3 dose levels CCI µg) in a 3-dose regimen administered at 0, 2, and 6 months (Days 1, 57, and 169). In contrast, mRNA-1975 contains CCI mRNAs encoding different OspA antigens of *Borrelia* SR1-7, and thus a higher dose range CCI µg) will be tested in a 3-dose regimen administered at 0, 2, and 6 months. Doses of CCI and CCI µg will be tested in both IMPs to allow comparison of similar levels of mRNAs against one or more serotype OspA antigens. Results from preclinical studies of both the monovalent (mRNA-1982) and heptavalent (mRNA-1975) formulations (see the most recent edition of IB for more detailed information), including non-GLP rodent toxicity and immunogenicity, support the dose range selected for this study. The 3-dose regimen of 0, 2, and 6 months is designed to maintain high levels of OspA antibodies during the tick season(s) when infection from tick bites occurs.

The mRNA-1975 and mRNA-1982 vaccines have been developed using the same mRNA/LNP platform as the Sponsor's COVID-19 vaccine and will be studied in similar CCI dosing schedules (typically 2 to 3 doses separated by 1-to-6-month intervals). The Sponsor has accumulated extensive platform experience and safety data with an estimated >1.04 billion doses administered globally to ages 6 months and older, using the mRNA-based platform, CCI, to develop vaccines against SARS-CoV-2 (mRNA-1273, mRNA-1273.222 and additional variants (NCT04283461; NCT04405076; NCT04470427)). Previous studies of the Sponsor's mRNA/LNP CCI platform have assessed dose levels as high as CCI µg for mRNA-1273, a SARS-CoV-2 vaccine (Jackson et al 2020), and mRNA-1893, a Zika vaccine (NCT04917861). Additionally, doses up to CCI µg of the multivalent mRNA-1647, a cytomegalovirus vaccine (NCT03382405), and the multivalent mRNA-1653, a combination vaccine against human metapneumovirus and parainfluenza virus type 3 (NCT03392389), have been tested in Phase 1 studies (August et al 2022). Other programs, under IND and being tested in Phase 3 studies have tested a range of dose levels up to CCI µg, including mRNA-1010 influenza virus vaccine (NCT05606965) and mRNA-1345 respiratory syncytial virus vaccine (NCT 05127434).CCI [redacted]

There is currently no licensed Lyme vaccine available globally to serve as an active control. Therefore, injection with 0.9% sodium chloride solution (normal saline) will be used as placebo control to allow for blinding of study treatments so that the effects of vaccine administration on both safety and immunogenicity findings can be isolated, including adverse effects from the intramuscular injection.

4.4. End-of-Study Definition

A participant's completion of the study, or EoS, is defined as the date of the last visit or last scheduled procedure as shown in Section 1.3.

Participants will be considered to have completed the study if they have completed the EoS Visit approximately 12 months (Month 18/Day 505) after the last IMP injection.

The end of the study is defined as the date the last study sample is processed for the primary and secondary endpoints.

5. STUDY POPULATION

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

A total of 800 healthy participants aged 18 through 70 years will be enrolled to receive mRNA-1975, mRNA-1982, or placebo in this study.

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

5.1. Inclusion Criteria

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

1. Participants, 18 through 70 years of age inclusive at the time of signing the informed consent.
2. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. According to the assessment of the Investigator, is in good general health and can comply with study procedures.
3. BMI of 18 kg/m^2 to 39 kg/m^2 (inclusive) at the Screening Visit.
4. Participants of nonchildbearing potential (PONCBP) may be enrolled in the study.
5. A participant is eligible to participate if they are not pregnant or breastfeeding, and one of the following conditions applies:
    - Is a PONCBP as defined in Section 10.4, Appendix 4, Contraceptive and Barrier Guidance, or
    - POCBP are eligible to participate if they meet both of the following criteria:
        - Use of contraceptive method that is highly effective, with a failure rate of <1%, as per Section 10.4, Appendix 4, Contraceptive and Barrier Guidance, during the study intervention period and for at least 3 months after the last dose of study intervention. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention, and
        - Negative pregnancy test using a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at Screening and Day 1 before the first dose of study intervention, see Section 8.3.5, Pregnancy Testing.

5.2. Exclusion Criteria

The Sponsor advises that any individual who is working as or has worked as study personnel or is an immediate family member or household member of past or present study personnel, study site staff, or Sponsor personnel should not be screened or enrolled in the study.

As a guiding principle for this and other FIH vaccine studies, enrolled participants should be generally healthy, and any underlying conditions or medications used to manage those conditions should not appreciably risk impacting the immune response to the vaccine or manifesting as an AE during follow-up (Section 1.3) that could confound the safety assessment. The intent of allowing some underlying diseases /conditions is to not be overly restrictive on enrollment of older participants, taking into account increased prevalence of age-related conditions (eg, osteoporosis) in this subgroup. Autoimmune diseases may be acceptable if the participant is not receiving systemic immunomodulatory therapy and the disease is well-controlled and stable. However, the Investigator should have a good rationale to support that the participant is generally healthy and that any underlying condition is well-controlled, stable, and unlikely to impact vaccine immune response or manifest as a clinically significant AE during the follow-up period.

Participants are excluded from the study if any of the following criteria apply at Screening or Day 1:

1. Have chronic illness related to Lyme disease or an active symptomatic Lyme disease infection as suspected or diagnosed by a physician.
2. Received treatment for Lyme disease within the prior 3 months.
    - Participants who were diagnosed and treated for Lyme disease >3 months prior to Screening (self-reported or in medical chart) are eligible to participate in the study.
    - Participants who are diagnosed Lyme seropositive at Screening with no known history receiving treatment are excluded.
3. Had previous vaccination against Lyme disease or participated in the past in any vaccine study for Lyme disease.
4. Had a tick bite within 4 weeks prior to the study injection visit.
5. Acutely ill or febrile (temperature ≥38.0°C/100.4°F) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 28-day Screening window and will retain their initially assigned participant number.
6. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 60 days prior to Screening and includes an ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
7. Reported history of congenital or acquired immunodeficiency disorders.
8. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos; psoriasis patches affecting skin over the deltoid areas).

9. Previous dermal filler injection (either lips or face fillers).
10. Reported history of bleeding disorder that is considered a contraindication to intramuscular injection or phlebotomy.
11. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
12. Received systemic immunosuppressants for >14 days in total within 180 days prior to the Screening Visit (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study.
13. History of myocarditis, pericarditis, or myopericarditis regardless of the timing of past medical history.
14. Asymptomatic conditions and conditions with no evidence of end organ involvement (eg, mild hypertension, dyslipidemia) are not exclusionary, provided that they are being appropriately managed and are clinically stable (ie, unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, immune-modifying treatments), at the discretion of the Investigator.
15. Participants with any ≥Grade 2 laboratory abnormality or clinically important Grade 1 laboratory abnormality at Screening, based on reference laboratory value ranges (Table 11). The inclusion of participants with Grade 1 laboratory abnormalities considered not clinically important is allowed based on the Investigator's discretion.
16. Symptomatic acute or chronic illness requiring ongoing medical or surgical care, including changes in medication in the past 2 months indicating that chronic illness/disease is not stable (at the discretion of the Investigator). This includes any current workup of undiagnosed illness that could lead to a new medical condition.
    - Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (eg, diabetes), at the discretion of the Investigator.
    - Suspected active hepatitis.
    - History of febrile seizure (in the past 10 years).
17. History of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine or intervention that includes one or more of the same components contained in the study injection.
18. Has received or plans to receive any licensed vaccine ≤28 days prior to the first injection or plans to receive a licensed vaccine within 28 days before or after any study injection, with the exception of licensed influenza vaccines, which may be received >14 days before the first study injection or >14 days after the second or the third study injection.
19. Has received systemic immunoglobulins, long-acting biological therapies that affect immune responses (eg, infliximab) or blood products within 90 days prior to the Screening Visit or plans to receive them during the study.

20. Diagnosis of malignancy within previous 10 years (excluding non-melanoma skin cancer).
21. Has donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
22. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.

5.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the condition leading to exclusion has resolved (ie, febrile illness). 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.

Participants who test seropositive to Lyme serology at Screening but with no known history of treatment for Lyme infection will be excluded (see Section 5.2 for exclusion criteria) as it would be difficult to differentiate signs and symptoms of late-stage Lyme with reactogenicity from IMPs. Site Investigators will be asked to report these untreated positive Lyme testing results to participants' medical provider for further evaluation and consideration of treatment.

5.4. Criteria for Temporarily Delaying Administration of Study Intervention

Vital signs, including oral body temperature, must be measured at the Day 1, Day 57, and Day 169 visits (administration visits) prior to the administration of the study intervention. The following events constitute criteria for delay of study injection, and if any of these events occurs at the time scheduled for injection, the participant may be injected at a later date within the time window specified for Screening in the SoA (Section 1.3).

- Acute moderate or severe infection with or without fever
- Fever, defined as body temperature ≥38.0°C (100.4°F)
- In the opinion of the Investigator, any clinically significant change in vital sign measurements or general condition from the Screening Visit
- Participant has received a nonstudy vaccine within protocol-specified Exclusion Criterion 18.

Participants with a minor illness without fever, as assessed by the Investigator, can be administered the study intervention. Participants with a fever of 38.0°C (100.4°F) or higher and/or who meet any of these criteria for a delay in injection will be contacted within the time window acceptable for participation and reevaluated for eligibility.

6. STUDY INTERVENTION(S)

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 Interventions Administered

The study interventions and their forms are described in Table 5. All study interventions (designated in this protocol as IMP) will be administered IM and will be prepared, packaged, and labeled in accordance with the standard operating procedures of ModernaTX, Inc. or those of its designee, CFR Title 21, GMP guidelines, ICH and GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

Table 5: Study Interventions Administered and Intervention Form

Intervention Label	mRNA-1975	mRNA-1982	Placebo
Intervention Description	mRNA-1975 is an IMP that consists of mRNA, formulated in LNPs, encoding 7 serotypes of the OspA antigen expressed by the major *Borrelia* species in US and Europe, *B. burgdorferi* (SR1), *afzelii* (SR2), *bavariensis* (SR4) and *garinii* (SR3, 5-7).	mRNA-1982 is an IMP, formulated in LNPs, that consists of mRNA encoding the *B. burgdorferi* (SR1) OspA antigen.	0.9% Sodium Chloride [NaCl] Solution, USP.
Type	Vaccine	Vaccine	Placebo
Appearance	White to off-white dispersion.	White to off-white dispersion.	Clear solution.
Dose Levels	CCI µg CCI µg CCI µg CCI µg	CCI µg CCI µg CCI µg	0.9% (9 g/L)

Abbreviations: IMP = investigational medicinal product; LNP = lipid nanoparticle(s); mRNA = messenger ribonucleic acid; NaCl = sodium chloride; OspA = outer surface protein A; SR = serotype; US = United States; USP = United States Pharmacopoeia.

6.2. Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate storage conditions have been maintained through the life of the study intervention destruction, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator or designee must maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study treatment, and the return to the Sponsor or

alternative disposition of used/unused study treatment in a drug accountability log. Drug accountability will be reviewed by the unblinded CRA during site visits and at the completion of the study.

5. The designated unblinded CRA will reconcile the clinical study material in the interim and at the end of the study for compliance. Once fully reconciled at the site, the clinical study material can be destroyed at the investigational site or Sponsor-selected third party, as appropriate. Study products may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction or alternative documentation of destruction must be obtained and sent to the Sponsor or designee. Further guidance on preparation, handling, storage, and accountability is provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

Randomization will occur in the IRT, in accordance with pregenerated randomization schedules.

A total of 800 healthy participants will be randomized equally into the 8 study groups as described in Table 4. There will be no more than 20% of participants overall who test seropositive for Lyme serology testing. In the dose expansion groups, randomization to each study intervention group will be stratified by past treated Lyme infection (seropositive at Screening) to ensure balanced distribution in each group.

Only the unblinded personnel (Section 6.4) will have controlled access to study injection group assignments.

6.4. Blinding, Masking

Table 6: Type of Study – Observer-blind

Type of Study	Observer-blind
Blinded study with unblinded third party who is dispensing intervention	Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. This third party will instruct the participant to avoid discussing dosing frequency, or packaging of the study intervention with the Investigator. In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.

This is an observer-blinded study in which the Investigators are blinded to study intervention. The IRT system will be programmed to allow blind-breaking in case of 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 intervention assignment unless this could delay emergency treatment for the participant. If a

participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

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

Unblinded personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare mRNA-1975, mRNA-1982, or placebo for all participants. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded clinic personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

Unblinded study-site staff will administer the study intervention. They will not be involved in assessments of any study endpoints.

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

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the qualified unblinded study site personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.6. Dose Modification

Not applicable.

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

Not applicable.

6.8. Treatment of Overdose

In the event of an overdose, the Investigator should:

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

6.9. Prior and Concomitant Therapy

Medications administered within the period starting 28 days before the study intervention must be recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines and recreational drugs, and excluding vitamins and/or herbal supplements) or other specific categories of interest that the participant is receiving at 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.

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

The Investigator is responsible for ensuring that details regarding the concomitant medication are adequately recorded in the eCRF, eDiary (as applicable), and AE report (as applicable).

At each study visit, the site personnel should question the participant regarding any medications taken and vaccinations received and record the information as specified in Section 6.9.1.

6.9.1. Recording of Concomitant Medications and Concomitant Vaccinations

The following concomitant medication(s) and vaccine(s) must be recorded in the eCRF:

- All concomitant medications and vaccines, except vitamins and/or herbal supplements, administered from Screening (up to 28 days before the first IMP injection) through 28 days post last dose.
- Any concomitant medications and vaccines listed in Section 6.9.2.
- Any concomitant medications and vaccines relevant to an SAE/AESI/MAAE or administered from the signing of the ICF through the last study visit for the treatment of an SAE/AESI/MAAE.
- Any antipyretic or analgesic to treat or prevent fever or pain within 7 days post vaccination, including day of vaccination.
- Any concomitant medications and vaccines relevant to an MAAE administered from Day 1 through the 6 months after the last study injection.
- Prophylactic medications (ie, medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination) from Day 1 to 28 days post last dose. For example, an antipyretic or analgesic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.

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

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

- Any vaccine authorized or approved by the local health agency, including mRNA vaccine, ≤28 days prior to study intervention (Day 1) through 28 days after the last dose with the exception of licensed influenza vaccines, which may be received >14 days before the first study injection or >14 days after the second or the third study injection.
- Any investigational or nonregistered product (drug or vaccine) other than the IMP 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. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

Other concomitant medications may be considered on a case-by-case basis.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. See the EoS Visit in the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study intervention and the study at that time.
- 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 including but not limited to:

- AE (including SAE and AESI)
- Solicited AR/reactogenicity event
- Death
- Lack of efficacy
- LTFU
- Physician decision
- Pregnancy
- Protocol violation
- Withdrawal of consent
- Other

Participants who are withdrawn from the study because of SAEs/AESI/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study because of an SAE, AESI, or AE until resolution of the event.

7.3. Lost to Follow-up

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

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- The Investigator or designee must make every effort to regain contact with the participant at each missed visit. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- A participant should be not considered LTFU until due diligence has been completed.

7.4. Pause Rules

Study pause rules will be continuously monitored during the study by the study Investigators, medical monitoring team (see Section 8.5, Safety Monitoring), and Sponsor's IST. The medical monitoring team will conduct blinded safety reviews on an ongoing basis during the study and will be responsible for notifying the IST of potential safety signal events or the triggering of pause rules.

Study enrollment will begin with an initial sentinel cohort consisting of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 4 participants randomized to placebo (N = approximately 34 total). Study enrollment will then pause for an independent IST review of unsolicited AEs through Day 8 focused on AEs potentially concerning for myocarditis/pericarditis. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, enrollment will resume with a second sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for a second focused IST review of unsolicited AEs reported in the study overall through Day 8 of follow-up for the second sentinel cohort. If no AEs concerning myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, study enrollment will resume with a third and final sentinel cohort of approximately 10 participants 18 to 70 years of age randomized to each of the CCI µg and CCI µg dose groups, plus approximately 3 participants randomized to placebo (N = approximately 23 total). Study enrollment will then pause again for a third focused IST review of all available safety data for the study overall through Day 8 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified in the third scheduled IST review, dose expansion with enrollment of the remaining 90 participants in each of the dose groups will proceed in parallel.

Similarly, administration of Dose 2 (Day 57) will begin with the initial sentinel cohort. Administration of Dose 2 will then pause for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of the initial sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the second sentinel cohort. Administration of Dose 2 will then pause again for a focused IST review of unsolicited AEs reported in the study overall through Day 64 of follow-up for the second sentinel cohort. If no AEs concerning for myocarditis/pericarditis are identified by the IST, and no study pause rules have been identified through continuous medical monitoring, administration of Dose 2 will resume with the third and final sentinel cohort. Administration of Dose 2 will then pause again for an IST review of all available safety data for the study overall through Day 64 of follow-up for the third sentinel cohort. If no pause rule criteria have been met and no other safety concerns are identified, administration of Dose 2 to the remaining 90 participants in each of the dose groups will proceed in parallel. An unblinded statistician may support the IST's determination if the threshold for any study pause rule has been met. If after review of the treatment assignments, as needed, the unblinded statistician confirms that the criteria for a study pause rule may have been met, the study team will be notified so that the IST can perform an unblinded review of the AEs.

The specific type and frequency of safety events that will result in a pause in further study dosing are summarized in Table 7 and Table 8.

Table 7: Pause Rule Criteria, Events, and Thresholds - Single Event

Pause Rule	Event	Number of Participants
1	Any SAE, including any event of laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study vaccine, for which there is a reasonable possibility of a causal relationship to study injection	≥1
2	Any Grade 4[a] solicited local or systemic AR or Grade 4[a] laboratory abnormality for which there is a reasonable possibility of a causal relationship to study injection	≥1
3	Any case of myocarditis and/or pericarditis for which there is a reasonable possibility of a causal relationship to study injection	≥1

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

a. Grading of parameters will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007).

Table 8: Pause Rule Criteria, Events, and Thresholds – Number or Proportion of Participants

Pause Rule	Event	Number or Percentage of Participants[a]
4	Any severe unsolicited nonserious AE[b] for which there is a reasonable possibility of a causal relationship to the study injection.	≥2 of the initial 10 participants in the same IMP dose group or ≥20% of participants within the same IMP dose group after the initial 10 participants have been dosed.
5	Any Grade 3 or higher[c] solicited local AR, starting within the 7-day postdosing period and lasting more than 48 hours, for which there is a reasonable possibility of a causal relationship to study injection.	≥2 of the initial 10 participants in the same IMP dose group or ≥20% of participants within the same IMP dose group after the initial 10 participants have been dosed[d].
6	Any Grade 3 or higher[c] solicited systemic AR, starting within the 7-day postdosing period and lasting more than 48 hours (24 hours for fever) for which there is a reasonable possibility of a causal relationship to study injection.	≥2 of the initial 10 participants in the same IMP dose group or ≥20% of participants within the same IMP dose group after the initial 10 participants have been dosed[d].

Abbreviations: AE = adverse event; AR = adverse reaction; eDiary = electronic diary; FDA = Food and Drug Administration; IMP = investigational medicinal product; US = United States.

a. The proportion of AR/AEs and laboratory abnormalities will be computed based on the number of exposed participants in each IMP dose group excluding placebo. For solicited ARs, participants need to experience the same solicited AR within the IMP dose group. Unsolicited events including laboratory abnormalities will be counted independent of within or not within the same system organ class.

b. Includes severe nonserious laboratory abnormality assessed by the Investigator as clinically significant.

c. Grading of parameters will be based on the US FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (DHHS 2007).

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

If at any time an Investigator or the medical monitoring team raises a concern that a pause rule criterion has been met, following confirmation with the Investigator of the clinical details and attribution of causality for the AE(s) of concern further study injection and enrollment in all IMP dose groups will be temporarily paused, and the IST will meet ad hoc to review available safety data relevant to the concern. If, after this review, the IST confirms that a pause rule criterion has been met, study enrollment and dosing will be paused as follows:

- For pause rule criteria 1, 2, 3, and 4, study enrollment and dosing will be officially paused for all IMP dose groups.
- For pause rule criteria 5 and 6 (tolerability criteria based on defined threshold levels for solicited adverse reactions, which are either absolute numbers of events or aggregate incidences relative to the number of exposed participants within a dose group), study enrollment and dosing of IMP will be officially paused for all IMP dose groups assigned to the same or higher dose level as the IMP dose group(s) in which the pause rule criterion was met. Study enrollment and dosing may resume (ie, no longer be paused) for IMP dose groups assigned to lower dose levels.

Alternatively, if the IST determines that the AE(s) triggering the pause concern did not actually meet the pause rule criteria (eg, because the IST unblinded review identifies placebo as the administered IMP, or if the Investigator confirms a data entry error), then the IST may recommend to resume dosing of IMP as appropriate.

All study Investigators will be informed of any pauses, and the IRT system will prevent additional administration of IMP. The Sponsor will notify FDA within 48 hours of an official pause being instituted. In all cases of a study pause, dosing will not resume until Investigators have been informed of the basis for resuming dosing and have received written approval from the Sponsor to do so.

During any pause, all planned procedures relating to safety, reactogenicity, and immunogenicity assessments will continue as described in the study protocol, and each participant's study-site visits will continue until EoS. If a pause affects a participant's study injection visit, the window for that participant's study injection visit will be suspended until the pause is lifted and study injection can resume. Once the pause is lifted, study injection should be reinstated as soon as possible.

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

8. STUDY ASSESSMENTS AND PROCEDURES

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 (Section 1.3) 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.

All visits should be scheduled based off the date of the most recent injection.

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 (Section 1.3).

- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- Safety, laboratory and immunogenicity results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

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

8.1. Demography and Baseline Data

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

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

8.2. Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Section 1.3).

Blood samples for immunogenicity assessments will be collected and the following analytes will be measured:

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3). A participant can also be seen for an Unscheduled Visit at any time during the study. Reasons for an Unscheduled Visit may include, but are not limited to, reactogenicity issues or new or ongoing AEs.

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

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported from the day of injection and 27 subsequent days.
- MAAEs from injection on Day 1 through 6 months after the last study injection.
- SAEs, AESIs, and AEs leading to discontinuation from dosing or study participation from injection on Day 1 through EoS or withdrawal from the study.
- Details of all pregnancies in participants will be collected after the start of study treatment and until the end of their participation in the study. All pregnancies must be followed to determine the outcome; however, pregnancy related data received after the end of the study may not be collected in the clinical database.
- Results of safety laboratory tests through 7 days after each injection. Any clinically significant finding identified on the safety laboratory testing post injection will be reported as an AE.
- Physical examination and vital sign measurements. (Section 8.3.1).
- Vital signs (Section 8.3.2).
- Concomitant medications and nonstudy vaccinations (Section 6.9.1).

8.3.1. Physical Examinations

- At the Screening Visit a complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- On the day of study intervention administration but before administration, a focused physical exam of the arm receiving the injection and associated lymph node(s) must be examined and documented, at a minimum.
- Physical examinations at nondosing visits and unscheduled visits not related to potential Lyme infection can be performed at the discretion of the Investigator.

- Investigators should pay special attention to clinical signs related to previous serious illnesses, as well as during unscheduled visits, to evaluate for potential Lyme infection.

8.3.2. Vital Signs

Oral cavity temperature, pulse, and blood pressure will be recorded (before blood collection for laboratory tests).

The participant will be seated for at least 5 minutes before all measurements are taken. On study injection days, vital sign measurements will be collected once before study injection and at least 60 minutes after study injection (before participants are discharged from the study site). If vital signs are clinically concerning, participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection.

Febrile participants on study injection days (fever is defined as a body temperature ≥38.0°C/100.4°F) may be rescheduled within the relevant window periods. Criteria for delay of study injection 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.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 3 or greater and/or are clinically significant, the abnormal value and grade will be documented in EDC as an AE (unless there is another known cause of the abnormality that would result in an AE classification). The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at Baseline, is considered stable, or until the Investigator determines that follow-up is no longer medically necessary.

8.3.3. Electrocardiograms

A Baseline 12-lead ECG will be obtained, after 10 minutes of supine rest, at the Screening Visit. The purpose of the ECG is to serve as a stored Baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis/pericarditis, Lyme carditis, or any other cardiac AE occurs within the conduct of the study. The ECG output should be filed in the participant's binder, and the Investigator will not be expected to document an ECG reading. Central reading of the ECG will not be performed. Clinically significant abnormal ECG findings, if incidentally observed by the Investigator, may contribute to Investigator's assessment of eligibility, at their discretion.

Additional ECGs may be done to compare against the Baseline at the Investigator's discretion during an Unscheduled Visit for evaluation of any concern for cardiac AEs.

8.3.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study, intervention should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.3.5. Pregnancy Testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria. Timepoints for pregnancy testing are described in the SoA (Section 1.3).

Pregnancy testing (urine or serum as required by local regulations) should be conducted before administration of study intervention as described in the SoA.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.

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

8.3.6. Use of Electronic Diaries

At the time of consent, the participant must confirm they will be willing to complete an eDiary (for 7-day reactogenicity). The local and systemic ARs that will be solicited by the eDiary are described in Section 8.4.3.

Solicited local and systemic reactogenicity ARs will be collected on the day of each study injection and during the 7 days after study injection (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.4.3.

At each dosing visit, participants will record data into the eDiary starting approximately 60 minutes after dosing under supervision of the site staff to ensure successful entry of assessments. The 60-minute observation period is an opportunity for site staff to train the participant on eDiary completion requirements. The site staff will perform any retraining as necessary.

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

The participant will be trained on how to complete the eDiary questions according to the SoA (Section 1.3) and also reminded to call the site immediately if they experience any infection. If eDiary questions result in identification of relevant safety events according to the study period or

symptoms of infection, a follow-up safety call will be triggered. The results of the safety call should be recorded in the appropriate source documentation.

If a participant does not respond to the eDiary questions according to the SoA (Section 1.3), site staff will follow-up with the participant.

8.4. Safety Definitions and Related Procedures

The definitions of AEs, SAEs, MAAEs, and AESIs can be found in Section 8.4.1, Section 8.4.2, Section 8.4.4, and Section 8.4.5, respectively. The definitions of solicited ARs and unsolicited AEs also can be found in Section 8.4.3 and Section 8.4.1.

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. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.4.8 to Section 8.4.15.

8.4.1. Adverse Events

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 Adverse Event Definition:

Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition, after IMP injection.

New conditions detected or diagnosed after the IMP injection even though they may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition:

Medical or surgical procedure (eg, endoscopy, appendectomy). The condition that leads to the procedure should be the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the IMP caused the AE (Section 8.4.3). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the study intervention and the AE.

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 but starts outside the protocol-defined period for reporting solicited ARs (7 days after vaccine administration).

8.4.2. Serious Adverse Events

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

- **Death**

  A death that occurs during the 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 IMP.

- **Is life-threatening**

  An AE is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- **Inpatient hospitalization or prolongation of existing hospitalization**

  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Congenital anomaly or birth defect**

- **Medically important event**

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

8.4.3. Solicited Adverse Reactions

Solicited ARs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

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

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 9, which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

If a participant reported a solicited AR during the solicited period and did not record the event in the eDiary, the event should be recorded by the site staff in EDC where reactogenicity is collected.

If a solicited AR starts during the solicited period, but continues beyond 7 days after dosing, the site should collect an end date from the participant, to close out the event in the EDC.

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

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

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (medically attended solicited AR).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (solicited AR leading to discontinuation).
- Solicited local or systemic AR lasting beyond 7 days post injection.
- Solicited local or systemic AR that leads to participant discontinuation from study intervention.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

Table 9: Solicited Adverse Reactions and Grades

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

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Nausea/vomiting	None	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	<38.0°C <100.4°F	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	>40.0°C >104.0°F

Abbreviations: AE = adverse event; eCRF = electronic case report form.
Note: Events listed above but starting >7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the Investigator.
Source: Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

8.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an Unscheduled Visit to a healthcare practitioner, except as noted in Section 8.6 for unscheduled visits for potential Lyme infection where the participant would not otherwise have sought medical care. MAAEs will include visits to a study site for other unscheduled assessments (eg, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (eg, emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured in EDC.

8.4.5. Adverse Events of Special Interest

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

AESIs for this protocol are listed in Section 10.3, Appendix 3.

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in (Section 8.4.14).

8.4.5.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study injection administration should be recorded as AESIs and reported as an SAE (Section 8.4.2), based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

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

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

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

8.4.5.2. 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 8.4.2).

The Investigator's medical judgment must be applied when assessing participants reporting symptoms concerning for myocarditis and/or pericarditis contained within the CDC case definition. Diagnostic evaluation (eg, EKG, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition (Section 10.5) 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 tests results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated. The Investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination but should continue to be followed for study endpoints assuming consent is not withdrawn.

An independent CEAC will review suspected cases of myocarditis, pericarditis, and myopericarditis that are reported in ongoing interventional clinical studies per the CEAC charter, to determine if they meet CDC criteria of "probable" or "confirmed" events. The CDC Working Case Definitions are provided in Section 10.5 as guidance and the CEAC is described in Section 8.5.2.

8.4.6. Suspected Unexpected Serious Adverse Reactions

A SUSAR is an AE that occurs in a clinical study participant, which is assessed by the Sponsor and/or the Investigator as being unexpected, serious, and having a reasonable possibility of a causal relationship with the study intervention.

8.4.7. Recording and Follow-up of Pregnancy

Individuals who have a positive pregnancy test at Screening should not be enrolled. Participants who have a positive pregnancy test at Day 1 should not receive the study intervention and should be withdrawn from the study. Participants who have a positive pregnancy test at Day 57 or Day 169 should not receive the second or third study intervention. Participants who become pregnant at any time during the study after receiving the study intervention should be asked to remain in the study and be followed-up for safety.

Details of all pregnancies in participants will be collected after the study intervention (Day 1) through EoS. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as SAEs. The Investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose.

The Investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

8.4.8. Eliciting and Documenting AEs

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor as specified in the SoA (Section 1.3).

Solicited ARs will be collected during the solicited period, for 7 days (the day of each study injection and the subsequent 6 days). Other (unsolicited) AEs will be collected from the time of the first administration of study injection through 28 days (the day of each study injection and the subsequent 27 days) after study injection administration.

The SAEs, AESIs, MAAEs, and AEs leading to study discontinuation will be collected from participants until the end of their participation in the study.

At every study-site visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their wellbeing according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any nonstudy vaccinations.

In addition to participant observations, physical examination findings and other documents relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

8.4.9. Assessment of Intensity

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 8.4.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant’s daily activities. The toxicity grading scale for healthy adult and adolescent volunteers enrolled in Preventive Vaccine Studies (DHHS 2007), or a modified version thereof, will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.4.3.

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

- Mild: These events do not interfere with the participant’s daily activities.
- Moderate: These events cause some interference with the participant’s daily activities and require limited or no medical intervention.

- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

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

8.4.10. Assessment of Causality

The Investigator's assessment of an AE's relationship to IMP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

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

Not related: There is not a reasonable possibility of a relationship to the IMP. Participant did not receive the IMP OR temporal sequence of the AE onset relative to administration of the IMP is not reasonable OR the AE is more likely explained by another cause than the IMP.

Related: There is a reasonable possibility of a relationship to the IMP. There is evidence of exposure to the IMP. The temporal sequence of the AE onset relative to the administration of the IMP is reasonable. The AE is more likely explained by the IMP than by another cause.

8.4.11. Follow-up of AEs and SAEs

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

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any available postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

8.4.12. Reporting AEs

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IMP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes type of event, time of onset, the Investigator's assessment of intensity (Section 8.4.9) and relationship to IMP (Section 8.4.10), 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. MedDRA will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE (Section 8.4.1).

8.4.13. Reporting SAEs

Prompt notification within 24 hours by the Investigator to the Sponsor of an SAE, including those considered to be a SUSAR (Section 8.4.6), is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of an IMP under clinical investigation are met.

Any AE considered serious by the Investigator or that meets SAE criteria (Section 8.4.1) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The Investigator will assess whether there is a reasonable possibility that the IMP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The Investigator is responsible for notifying the IRB directly.

If the eCRF is unavailable at the time of the SAE, the site can report this information by completing the paper SAE/AESI report form provided by the Sponsor via the Safety reporting email address: Drugsafety@modernatx.com

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 that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue the study.

8.4.14. Reporting AESIs

The following process for reporting an AESI ensures compliance with 21 CFR 312 and ICH GCP guidelines. After learning that a participant has experienced an AESI, the Investigator or designee is responsible for reporting the AESI to the Sponsor, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. If the AESI meets the criteria for an SAE, the SAE reporting procedure should be followed.

8.4.15. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.5. Safety Monitoring

8.5.1. Independent IST

A Sponsor's IST is chaired by a clinical development physician and also includes a safety physician, both of whom are not involved in the study, and who will oversee the safety of study participants, in addition to the clinical development team in charge of the study. The IST, assisted by an unblinded statistician, will perform scheduled reviews of safety data, as described in Section 4.1, during dose escalation enrollment and dosing (first and second study vaccinations) of sentinel cohorts and prior to expanding enrollment and administration of first and second study vaccinations, respectively, to dose expansion groups. The IST will also conduct ad hoc reviews as requested by the study medical monitoring team. The main scope of the IST will be to determine if any AEs concerning for myocarditis or pericarditis occur following dosing of sentinel group participants, and to determine following completion of sentinel group enrollment whether dose expansion in each dose group should proceed or if dosing in any dose group or in the study overall should be paused. If the IST decides to pause further dosing in the study, the IST will make specific recommendations about the possibility to resume dosing in the study, pending modifications to the study protocol and ICF. Details regarding the composition, responsibilities, and procedures of the IST will be described in a charter.

8.5.2. Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis, 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 CEAC charter.

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Section 10.5, as guidance.

8.6. Clinical Assessment for Potential Lyme Infection

As an exploratory objective, study participants CCI [redacted]

At the beginning of the study and at each subsequent study visit, participants will be reminded to contact the site with development of any new signs and/or symptoms potentially consistent with Lyme disease. The site Investigator will review the medical history to determine whether the reported signs and/or symptoms are consistent with potential Lyme disease, and if so, an in-person Unscheduled Visit for potential Lyme infection will be arranged as soon as possible and within 7 days.

Any reported signs and/or symptoms which fall into the 5 groups of clinical presentations (#1 to 5) should trigger consideration for an Unscheduled Visit for potential Lyme infection:

1. EM skin rash (red expanding rash with central clearing, single or multiple skin lesions).
2. Neurological manifestations (meningitis, cranial neuritis/facial palsy, radiculitis with radicular pain or radicular paresis).
3. Musculoskeletal manifestations (objective evidence of swelling in one or more joints).
4. Cardiovascular manifestations (new atrioventricular conduction abnormality or suspected myocarditis/pericarditis).
5. Acute systemic symptoms occurring outside of any reactogenicity evaluation period (7 days after each study injection): any combination of fever, fatigue, chills, neck stiffness, headache, myalgia, arthralgia or regional lymphadenopathy, and *in the absence of:*
    a. gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain).
    b. upper respiratory symptoms (cough, runny nose, sneezing, or sore throat).

During the Unscheduled Visit for potential Lyme infection, protocol-specified evaluation of participants will include several factors: medical history (eg, history of or risk factors for tick exposure), review of symptomatology, focused physical examination, serological testing with Lyme MTTT, CCI [redacted] The focused physical examination should be symptom-directed based on the Investigator's clinical suspicion for Lyme disease versus other etiologies, but should include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems, as well as skin and musculoskeletal (joints) exam. Collection tubes for MTTT serology CCI [redacted] will be stored and used specifically for unscheduled visits. MTTT serology results will be used for research purposes only and will not be provided to clinical sites.

Lyme serology is evaluated by a protocol-specified central laboratory MTTT, in which a positive or inconclusive screening test (Tier 1) is reflexed to a confirmatory (Tier 2) test. Preliminary data suggest that the immune response to the study vaccine OspA antigen may cause a false positive Tier 2 test due to vaccine-induced OspA antibody response rather than a genuine exposure to *B. burgdorferi* infection. Available information does not support that the immune response to the study vaccine would cause a false positive Tier 1 test, but the Tier 1 test can be falsely positive or inconclusive due to the limits of the specificity (not 100%) of the Tier 1 diagnostic test.

Consequently, when indicated per IDSA guidelines (IDSA 2020), Lyme serology evaluation of participants who present with symptoms clinically concerning for Lyme disease should include a commercially available STTT, consisting of a first step Lyme antibody screening serology with reflex to second step Western blot, to inform diagnostic or treatment decisions. With the Lyme STTT, the immune response to the study vaccine may result in a positive first tier Lyme antibody screening serology and the Tier 2 Western blot should be interpreted per IDSA guidelines (IDSA 2020) with consideration that the immune response to the study vaccine may result in one or more positive bands, in particular the 31 kDa band corresponding to OspA (Steere et al 1998). Consultation with an infectious disease specialist should be considered when Western blot interpretation is uncertain in the context of clinical presentation and exposure to study vaccine.

Site Investigators may pursue additional diagnostic testing for Lyme disease (eg, ECG for participants presenting with symptoms and signs of cardiac involvement including dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope), pursue diagnostic workup for alternative etiologies (eg, nasopharyngeal swab testing for multiplex PCR testing since Lyme disease symptoms may overlap with symptoms of influenza, COVID-19, or other viral infections), or refer the participant to a nonstudy HCP for further evaluation and management at their discretion. An eCRF specific for the Unscheduled Visit for potential Lyme infection will document the data collected from the evaluation, as well as any objective data that is collected by nonstudy HCP for evaluation or management of the presenting signs and/or symptoms. Any nonstudy diagnostic tests (eg, additional serology, PCR, culture, or imaging studies) performed at the discretion of the site Investigator or nonstudy HCP prior to or after the Unscheduled Visit will be documented and reports/records requested. Any participant with a clinical diagnosis of Lyme disease will either be treated by the site Investigator according to published guidelines (IDSA 2020) or referred to a nonstudy HCP for further management.

Symptoms precipitating the Unscheduled Visit for potential Lyme infection may be recorded as MAAEs if symptom onset is within 6 months after the last study injection; however, if no external healthcare providers are involved in evaluation and management of the symptoms, and the unscheduled visit for potential Lyme infection does not include any diagnostic or management interventions beyond medical history, review of symptomatology, focused physical examination, Lyme serological testing,CCI [redacted]
Symptoms will be documented as SAEs if they meet regulatory criteria for an SAE (see Section 8.4.2). Symptoms not documented as SAEs or MAAEs will be documented as AEs if symptom onset occurs within 28 days following an IMP injection (collection period for nonserious unsolicited AEs).

In addition to CCI [redacted] throughout the duration of the study as an exploratory objective. Because the study vaccine may cause a vaccine-induced positive MTTT serology, the central laboratory MTTT will be used for research purposes only and should not be used to inform Lyme disease diagnosis or treatment decisions.

8.7. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.8. Pharmacodynamics

Pharmacodynamic parameters and genetics are not evaluated in this study.

8.9. Biomarkers

CCI [redacted] as shown in the SoA (Section 1.3). If indicated, and requested by the Sponsor, testing of cardiac biomarkers may be performed. Additionally, as shown in the SoA (Section 1.3) CCI [redacted]

8.10. 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 primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

9.1. Blinding and Responsibility for Analyses

This is an observer-blind 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 study database is locked and unblinded, with the following exception:

- An independent unblinded statistical and programming team will perform the 2 preplanned IAs (Section 9.6). Prespecified Sponsor team members will be unblinded for the IA results and will not communicate the results to the blinded Investigators, study-site staff, clinical monitors, or participants.

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

Procedures for breaking the blind in the case of a medical emergency are provided in Section 6.4.

9.2. Statistical Hypothesis

There is no hypothesis testing planned in this study.

9.3. Sample Size Determination

The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1975 and mRNA-1982. A total of 800 healthy participants will receive mRNA-1975, mRNA-1982, or placebo. Of these, 100 participants in each dose group and placebo group will be included. With 100 participants in each group, there is approximately 95% probability to observe at least 1 participant with an AE with a true AE rate of 3%.

9.4. Analysis Sets

Analysis sets are described in Table 10.

Table 10: Analysis Sets

Participant Analysis Set	Description
Randomization Set	The randomization set consists of all participants who are randomly assigned.
Full Analysis Set[1]	The FAS consists of all randomly assigned participants who receive the study injection.
Per Protocol Set[2]	The PP set consists of all participants in the FAS who comply with the injection schedule, comply with the timings of immunogenicity blood sampling to have a Baseline and at least one post-injection assessment, and have no major protocol deviations that impact the immune response.
Safety Set[3]	The safety set consists of all randomly assigned participants who receive the study intervention.
Solicited Safety Set[4]	The solicited safety set consists of all participants in the safety set who contribute any solicited adverse reaction data.

Abbreviations: AR = adverse reaction; FAS = full analysis set.

1. For the FAS, participants will be analyzed according to the group to which they were randomized.
2. The PP set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.
3. The safety set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the study injection group corresponding to what they actually received.
4. The solicited safety set will be used for the analyses of solicited ARs, and participants will be included in the study injection group corresponding to what they actually received.

9.5. Statistical Analyses

All analyses will be performed separately by vaccine candidate, unless otherwise specified. Participants from sentinel cohorts and dose expansion groups will be pooled and analyzed by dose groups. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

The SAP will be developed and finalized before database lock and will describe the preplanned statistical analysis details/data derivations, 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. Analysis of exploratory endpoints will be described in the SAP.

9.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, sex, race, ethnicity, height, weight, and body mass index) and Baseline characteristics will be summarized by study injection group.

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

9.5.2. Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP set. If the number of participants in the FAS and PP set differ (defined as the difference divided by the total number of participants in the

PP set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS. All immunogenicity analyses will be provided by study injection group unless otherwise specified.

For the immunogenicity endpoints, GMC of anti-OspA binding IgG antibody against each OspA serotype (SR1-7) with corresponding 95% CI at each timepoint and GMFR of anti-OspA binding IgG Ab concentrations against each OspA serotype with corresponding 95% CI at each postbaseline timepoint over preinjection Baseline at Day 1 will be provided by 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. Descriptive summary statistics, including median, minimum, and maximum will also be provided. Additional analysis using a modeling approach will be performed to evaluate geometric means in each mRNA vaccine group.

For calculation of geometric mean concentrations, antibody concentrations reported as below the LLOQ will be replaced by 0.5 × LLOQ.

Vaccine seroresponse for IgG against each OspA serotype (SR1-7 when applicable) from Baseline is defined as an anti-OspA-specific bAb ≥4-fold if Baseline bAb concentration is above the LLOQ or ≥4 × LLOQ if Baseline bAb concentration is <LLOQ prior to study injection. Vaccine seroresponse rate is defined as the proportion of participants with seroresponse against each serotype 1-7 (SR1-7 when applicable) during the study. Vaccine seroresponse rate will be summarized with a 2-sided 95% CI using the Clopper-Pearson method at each postbaseline timepoint.

Additional details will be described in the SAP.

9.5.3. Safety Analyses

All safety analyses will be based on the safety set, except summaries of solicited ARs, which will be based on the solicited safety set. All safety analyses will be provided by study injection group unless otherwise specified. Participants will be included in the study injection group corresponding to what they received.

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

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

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

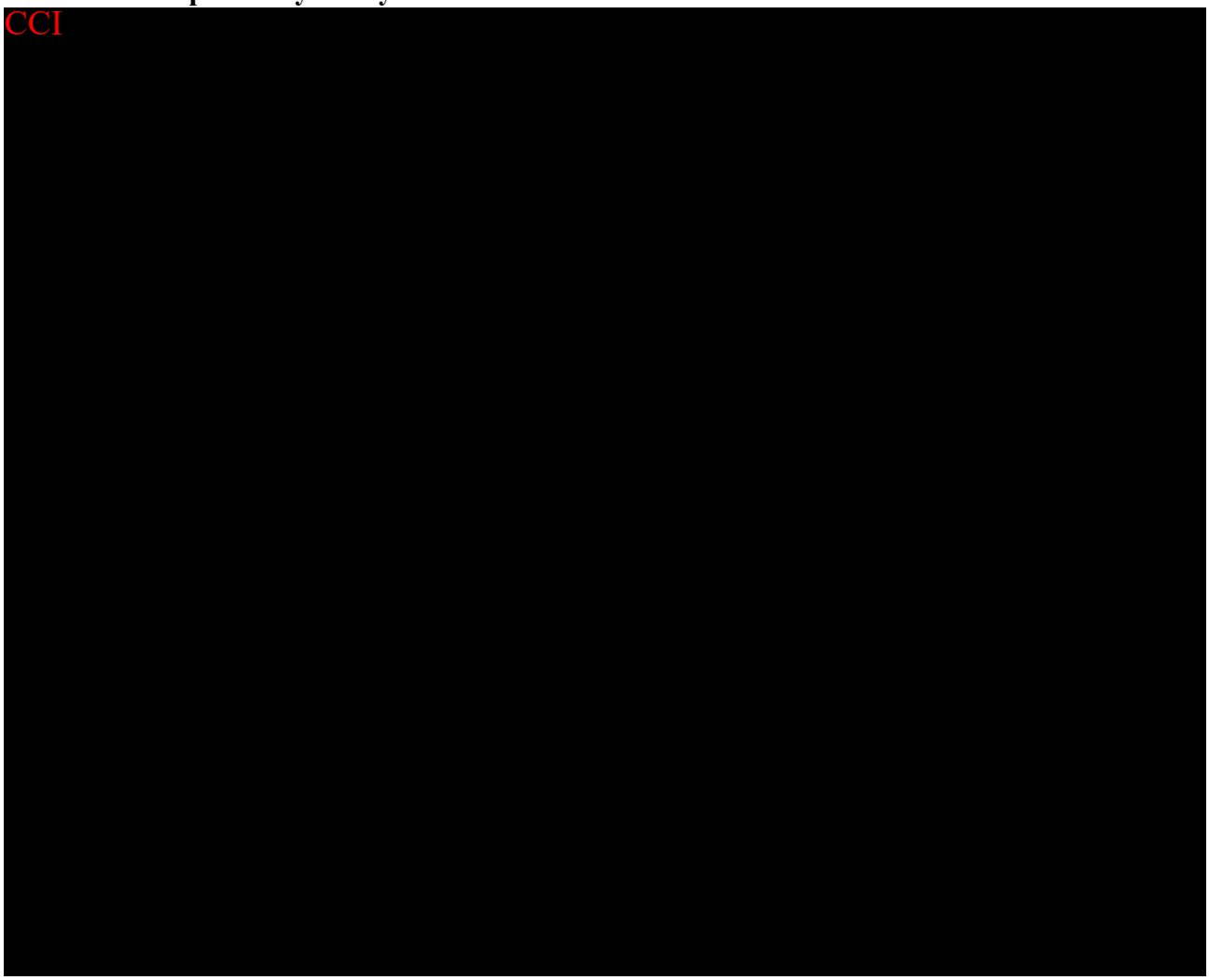
Solicited ARs will be coded according to the MedDRA for AR terminology. The toxicity grading scale for healthy adult and adolescent volunteers enrolled in Preventive Vaccine Studies will be used in this study with modification for rash, solicited ARs, and vital signs (DHHS 2007). Unsolicited AEs will be presented by MedDRA system organ class and preferred term.

The number of events of unsolicited AEs/SAEs, AESIs, and MAAEs will be reported in summary tables accordingly. For all other safety parameters, descriptive summary statistics will be provided.

The number and percentage of participants who have chemistry and hematology results below or above the normal laboratory ranges will be tabulated by timepoint. For treatment-emergent safety laboratory test results, the raw values and change from the most recent safety laboratory values before each study injection will be summarized by study injection group and visit at each timepoint; in general, Day 8 will be compared with Screening Visit, Day 64 will be compared with Day 57, and Day 176 will be compared with Day 169.

9.5.4. Exploratory Analyses

CCI



9.6. Planned Analyses

The following analyses will be conducted:

1. Two IAs are scheduled to occur. IAs will be performed by a separate team of unblinded programmers and statisticians. Preidentified Sponsor team members will be unblinded to review treatment level results. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded until the conclusion of the study.
   - IA-1 will occur when at least 50% of participants reach Day 85 (PD2).
   - IA-2 will occur when 100% of participants reach Day 197 (PD3).

   Additional IAs may occur as determined by Sponsor team members.
2. The final CSR will occur when all the eligible participants have completed Day 505 (Month 18) Visit and will include the available safety and immunogenicity data.

Additional details 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 CIOMS 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 implementation.
- 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.
- All Protocols and protocol amendments will be submitted by the Sponsor for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies conducted in the EU, and all other applicable local regulations.
- Designation of Coordinating Investigators:
  - The Sponsor will select an Investigator to serve as the Coordinating Investigator responsible for overseeing day-to-day study activities and/or signing the CSR.
  - The Coordinating Investigator will be appointed by mutual agreement with the Sponsor.

10.1.2. Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF unless rescreening occurs within 28 days from the previous ICF signature date.

10.1.4. Recruitment Strategy

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

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

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

10.1.6. Dissemination of Clinical Study Data

The Sponsor shares information about studies and results on publicly accessible websites, based on international and local legal and regulatory requirements and other study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register, and some national registries.

In addition, results from studies are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in-clinic studies sponsored by the Sponsor is ensured. Details on data sharing criteria and the process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7. Data Quality Assurance

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

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines (eCCGs).
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance

issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CRO).
- 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.

10.1.8. Source Documents

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

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

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 11: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters[1]
Hematology	• Platelet count • WBC count • Hemoglobin
Clinical Chemistry[2]	• AST • ALT • Alkaline phosphatase[3] • Total bilirubin • Creatinine
Pregnancy Testing	• hCG pregnancy test (as needed for participants of childbearing potential)[4]
Other Screening Tests	• Follicle-stimulating hormone (as needed in participants of nonchildbearing potential only)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; IRB = institutional review board; ULN = upper limit of normal; WBC = white blood cell.

1. Grading of laboratory tests based on 2007 FDA Guidance "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."
2. All events of ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT (or AST) ≥3 × ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

10.3. Appendix 3: Adverse Events of Special Interest

Investigators should report all events that fall into the categories presented in Table 12 as an AESI per the reporting processes in Section 8.4.14. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines.

Table 12: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $\leq 125 \times 10^9$ • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome • Acute disseminated encephalomyelitis (ADEM) • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions
Anaphylaxis	• Anaphylaxis associated with IMP administration as defined per protocol (Section 8.4.5.1) • Follow reporting procedures in Section 8.4.14
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis

Abbreviations: ADEM = Acute disseminated encephalomyelitis; HELLP = hemolysis, elevated liver enzymes, low platelet count; IMP = investigational medicinal product.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

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

Participant of Childbearing Potential

Participants in the following categories are considered POCBP (fertile):

a. Following menarche

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 non-estrogen 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.

Participant of Nonchildbearing Potential

Participants in the following categories are considered PONCBP:

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

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

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.

10.4.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
– Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
– Intrauterine device (IUD)
– Intrauterine hormone-releasing system (IUS)[c]
– Bilateral tubal occlusion or bilateral tubal ligation
– Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: – Oral – Intravaginal – Transdermal – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation – Oral – Injectable
– Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in-clinic 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. 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).

10.5. Appendix 5: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 13 as guidance.

Table 13: CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms*. • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.	Presence of ≥1 new or worsening of the following clinical symptoms* • Chest pain, pressure, or discomfort. • Dyspnea, shortness of breath, or pain with breathing. • Palpitations. • Syncope.
	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability. • Vomiting. • Poor feeding. • Tachypnea. • Lethargy.
	AND ≥1 new finding of • Troponin level above upper limit of normal (any type of troponin). • Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§. • Abnormal cardiac function or wall motion abnormalities on echocardiogram.	**AND** ≥1 new finding of • Histopathologic confirmation of myocarditis†. • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin).
	AND • No other identifiable cause of the symptoms and findings.	**AND** • No other identifiable cause of the symptoms and findings.

Condition	Definition
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • Acute chest pain††. • Pericardial rub on exam. • New ST-elevation or PR-depression on EKG. • New or worsening pericardial effusion on echocardiogram or MRI.
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

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

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

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

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

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria.
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** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

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

Reference: (Gargano et al 2021).

10.6. Appendix 6: Protocol Amendment History

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

Amendment 3 (18 Nov 2024)

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

Overall Rationale for the Amendment:

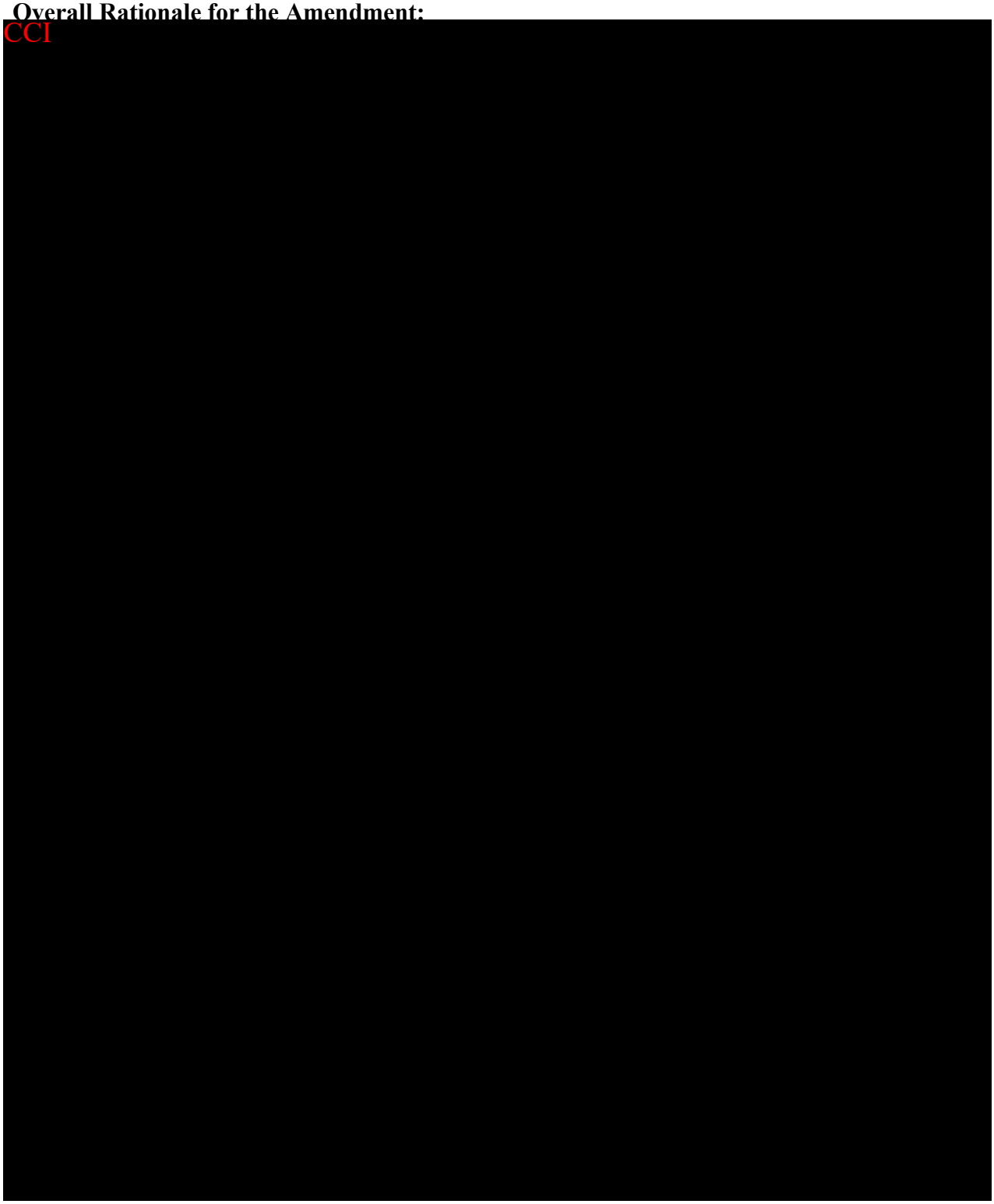
CCI

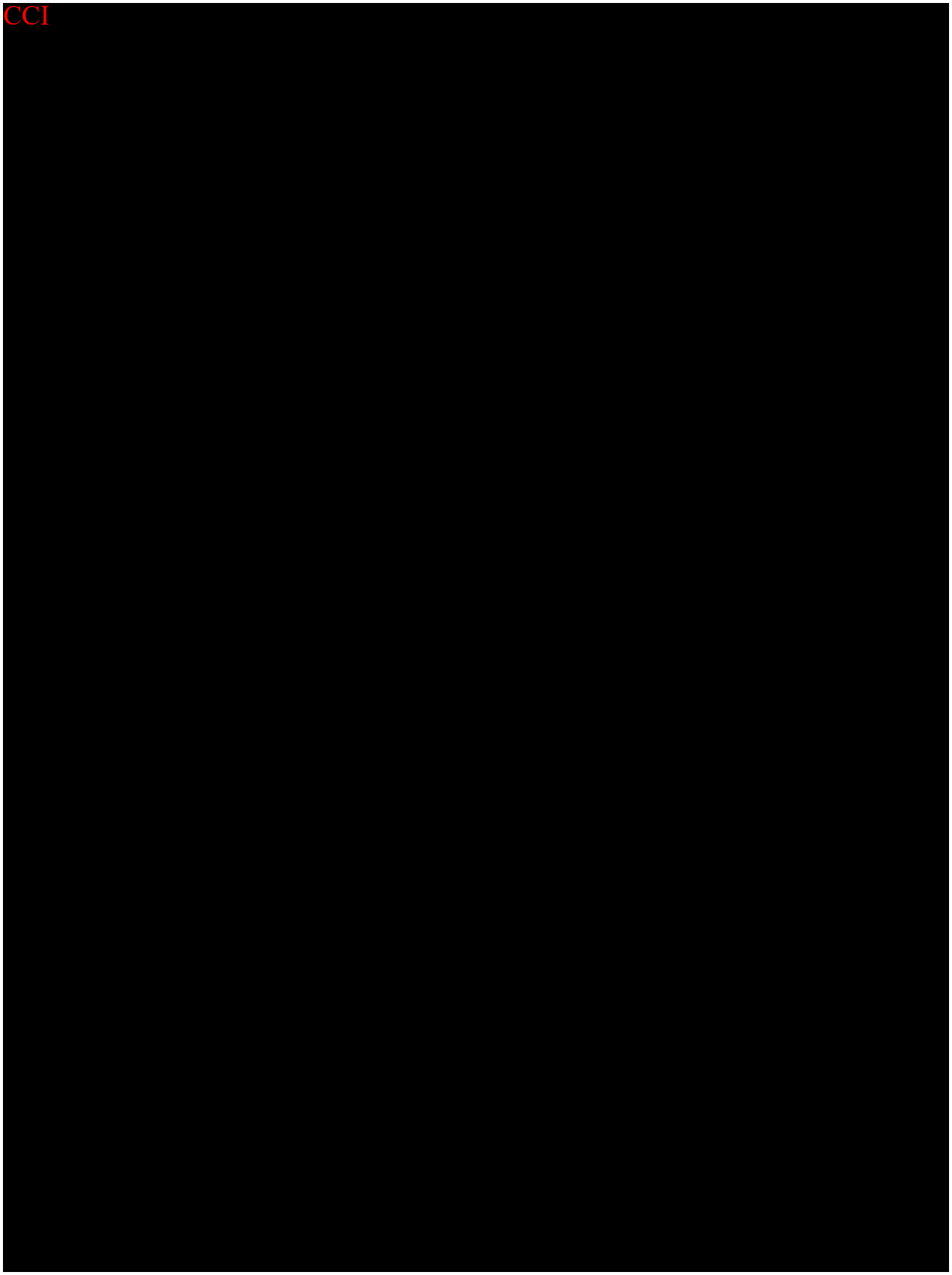
Amendment 2 (16 Apr 2024)

This amendment is considered to be nonsubstantial because it includes administrative changes such as editorial changes that clarify, but do not alter, the existing meaning or intent of the context.

Overall Rationale for the Amendment:

CCI

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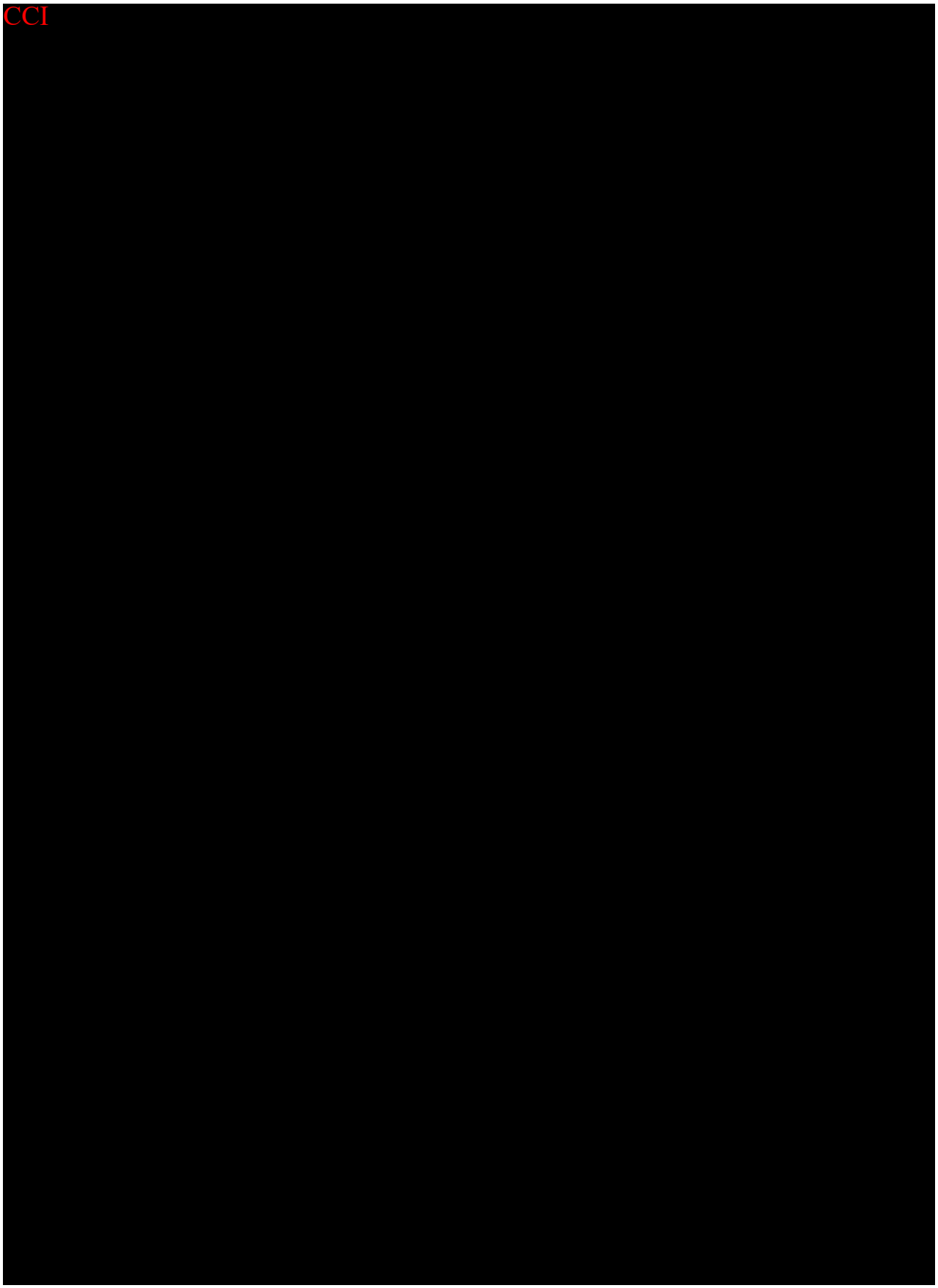
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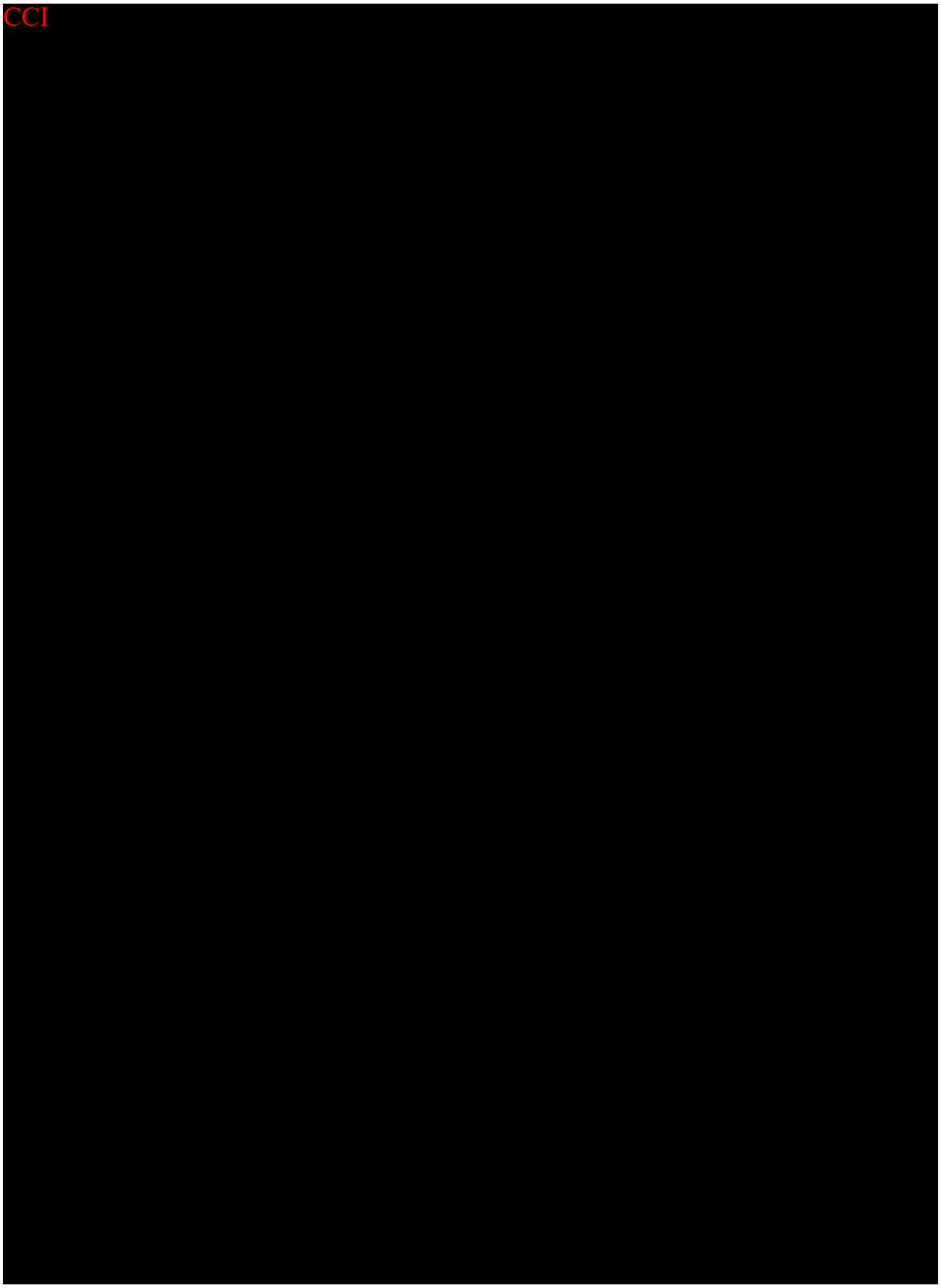
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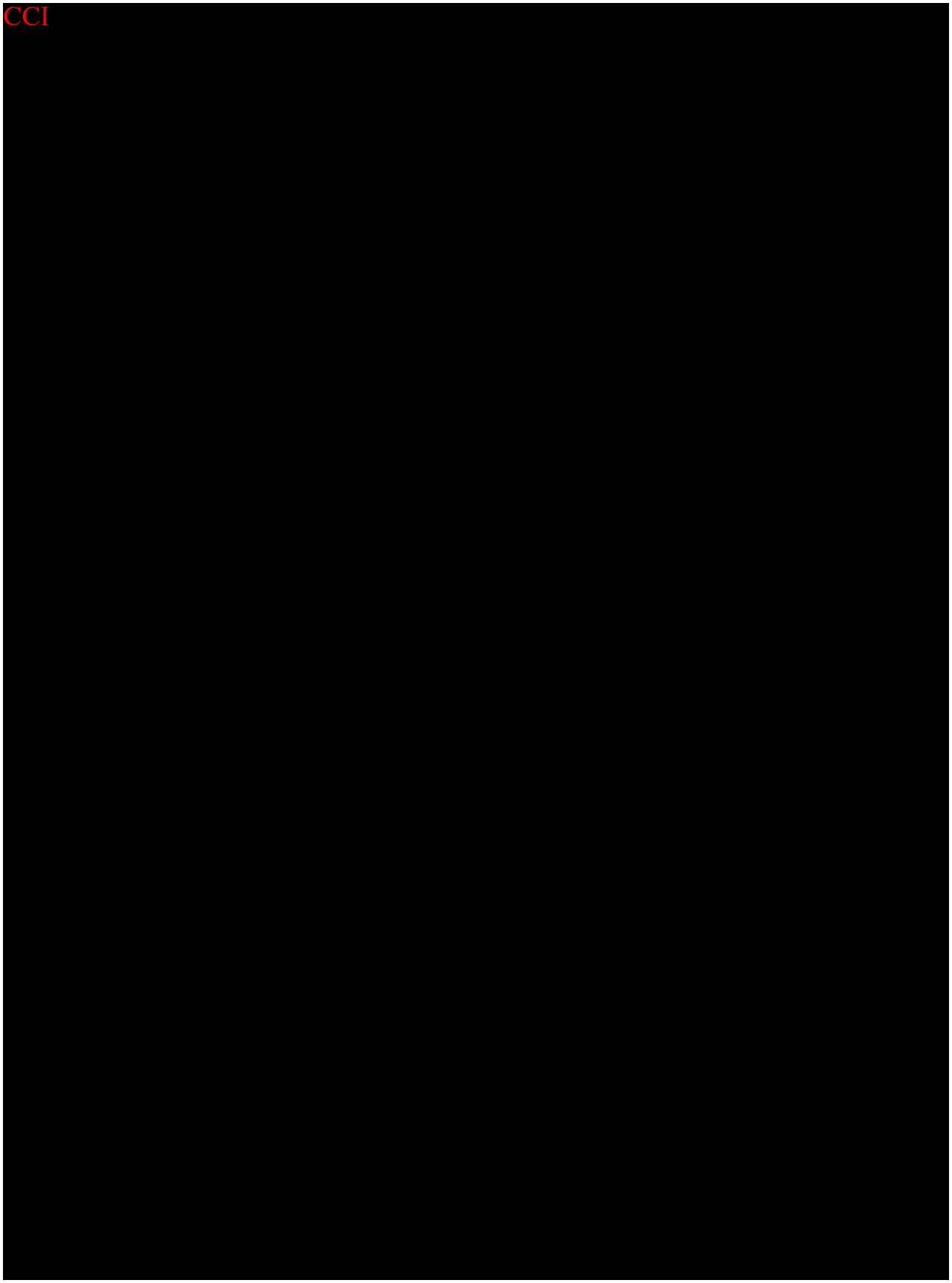
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Amendment 1 (08 Jun 2023)

This amendment is considered to be substantial because it impacts safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment:

CCI

[redacted]

CCI

[redacted]

CCI

10.7. Appendix 7: Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crises, Natural Disaster, or Public Health Crisis.

Note: These changes should only be implemented if allowable by local/regional guidelines and following written agreement from or notification by the Sponsor. Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, or regional travel restrictions) during which participants may not wish to or may be unable to visit the study site for study visits.

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary (eg, remote/decentralized visits). Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section 1.3. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local/regional guidelines (**Note:** in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment/randomization into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 1.3, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 5.3. The procedures detailed in Section 1.3 must be undertaken to confirm eligibility using the same randomization number as for the participant.

Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term "telemedicine visit" refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine visit with the participants will allow AEs, concomitant medication, and other applicable study data to be reported and documented.

Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified health care professional from the study site in the source documents, or by the participant themselves.

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