CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, Randomized, Observer-Blind, Controlled, Dose-Ranging Study of mRNA-1608, an HSV-2 Therapeutic Candidate Vaccine, in Healthy Adults 18 to 55 Years of Age with Recurrent HSV-2 Genital Herpes
Protocol Number:	mRNA-1608-P101
Amendment Number	1
Amendment Scope	Global
Date	16 Aug 2023
Compound	mRNA-1608
Brief Title	A Phase 1/2, Randomized, Observer-Blind, Controlled, Dose-Ranging Study of mRNA-1608, an HSV-2 Therapeutic Candidate Vaccine, in Healthy Adults 18 to 55 Years of Age with Recurrent HSV-2 Genital Herpes
Study Phase	1/2
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Regulatory Agency Identifier Numbers:	IND: 29703

Sponsor Signatory:

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

Sponsor Signatory and Contact Information

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 1/2, Randomized, Observer-Blind, Controlled, Dose-Ranging Study of mRNA-1608, an HSV-2 Therapeutic Candidate Vaccine, in Healthy Adults 18 to 55 Years of Age with Recurrent HSV-2 Genital Herpes," dated 16 Aug 2023 and the most recent version of the Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB 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 site staff and members of the IRB. 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, US federal regulations, and ICH E6(R2) GCP guidelines.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	16 Aug 2023
Original Protocol	14 Jun 2023

Amendment 1, 16 Aug 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. This amendment is primarily to exclude individuals who have previously received a vaccine against serogroup B meningococcal disease and to clarify expectations for unblinding in the event of a medical emergency.

Main Rationale for the Amendment:

The main purpose of this amendment is to incorporate health authority recommendations. Additionally, the amendment clarifies expectations regarding unblinding in the event of a medical emergency. The summary of changes table provided below describes the major changes made in Amendment 1 compared with the original protocol, including the sections modified and the corresponding rationales.

Summary of Major Changes in Protocol Amendment 1

Section # and Name	Description of Change	Brief Rationale
Section 1.3. (Schedule of Events [SoE])	Assessment day "Xs" for Anogenital Swab and eDiary Follow-up calls moved from under safety Ccll visits to Day 85 and Day 197 visits.	Per footnote "r" of the SoE (Section 1.3.) and safety calls (Section 8.7.), the assessment will be carried out at approximately 14 days (±3 days) after the beginning of each 28-day swabbing period (approximately Day -13, Day 99, Day 211). Trained study site staff will conduct an anogenital swab and eDiary follow-up call via telephone or telehealth visit to discuss participant progress with daily self-collection of anogenital swabs and use of the GHSS, PGI-S and PGI-C eDiaries (as relevant).
Section 1.3 SoE	"X" added to Screening Visit in SOE for "Recording of con meds and non-study injections" and footnote "v" updated	Clarifying that concomitant medications or vaccines relevant to or for the treatment of a SAE will be recorded from the signing of ICF through the Day 393/EoS as described in Section 6.7.2.

Section # and Name	Description of Change	Brief Rationale
Section 5.2. (Exclusion Criteria)	Updated Exclusion Criteria number 14 from "Received BEXSERO or other vaccine to prevent meningococcal group B disease (also known as meningitis B) in the prior 12 months" to "Previously received BEXSERO or other vaccine to prevent serogroup B meningococcal disease (also known as meningitis B)."	At the request of health authorities, potential participants who ever received a vaccine against serogroup B meningococcal disease will be excluded from the study.
Section 5.4. (Screen Failures)	Changed "Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled and randomized to treatment" to "Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled."	To clarify that Screen Failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled into the study (at Day -27).
Section 6.2. (Randomization)	Added text related to unblinding during emergency as follows: "In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination and ideally the need for unblinding should be discussed with the Sponsor before unblinding. If the Investigator determines that there is an urgent need to know the treatment assignment to provide medical care for the study participant, they may proceed to unblind without permission from the Sponsor. However, if unblinding has occurred, the Sponsor must be notified within 24 hours. The date and reason for the unblinding must be recorded."	Added language to clarify expectations in the event an Investigator determines that there is an urgent need to know the treatment assignment to provide appropriate medical care for a participant during an emergency.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1.1. (Pause Rules Based on the Occurrence of Events in a Proportion of Participants)	To footnote "b" under Table 5, added: "as described in Section 8.10.13."	Directs reader to expectations for evaluating, reporting, and following participants experiencing an abnormal laboratory result.
Section 7.2. (Criteria for Delay or Withholding of Study Injection)	Added "Participants who report a SAE assessed as related to study intervention will be discontinued from further study injection."	At the request of health authorities, participants who report a SAE assessed as related to study intervention will be discontinued from further study injection.
Section 7.4. (Lost to Follow-up)	Added "or Day 57" to: "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 (ie, relative to their Day 1 or Day 57 visit)."	Clarified language to be consistent with the expectation for scheduling Study Visits and safety calls which are calculated by the days before Day 1 or the days since the most recent vaccination (after Day 1 or Day 57).
Global	Minor editorial changes	

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LIST OF ABBREVIATIONS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AR	Adverse reaction
AST	Aspartate aminotransferase
bAbs	Binding antibodies
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CDC	United States Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
DHHS	Department of Health and Human Services
DP	Drug product
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic case report form
eDiary	Electronic Diary
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
EoS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone

Abbreviation or Specialist Term	Definition
gB	Glycoprotein B
gC	Glycoprotein C
GCP	Good Clinical Practice
gD	Glycoprotein D
GHSS	Genital Herpes Signs and Symptoms (eDiary)
GLP	Good Laboratory Practice
GMFR	Geometric mean fold rise
GMP	Good manufacturing practices
GMT	Geometric mean titer
HCP	Healthcare practitioner
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICP	Immediate early proteins
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IND	Investigational new drug application
IRB	Institutional review board
IRT	Interactive response technology
IST	Internal safety team
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LTFU	Lost to follow-up
MAAE	Medically attended adverse event

Abbreviation or Specialist Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
mRNA	Messenger ribonucleic acid
nAb(s)	Neutralizing antibody(ies)
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PP	Per-Protocol
QA	Quality assurance
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
AR	Adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoE	Schedule of events
TEAE	Treatment-emergent adverse event
US	United States
USV	Unscheduled Visit
WBC	White blood cells
WOCBP	Women of childbearing potential
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Products: mRNA-1608

Protocol Number: mRNA-1608-P101

Protocol Title: A Phase 1/2, Randomized, Observer-Blind, Controlled, Dose-Ranging Study of mRNA-1608, an HSV-2 Therapeutic Candidate Vaccine, in Healthy Adults 18 to 55 Years of Age with Recurrent HSV-2 Genital Herpes

Brief Title: A Phase 1/2 Study of mRNA-1608, an HSV-2 Therapeutic Candidate Vaccine, in Healthy Adults 18 to 55 Years of Age with Recurrent HSV-2 Genital Herpes

Regulatory agency identifier number: IND: 29703

Rationale: A therapeutic vaccine to reduce genital herpes disease and viral shedding in individuals with recurrent HSV-2 genital herpes would provide significant personal and public health benefits. mRNA-1608 (drug product [DP]) is a LNP dispersion containing 5 different mRNAs encoding 3 HSV-2 glycoprotein antigens (gB, gC, and gD) and 2 HSV-2 immediate early proteins (ICP0 and ICP4) formulated in LNPs composed of 4 lipids. Together, the 5 proteins are known targets of humoral and/or cell-mediated immune responses in healthy individuals following natural infection. The purpose of this Phase 1/2 mRNA-1608-P101 study is to generate safety and immunogenicity data and establish a proof-of-concept of clinical benefit of the mRNA-1608 vaccine candidate.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 3 dose levels (25, 50, and 100 µg) of mRNA-1608 administered as 2 doses at 0 and 2 months, in healthy adults 18 to 55 years of age with recurrent HSV-2 genital herpes.	• Frequency and grade of solicited local and systemic reactogenicity ARs during a 7-day follow-up period after each study injection. • Frequency and severity of unsolicited AEs during the 28-day follow-up period after each study injection. • Frequency of SAEs, AESIs, and AEs leading to discontinuation of study injection or withdrawal from the study from D1 to EoS. • Frequency of MAAEs from D1 through 6 months after last study injection. • Safety laboratory abnormalities through 7 days after each study injection in a subset of participants.

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50, and 100 µg]) versus control (BEXSERO®) in the reduction of genital herpes recurrences at 6 months and 12 months after the second study injection.	• Frequency of genital herpes recurrences counted starting 14 days after the second study injection to 6 months after the second study injection as measured by participant report of genital recurrences via eDiary. • Frequency of genital herpes recurrences counted starting 14 days after the second study injection to 12 months after the second study injection as measured by participant report of genital recurrences via eDiary.
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO) in the reduction of genital herpes lesion rate from baseline to 2 months and 6 months after the second study injection.	• Reduction in genital herpes lesion rate (proportion of days with lesions present) from 28 days prior to the first study injection (baseline lesion rate) to 2 months after the second study injection as measured by participant report of genital lesions via eDiary from Month 3 to Month 4. • Reduction in genital herpes lesion rate (proportion of days with lesions present) from 28 days prior to the first study injection (baseline lesion rate) to 6 months after the second study injection as measured by participant report of genital lesions via eDiary from Month 7 to Month 8.
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO) in the reduction of HSV-2 genital shedding rate from baseline to 2 months and 6 months after the second study injection.	• Reduction in HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 2 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 3 to Month 4. • Reduction in HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 6 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 7 to Month 8.
• To evaluate the humoral immunogenicity of mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) at 1 month and 6 months after the second study injection.	• GMT of mRNA-1608 antigen-specific bAbs at 1 and 6 months after the second study injection. • GMFR of bAbs at 1 and 6 months compared to D1 (baseline).

Objectives	Endpoints
	• Vaccine seroresponse as defined by an increase in HSV-2 bAb levels at D85 ≥4-fold if baseline level is above the LLOQ or ≥4 × LLOQ if baseline bAb level is <LLOQ prior to study injection.

Abbreviations: AEs = adverse events; AESIs = AEs of special interest; ARs = adverse reactions; bAbs = binding antibodies; BEXSERO = Meningococcal Group B vaccine; D = day; DNA = deoxyribonucleic acid; eDiary = electronic diary; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HSV = herpes simplex virus; LLOQ = lower limit of quantification; MAAEs = medically attended AEs; mRNA = messenger ribonucleic acid; PCR = polymerase chain reaction; SAEs = serious AEs.

Exploratory objectives and associated endpoints are provided in Section 3.

Overall Study Design: This first-in-human (FIH) study (mRNA-1608-P101) is a Phase 1/2, randomized, observer-blind, controlled, dose-ranging study to evaluate mRNA-1608 in healthy adults 18 to 55 years of age with recurrent HSV-2 genital herpes. Participants with a history of recurrent genital herpes will be randomly assigned in a 1:1:1:1 ratio to receive mRNA-1608 at 1 of the 3 dose levels (25, 50 and 100 μg) administered as 2 doses at 0 and 2 months, or control (BEXSERO).

Randomization into each study arm (3 active arms, 1 control arm) will proceed in parallel.

Brief Summary:

- The purpose of this study is to generate safety, immunogenicity, and proof-of-concept of clinical benefit of the mRNA-1608 vaccine candidate. mRNA-1608 is administered as an intramuscular (IM) injection. Participants will receive 2 injections of mRNA-1608 at 1 of 3 dose levels of 25, 50, or 100 μg (study arms #1-3), administered as 2 doses at 0 and 2 months. The control that will be used in the study is BEXSERO, a vaccine indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B.
- The study comprises up to 10 scheduled study site visits: Screening (up to 56 days before Day 1 visit), Enrollment Visit for participant anogenital swab self-collection and genital herpes eDiary training (Day -27 [Month -1]), study injection visits at Day 1 (Month 0) and Day 57 (Month 2); visits for safety, reactogenicity, and safety laboratory testing in a subset of participants at Day 8, Day 57, and Day 64; and follow-up visits at Day 29 (Month 1), Day 85 (Month 3), Day 197 (Month 7), and Day 393 (Month 14).
- Participants will use eDiary tools to determine the frequency of genital herpes recurrences and genital herpes lesion rate (proportion of days with lesions present).
- Participants experiencing symptoms consistent with genital herpes between the first injection (Day 1), and the second injection (Day 57), will have the option to report for a USV for clinical evaluation including collection of an anogenital swab sample or to self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA as soon as possible (within 24 hours), but no later than 72 hours after the onset of symptoms.

- Participants experiencing symptoms consistent with genital herpes for the first time starting after the second injection (Month 2) will be asked to report for an unscheduled visit (USV) for clinical evaluation of genital herpes including collection of anogenital swab samples for detection of HSV DNA and culturable HSV virus as soon as possible (within 24 hours), but no later than 72 hours after the onset of symptoms.

Number of Participants: Approximately 300 participants with a history of recurrent genital herpes will be randomized in a 1:1:1:1 ratio to receive 1 of 3 dose levels of mRNA-1608 or control (BEXSERO) with approximately 75 participants in each study arm (3 active arms,1 control arm), at least 35% of which will be male assigned at birth, balanced across study arms.

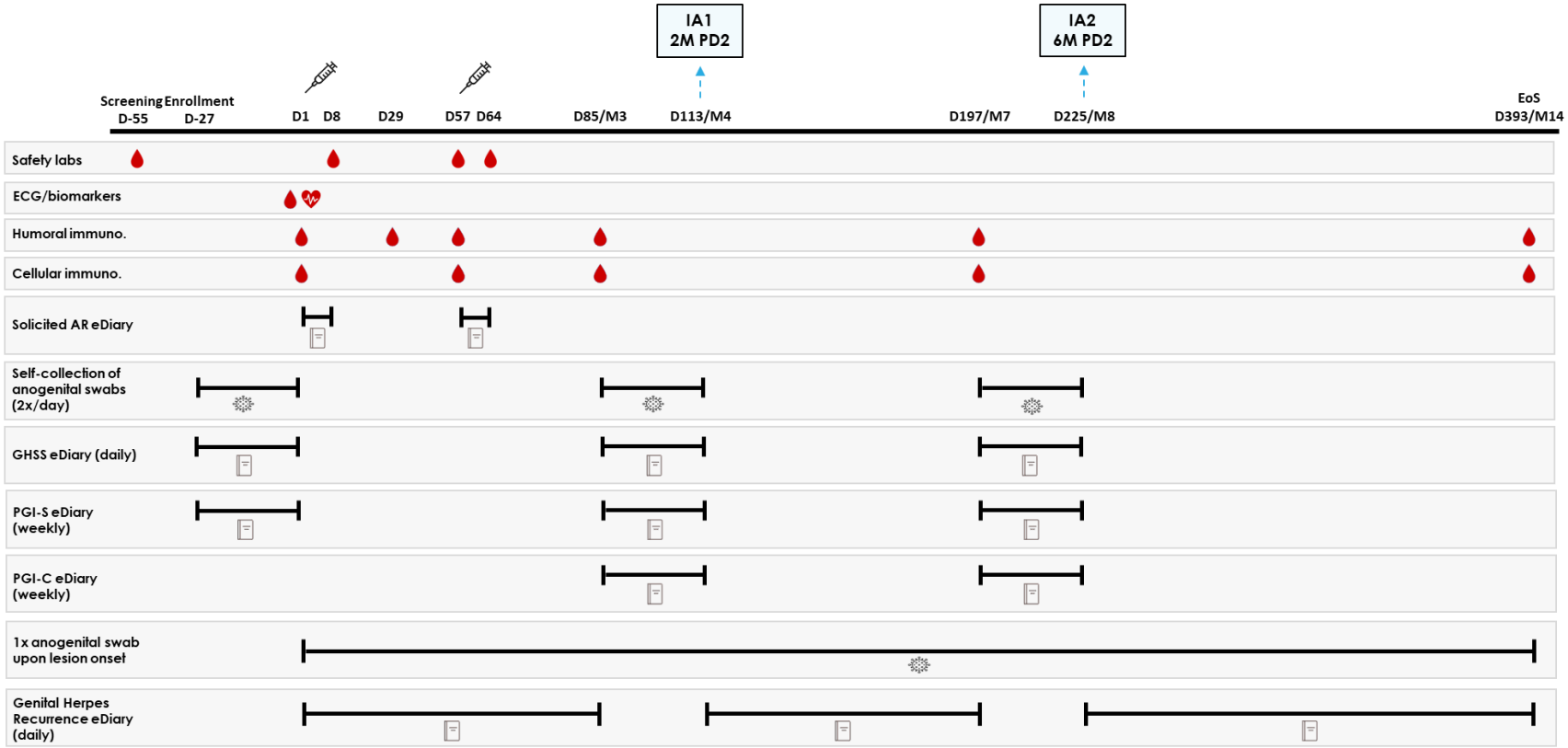
Note: Enrolled means participants' agreement to participate in the clinical study following completion of the informed consent and screening process. Potential participants meeting eligibility criteria for enrollment and willing to participate in the study will be enrolled at the Enrollment Visit (approximately Day-27). Enrolled participants will use the daily Genital Herpes Signs and Symptoms (GHSS) eDiary to report signs and symptoms of genital herpes and self-collect swabs from the anorectal and genital areas twice a day during the 28-day period prior to the first injection (approximately Day -27 to Day 0). Participants who collect less than 45 of the anticipated 56 anogenital swabs between the Enrollment Visit (Day -27) and Day 1 will not be randomized to receive the study injection. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Study Arms and Duration:

- The total duration of the study for each participant is approximately 15 months.
- The study comprises 4 study arms (3 active arms and 1 control arm).

1.2. Schema

Figure 1: Study Schema



Abbreviations: AR = adverse reaction; D = Day; ECG = electrocardiogram; eDiary = electronic diary; EoS = End of Study; GHSS = Genital Herpes Signs and Symptoms; IA1 = interim analyses 1; IA2 = interim analyses 2; immuno = immunogenicity; M = Month; PD = post-dose; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity.

1.3. Schedule of Events

Table 1: Schedule of Events

Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**–**	**8**	**--**	**9**	**USV[y]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**--**	**M-1**	**M0**	**--**	**M1**	**M2**	**--**	**M3**	**M4–M6**	**M7**	**M8-M13**	**M14**	**Up to M14**
Study Visit Day[z]	**D-55 Screening[a]**	**D-27 Enrollment**	**D1**	**D8**	**D29**	**D57**	**D64**	**D85**	**D113, D141, D169**	**D197**	**D225, D253, D281, D309, D337, D365**	**D393/EoS**	**N/A**
Window Allowance (Days)	**--**	**-48 to -27**		**-2 or +1**	**±4**	**±5**	**-2 or +1**	**±4**	**±3**	**±5**	**±3**	**±14**	**N/A**
Days Since Most Recent Injection	**-56**	**-28**	**0**	**7**	**28**	**0**	**7**	**28**	**56, 84, 112**	**140**	**168, 196, 224, 252, 280, 308**	**336**	**N/A**
ICF, demographics, con. meds., medical history	X												
IC/EC criteria	X		X			X[b]							
Blood for safety laboratory testing[c]	X			X		X	X						X
Blood for screening laboratory testing[d]	X												X
Blood for biomarker analysis[e]			X										X
Physical examination[f]	X		X										
Vital signs[g]	X		X			X							X
ECG[h]			X										X

Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**–**	**8**	**--**	**9**	**USV[y]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**--**	**M-1**	**M0**	**--**	**M1**	**M2**	**--**	**M3**	**M4–M6**	**M7**	**M8-M13**	**M14**	**Up to M14**
Study Visit Day[z]	**D-55 Screening[a]**	**D-27 Enrollment**	**D1**	**D8**	**D29**	**D57**	**D64**	**D85**	**D113, D141, D169**	**D197**	**D225, D253, D281, D309, D337, D365**	**D393/EoS**	**N/A**
Window Allowance (Days)	**--**	**-48 to -27**		**-2 or +1**	**±4**	**±5**	**-2 or +1**	**±4**	**±3**	**±5**	**±3**	**±14**	**N/A**
Days Since Most Recent Injection	**-56**	**-28**	**0**	**7**	**28**	**0**	**7**	**28**	**56, 84, 112**	**140**	**168, 196, 224, 252, 280, 308**	**336**	**N/A**
Pregnancy testing[i]	X		X			X							X
Randomization			X										
Study injection (including 60-minute post-dosing observation period)			X			X							
Symptom-directed physical examination[j]		X		X	X	X	X	X		X		X	X
Blood for humoral immunogenicity[k]			X		X	X		X		X		X	X
Blood for cellular immunogenicity[k]			X			X		X		X		X	X
eDiary activation for solicited ARs (7 days)[l]			X			X							
Review of Solicited AR eDiary				X			X						
safety calls[m]									X		X		X

Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**–**	**8**	**--**	**9**	**USV[y]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**--**	**M-1**	**M0**	**--**	**M1**	**M2**	**--**	**M3**	**M4–M6**	**M7**	**M8-M13**	**M14**	**Up to M14**
Study Visit Day[z]	**D-55 Screening[a]**	**D-27 Enrollment**	**D1**	**D8**	**D29**	**D57**	**D64**	**D85**	**D113, D141, D169**	**D197**	**D225, D253, D281, D309, D337, D365**	**D393/EoS**	**N/A**
Window Allowance (Days)	**--**	**-48 to -27**		**-2 or +1**	**±4**	**±5**	**-2 or +1**	**±4**	**±3**	**±5**	**±3**	**±14**	**N/A**
Days Since Most Recent Injection	**-56**	**-28**	**0**	**7**	**28**	**0**	**7**	**28**	**56, 84, 112**	**140**	**168, 196, 224, 252, 280, 308**	**336**	**N/A**
Participant training[n]		X	X	X	X	X	X	X	X	X	X		X
2x/day self-collection of anogenital swabs[o]		X						X		X			
GHSS eDiary, PGI-S, and PGI-C eDiaries[p]		X[q]						X		X			
Anogenital swab and eDiary follow-up calls[r]		X						X		X			
Anogenital swab upon genital herpes symptom onset[s]			X	X	X	X	X	X	X	X	X		X
Daily Genital Herpes Recurrence eDiary[p]			X	X	X	X	X		X		X		
Recording of unsolicited AEs[t]			X	X	X	X	X						

Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**–**	**8**	**--**	**9**	**USV[y]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**C**	**C**
Month Timepoint	**--**	**M-1**	**M0**	**--**	**M1**	**M2**	**--**	**M3**	**M4–M6**	**M7**	**M8-M13**	**M14**	**Up to M14**
Study Visit Day[z]	**D-55 Screening[a]**	**D-27 Enrollment**	**D1**	**D8**	**D29**	**D57**	**D64**	**D85**	**D113, D141, D169**	**D197**	**D225, D253, D281, D309, D337, D365**	**D393/EoS**	**N/A**
Window Allowance (Days)	**--**	**-48 to -27**		**-2 or +1**	**±4**	**±5**	**-2 or +1**	**±4**	**±3**	**±5**	**±3**	**±14**	**N/A**
Days Since Most Recent Injection	**-56**	**-28**	**0**	**7**	**28**	**0**	**7**	**28**	**56, 84, 112**	**140**	**168, 196, 224, 252, 280, 308**	**336**	**N/A**
Recording of SAEs, MAAEs, AESIs and AEs leading to discontinuation of study intervention or study withdrawal, and concomitant medications relevant to or for their treatment[u,v]	X[w]	X[w]	X	X	X	X	X	X	X	X	X[x]	X[x]	X[x]
Recording of con. meds. and non-study injections[v]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion												X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; C = clinic visit (ie, study site visit); con. meds. = concomitant medications; D = day; DNA = deoxyribonucleic acid; EC = exclusion criteria; ECG = electrocardiogram; EDC = electronic data capture; eDiary = electronic diary; EoS = end of study; FSH = follicle-stimulating hormone; GHSS = Genital Herpes Signs and Symptoms; HSV = herpes simplex virus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type-2; IC = Inclusion criteria; ICF = informed consent form; M = month; MAAE = medically attended adverse event; N/A = not applicable; PGI-S = Patient Global Impression of Severity; PGI-C= Patient Global Impression of Change; SAE = serious adverse event; SC = safety call (phone or contact by electronic means); USV = unscheduled visit; WBC = white blood cell.

a. Screening and D1 will NOT be performed on the same day. The Medical Monitor should be contacted if screening cannot be completed in 1 day.

b. Any changes to participant health or medications that could affect eligibility for the second injection will be reviewed prior to injection. A full review of IC/EC criteria is not required on D57.
c. Blood samples for safety testing will be taken in all participants at the Screening Visit. Additional collections for safety testing will occur on Days 8, 57, and 64 for the first approximately 100 participants randomized in the study (approximately 25 participants/Arm). Safety laboratory tests include total WBC count, hemoglobin, platelets, ALT, AST, creatinine, alkaline phosphatase, and total bilirubin. Samples must be collected prior to receipt of study injection if occurring on the same day as injection. Please refer to the Laboratory Manual for further instructions.
d. Screening laboratory tests include HSV-1 and HSV-2 antibodies.
e. Biomarker plasma and biomarker serum samples will be collected and stored for potential future biomarker assessment.
f. A full physical examination, including height, and weight, will be performed.
g. Vital sign measurements: Systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. Vital signs will only be collected at screening and on the days of study injection (D1 and D57), once before and at least 60 minutes after injection. Vital signs will be collected at other clinical visits only in conjunction with a symptom-directed physical examination. When applicable, vital sign measurements should be performed before blood collection (Section 8.5.2).
h. A 12-lead ECG will be obtained after 10 minutes of supine rest at Visit 1/D1 prior to injection (see Section 8.5.3).
i. Point-of-care urine pregnancy test will be performed at the Screening Visit and before study injection on D1 and D57. 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 (Section 8.8.1).
j. Symptom-directed physical examinations may be performed at all clinic visits at the discretion of the Investigator, except at Screening and Day 1, where a full physical examination will be performed. Please refer to Section 8.10.7 for details on reporting of any clinically significant findings identified by a healthcare professional.
k. Samples for humoral immunogenicity and cellular immunogenicity must be collected prior to receipt of study injection on D1 and D57. Samples for cellular immunogenicity will be collected in a subset of participants.
l. Solicited AR eDiary entries will be recorded by the participant starting approximately 60 minutes after injection while at the clinic with instruction provided by study site staff. Participants will continue to record in the eDiary after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection and for 6 days after injection (Section 8.5.4).
m. Trained study personnel will contact participants via telephone or telehealth visit to collect information relating to any AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation of study injection or withdrawal from study participation, information on concomitant medications associated with those events or any non-study vaccinations.
n. Participants will receive materials and training/retraining for self-collection of anogenital swabs and use of eDiaries. Participants will receive materials and training/retraining on the use of the GHSS eDiary and the PGI-S eDiary on Days -27, Day 85, and Day 197. Participants will receive training/retraining on use of the PGI-C eDiary on Days 85 and Day 197. On Day 1 and subsequent visits, participants will receive training/retraining on the use of the Daily Genital Herpes Recurrence eDiary, collection of 1 anogenital swab at the onset of each genital herpes recurrence and instructions for reporting for a USV upon onset of genital herpes symptoms (Section 8.8.5).
o. Participants will self-collect swabs from the anorectal and genital areas twice a day (2 individual swabs per day) for three 28-day periods to measure HSV viral shedding. On the first day of each 28-day swabbing period (Day -27, Day 85 and Day 197), participants will collect the first swab in the clinic and the second swab at home, preferably in the evening (Section 8.8.5).
p. Reporting of genital herpes signs and symptoms/recurrences via the GHSS eDiary, Genital Herpes Recurrence eDiary (Daily), and PGI-S and PGI-C eDiaries is discussed in Section 8.5.4.
q. During D-27 to D0 (M-1) the PGI-C eDiary will not be used; participants will use only the GHSS and PGI-S eDiaries.

r. At approximately 14 days (±3 days) after the start of each 28-day period (approximately Day -13, Day 99, Day 211), trained study site staff will contact participants via a phone or telehealth visit to discuss participant progress with daily self-collection of anogenital swabs and use of the GHSS eDiary (Section 8.5.4 and Section 8.8.5).

s. Collection of swabs from anorectal and genital areas after onset of genital herpes symptoms for detection of HSV. Participants experiencing symptoms between the first and second injections will have the option to report for a USV for clinical evaluation including collection of an anogenital swab or to self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA. Participants experiencing symptoms consistent with genital herpes for the first time starting after the second injection (Day 57), will be asked to report for a USV for clinical evaluation of genital herpes including collection of anogenital swabs for detection of HSV DNA and HSV culturable virus. Thereafter, participants experiencing genital herpes symptoms will have the option to report for a USV for clinical evaluation including collection of a swab and/or self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA (Section 8.8.5).

t. Unsolicited AEs will be collected during the 28 days after each study injection (ie, the day of study injections [D1 and D57] and 27 subsequent days).

u. Event terms listed in the appropriate section of the protocol will be considered as AESIs. All SAEs and AESIs will be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system.

v. Reporting of concomitant medications and vaccinations is discussed in Section 6.7.2.

w. SAEs will be reported from the time of signing the ICF through the last day of study participation. Please refer to Section 8.10.10 and Section 8.10.11 for further details on reporting of AEs and SAEs.

x. MAAEs will be reported from Day 1 through 6 months after the last study injection. Please refer to Section 8.10.10 and Section 8.10.11 for further details on reporting of AEs and SAEs.

y. Participants may experience AEs that necessitate a USV. Additionally, upon experiencing symptoms of genital herpes for the first time after the second study injection, participants should report for a USV that includes sampling for HSV PCR testing and HSV viral culture. For all recurrences thereafter, participants experiencing genital herpes symptoms have the option to report for a USV or self-collect 1 anogenital swab for PCR testing.

z. The expectation for scheduling study visits and safety calls will be calculated by the days before Day 1 or the days since the most recent vaccination (after Day 1 or Day 57).

2. INTRODUCTION

HSV-1 and HSV-2 are common infections that cause recurrent, painful oral and genital ulcers, and more rarely cause meningitis, encephalitis, neonatal infection, and keratitis (Johnston et al 2016). The 2 viruses can cause clinically indistinguishable primary infections but differ significantly in the ability to cause recurrent disease. Although the rate of HSV-1 genital herpes infections has increased in recent years, HSV-2 causes significantly more episodes of genital recurrence than HSV-1, while HSV-1 causes more frequent oral-facial disease than HSV-2. In addition to being the leading cause of genital ulcer disease globally, HSV-2 is associated with an increased risk of acquiring HIV infection and can be life-threatening to infected newborns (Stanberry 2018). It is estimated that as of 2016, approximately 13% of the global population has acquired HSV-2 (James et al 2020). In 2018, an estimated 18.6 million people aged 15 to 49 years were living with HSV-2 in the US, approximately 2/3 of which were women (Kreisel et al 2021).

Clinical manifestations of infection with HSV-2 are highly variable and depend on factors including the route of transmission, host immune status, and whether the infection is primary or recurrent (Johnston et al 2016). Although more than 80% of primary infections are unrecognized or asymptomatic, the initial presentation can be severe with painful genital ulcers, itching, dysuria, local lymphadenopathy, fever, and other systemic symptoms (Stanberry 2018).

In the case of genital herpes, HSV-2 initially infects epithelial cells at skin or mucosal surfaces in the anogenital region. Progeny virions infect nearby neurons, and in a retrograde process, travel up axons to establish a latent infection. First episode disease is characterized by the development of vesicles at the site of infection that evolve to shallow ulcers that resolve over a period of 1 to 3 weeks in the absence of treatment. At varying intervals, the virus is reactivated and travels back to the skin or mucosal surfaces to cause asymptomatic shedding or recurrent genital ulcers (Johnston et al 2016). Studies of HSV-2 genital shedding have shown that the virus is detected on 9% to 40% of all days during the year after the first episode, often in the absence of symptoms (Wald et al 1997; Gupta et al 2004; Fife et al 2006; Leone et al 2007; Mark et al 2007). Although the genital shedding rate decreases in subsequent years, shedding remains at high levels for many years following infection (Phipps 2011). In a study that evaluated the clinical course of genital HSV infection, HSV-2 infected individuals experienced a median of 5 clinical recurrences in the year following the first episode. While the majority of participants experienced a median decrease of 2 recurrences in the following 4 years, 25% had an increase of at least one recurrence, demonstrating the variability in genital herpes disease (Benedetti et al 1999). Clinical recurrences are usually less severe and of shorter duration than the primary episode (Whitley et al 1998). Factors including severity of the first genital herpes episode and time since the first episode can impact recurrence frequency (Benedetti et al 1994), while longer time since the first genital herpes episode is associated with reduced genital shedding (Phipps et al 2011).

There is currently no vaccine to prevent or treat genital herpes. Clinical recurrences can be treated episodically with antiviral drugs (acyclovir, valacyclovir, or famciclovir) or prevented with continual suppressive antiviral therapy (CDC Sexually Transmitted Infections Treatment Guidelines 2021). While suppressive therapy significantly reduces HSV-2 clinical recurrences and viral shedding, a clinical study evaluating suppressive valacyclovir therapy, found that

transmission of HSV-2 from infected individuals to uninfected partners was reduced by only 48% (Corey et al 2004). The burden of taking daily therapy that can have side effects likely decreases adherence and further increases the risk of onward transmission to intimate partners. Additionally, suppressive antiviral therapy does not reduce the risk of HIV acquisition that is increased with HSV-2 infection (Celum et al 2008; Celum et al 2010).

2.1. Study Rationale

A therapeutic vaccine to reduce genital herpes disease and viral shedding in individuals with recurrent HSV-2 genital herpes would provide significant personal and public health benefits. mRNA-1608 (DP) is a LNP dispersion containing 5 different mRNAs encoding 3 HSV-2 virus glycoprotein antigens (gB, gC, and gD) and 2 HSV-2 immediate early proteins (ICP0 and ICP4) formulated in LNPs composed of 4 lipids. Together, the 5 proteins are known targets of humoral and/or cell-mediated immune responses in healthy individuals following natural infection. The purpose of this Phase 1/2 study is to generate safety and immunogenicity data and establish a proof-of-concept of clinical benefit of the mRNA-1608 vaccine candidate.

2.2. Background and Overview

Lipid Nanoparticle-Encapsulated mRNA Development Program

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

2.2.1. Nonclinical Studies

A detailed review of the nonclinical study results with the mRNA-1608 vaccine is provided in the IB.

2.2.2. Clinical studies

No clinical studies with mRNA-1608 have been performed to date. mRNA-1608-P101 is a FIH study that the Sponsor is planning to conduct.

2.3. Benefit/Risk Assessment

2.3.1. Known Potential Benefits

Participants who receive mRNA-1608 may or may not directly benefit from study intervention as the efficacy of mRNA-1608 has yet to be established. Participants will obtain medical advice about their general health status through the medical evaluations/assessments associated with this study (ie, physical examination, vital signs measurement, and symptom-directed physical examination).

Participants will be contributing to the process of developing a new potentially efficacious therapeutic vaccine to reduce HSV-2 genital herpes disease and viral shedding.

2.3.2. Risks from Study Participation and Their Mitigation

As with all injectable vaccines, immediate systemic allergic reactions, ranging from mild reactions (eg, urticaria) to severe allergic reactions (eg, anaphylaxis) may occur following any vaccination. Systemic allergic reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). 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 vaccination and is usually triggered by pain or anxiety associated with the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures are followed to avoid injury from fainting.

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 adults within 7 to 14 days after the second or subsequent dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following conservative treatment (including rest, NSAIDs, and/or colchicine). Healthcare professionals and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021). It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of other non-COVID mRNA vaccines.

IM injection with other mRNA vaccines manufactured by the Sponsor containing SM-102, the custom-manufactured ionizable lipid formulation, have commonly resulted in transient and self-limiting local inflammatory reactions. These typically included pain, erythema (redness), or swelling (hardness) at the injection site which were mostly mild to moderate in severity and usually occurred within 24 hours of injection. Clinical laboratory abnormalities following injection have been observed in early phase clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline values over time. The clinical significance of these observations is unknown.

Although preclinical studies support the clinical evaluation of mRNA-1608, it is unknown whether mRNA-1608 will have any effect on the symptoms of genital herpes or viral shedding.

Participant symptoms will be monitored closely throughout the study and participants have the option to report for a clinic visit if experiencing symptoms of genital herpes after receiving the first study injection. Participants will be informed on the risks of transmitting genital herpes to a sexual partner, provided male latex condoms, and encouraged to talk to sexual partners about their risk.

Additional safety information is provided in the current IB.

2.3.3. Overall Benefit/Risk Conclusion

mRNA-1608 is an investigational vaccine that may or may not provide therapeutic benefit against recurrent HSV-2 genital herpes.

Serological data from all participants will be used to evaluate vaccine immunogenicity. Genital herpes recurrence rate, lesion rate, and viral shedding rate will be assessed to establish a proof-of-concept of clinical benefit. Safety findings will be monitored and reviewed by the study

team members to evaluate the safety status of all participants (Section 9.6). The IST will also review and assess the safety data as described in Section 8.11.

Considering the non-clinical safety data of mRNA-1608 and clinical safety data of other mRNA vaccines manufactured to date by the Sponsor that contain the custom-manufactured SM-102 lipid formulation (eg, mRNA-1273), the Sponsor considers the potential benefits of participation to exceed the risks.

3. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 2.

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 3 dose levels (25, 50, and 100 µg) of mRNA-1608 administered as 2 doses at 0 and 2 months, in healthy adults 18 to 55 years of age with recurrent HSV-2 genital herpes.	• Frequency and grade of solicited local and systemic reactogenicity ARs during a 7-day follow-up period after each study injection. • Frequency and severity of unsolicited AEs during the 28-day follow-up period after each study injection. • Frequency of SAEs, AESIs, AEs leading to discontinuation of study injection or withdrawal from the study from D1 to EoS. • Frequency of MAAEs from D1 through 6 months after last study injection. • Safety laboratory abnormalities through 7 days after each study injection in a subset of participants.
Secondary Objectives	**Secondary Endpoints**
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO®) in the reduction of genital herpes recurrences at 6 months and 12 months after the second study injection.	• Frequency of genital herpes recurrences counted starting 14 days after the second study injection to 6 months after second study injection as measured by participant report of genital recurrences via eDiary. • Frequency of genital herpes recurrences counted starting 14 days after the second study injection to 12 months after second study injection as measured by participant report of genital recurrences via eDiary.
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO) in the reduction of genital herpes lesion rate from baseline to 2 months and 6 months after the second study injection.	• Reduction in genital herpes lesion rate (proportion of days with lesions present) from 28 days prior to the first study injection (baseline lesion rate) to 2 months after the second study injection as measured by participant report of genital lesions via eDiary from Month 3 to Month 4. • Reduction in genital herpes lesion rate (proportion of days with lesions present) from 28 days prior to the first study injection (baseline lesion rate) to 6 months after the second study injection as measured by participant report of genital lesions via eDiary from Month 7 to Month 8.

Objectives	Endpoints
• To compare mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO) in the reduction of HSV-2 genital shedding rate from baseline to 2 months and 6 months after the second study injection.	• Reduction in HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 2 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 3 to Month 4. • Reduction in HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 6 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 7 to Month 8.
• To evaluate the humoral immunogenicity of mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) at 1 month and 6 months after the second study injection.	• GMT of mRNA-1608 antigen-specific bAbs at 1 and 6 months after the second study injection. • GMFR of bAbs at 1 and 6 months after the second study injection compared to D1 (baseline). • Vaccine seroresponse as defined by an increase in HSV-2 bAb levels at D85 ≥4-fold if baseline level is above the LLOQ or ≥4 × LLOQ if baseline bAb level is <LLOQ prior to study injection.
Exploratory Objectives (may be performed)	**Exploratory Endpoints**
• To further evaluate mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) versus control (BEXSERO) in the reduction of genital herpes recurrences at 6 months and 12 months after the second study injection.	• Time to first genital herpes recurrence (events counted starting 14 days after the second study injection) in the 12-month period after the second study injection as measured by participant report of genital recurrences via eDiary. • Frequency of virologically-confirmed genital herpes recurrences counted starting 14 days after the second study injection to 6 and 12 months after the second study injection as measured by PCR.
• To evaluate the humoral immunogenicity of mRNA-1608 (2 doses: 3 dose levels [25, 50, and 100 µg]) at all evaluable time points.	• GMT of mRNA-1608 antigen-specific bAbs at all evaluable time points. • GMT of HSV-2 nAbs at all evaluable time points. • GMFR of bAbs and nAbs at all evaluable time points compared to D1 (baseline).
• To further characterize antibody responses of mRNA-1608.	• Neutralizing antibody levels at additional time points, frequency, specificities, effector function, avidity, or other endpoints to be determined.

Objectives	Endpoints
• To evaluate the antigen-specific cellular immunogenicity of mRNA-1608 in a subset of participants.	• Frequency, magnitude, and phenotype of vaccine specific T-cell responses measured by flow cytometry or other methods.
• To evaluate reduction of HSV-1 genital shedding rate from baseline to 2 months and 6 months after the second study injection of mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) or control (BEXSERO).	• Reduction in HSV-1 genital shedding rate (proportion of HSV-1 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 2 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 3 to Month 4. • Reduction in HSV-1 genital shedding rate (proportion of HSV-1 DNA positive anogenital swabs) from 28 days prior to the first study injection (baseline shedding rate) to 6 months after the second study injection as measured by PCR from participant-collected anogenital swabs from Month 7 to Month 8.

Abbreviations: AEs = adverse events; AESIs = Adverse events of special interest; ARs = adverse reactions; bAbs = binding antibodies; BEXSERO = Meningococcal Group B vaccine; D = day; DNA = deoxyribonucleic acid; eDiary = electronic diary; EoS = end of study; GMFR = geometric mean fold rise; GMT = geometric mean titer; HSV = herpes simplex virus; LLOQ = lower limit of quantification; MAAEs = medically attended AEs; mRNA = messenger ribonucleic acid; nAbs = neutralizing antibodies; PCR = polymerase chain reaction; SAEs = serious AEs.

4. STUDY DESIGN

4.1. Overall Design

This FIH study (mRNA-1608-P101) is a Phase 1/2, randomized, observer-blind, controlled, dose-ranging study to evaluate mRNA-1608 in healthy adults 18 to 55 years of age with recurrent HSV-2 genital herpes. The purpose of this study is to generate safety, immunogenicity, and proof-of-concept of clinical benefit of the mRNA-1608 vaccine candidate.

In this Phase 1/2 study, approximately 300 participants with a history of recurrent genital herpes will be randomly assigned in a 1:1:1:1 ratio to receive mRNA-1608 at 1 of 3 dose levels (25, 50 and 100 µg) administered as 2 doses at 0 and 2 months, or the control (BEXSERO) (Bexsero Package Insert 2023).

Note: Enrolled means participants' agreement to participate in the clinical study following completion of the informed consent and screening process. Potential participants meeting eligibility criteria and willing to participate in the study will be enrolled at the Enrollment Visit (approximately Day -27). Enrolled participants will use the daily GHSS eDiary to report signs and symptoms of genital herpes and self-collect swabs from the anorectal and genital areas twice a day during the 28-day period prior to the first injection (approximately Day -27 to Day 0). Participants who collect less than 45 of the anticipated 56 anogenital swabs between the Enrollment visit (Day -27) and Day 1 will not be randomized to receive the study injection. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Randomization of approximately 75 participants into each study arm (3 active arms, 1 control arm) will proceed in parallel. Approximately 300 participants, 18 to 55 years of age with recurrent HSV-2 genital herpes will be randomly assigned to 1 of 4 study arms in an equal ratio, with at least 35% participants male assigned at birth, balanced across study arms. Randomization will be stratified by sex. A complete listing of inclusion and exclusion criteria is provided in Section 5.1 and Section 5.2, respectively.

Table 3 describes the study injection groups/study arms that will be evaluated in the study.

Table 3: Randomized Groups in mRNA-1608-P101 study

Arm #	Group Name	Dose level	Schedule	Sample Size (N = 300)
1	mRNA-1608	25 µg	2 doses (0, 2 M)	75
2	mRNA-1608	50 µg	2 doses (0, 2 M)	75
3	mRNA-1608	100 µg	2 doses (0, 2 M)	75
4	Control (BEXSERO)	N/A[1]	2 doses (0, 2 M)	75

Abbreviations: mRNA = messenger ribonucleic acid; M = month; N = number; N/A = not applicable.
1. Formulation described in Bexsero Package Insert 2023

The study duration will be approximately 15 months for each randomized participant, which includes screening, collection of baseline genital herpes lesion rate, and HSV-2 genital shedding rate data for 28 days prior to randomization, treatment period (2 injections of mRNA-1608 or control), and 12 months of follow-up after the study injection.

The study comprises up to 10 scheduled study site visits: Screening (up to 56 days before Day 1 visit), Enrollment Visit for participant anogenital swab self-collection and genital herpes eDiary training (Day-27 [Month -1]), study injection visits at Day 1 (Month 0) and Day 57 (Month 2); visits for safety, reactogenicity, and safety laboratory testing in a subset of participants at Day 8, Day 57, and 64; and follow-up visits at Day 29 (Month 1), Day 85 (Month 3), Day 197 (Month 7), and Day 393 (Month 14).

All participants will be followed for safety and reactogenicity. At each dosing visit, participants will be instructed (Day 1) and reminded (Day 57) on how to document and report solicited ARs in a provided eDiary. Solicited ARs will be assessed for 7 days (the day of study injection and the following 6 days) after each study injection and unsolicited AEs will be assessed for 28 days (the day of study injection and the following 27 days) after each study injection. MAAEs will be assessed from Day 1 through 6 months after last study injection. SAEs, AESIs, and AEs leading to discontinuation of study intervention or withdrawal from the study will be assessed from Day 1 through EoS.

Scheduled safety calls (via phone or telehealth visit) will collect MAAEs, SAEs, AESIs, AEs leading to discontinuation of study intervention or withdrawal from the study, information about concomitant medications associated with these events, and information about receipt of non-study vaccinations temporally associated with these events as designated in the SoE (Table 1).

Participants may experience AEs that necessitate a USV. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. eCRFs should be completed for each USV.

All participants in the study will provide a blood specimen at the Screening Visit, before study injection on Day 1 and Day 57, and additional blood specimens through the next 14 months for safety and immunogenicity as designated in the SoE (Table 1). Blood samples for safety laboratory testing will be taken on Days 8, 57, and 64 for the first approximately 100 participants randomized in the study (approximately 25 participants per study arm). Additional blood samples for safety or other medical concerns may be collected according to the Investigator's judgment at scheduled study site visits during the study.

Participants will use eDiary tools to determine the frequency of genital herpes recurrences and genital herpes lesion rate (proportion of days with lesions present). (Section 8.5.4).

To determine the HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs) before and after study injection, all participants will self-collect swabs from the anorectal and genital areas twice a day during the three 28-day periods (approximately Day -27 to Day 0, Day 85 to Day 112, and Day 197 to Day 224; Section 8.8.5). Participants who collect less than 45 of the anticipated 56 anogenital swabs between Enrollment Visit (Day -27) and Day 1 will not be randomized to receive study injection.

Participants experiencing symptoms consistent with genital herpes between the first injection (Day 1), and the second injection (Day 57), will have the option to report for a USV for clinical evaluation including collection of an anogenital swab sample or to self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA as soon as possible (within 24 hours), but no later than 72 hours after the onset of symptoms. Participants experiencing symptoms consistent with genital herpes for the first time starting after the second injection (Month 2), will be asked to report for a USV for clinical evaluation of genital herpes including collection of anogenital swab samples for detection of HSV DNA and HSV culturable virus as soon as possible (within 24 hours), but no later than 72 hours after the onset of symptoms. Thereafter, participants experiencing genital herpes symptoms will have the option to report for a USV for clinical evaluation including collection of a swab sample and/or self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA (Section 8.8.5). Participants experiencing genital herpes symptoms during the three scheduled 28-day swabbing periods, will continue to self-collect anogenital swabs and collect one additional swab at the first onset of symptoms for detection of HSV DNA. Genital recurrences will not be reported as AEs or MAAEs. This information will be used to determine the frequency of virologically-confirmed genital herpes recurrences after the second study injection.

Details regarding use of eDiary and timing of self-collected anogenital swabs are provided in Section 8.5.4 and Section 8.8.5.

In addition to the safety oversight provided by the study team, an IST composed of at least 3 Sponsor physicians who are independent from the study and vaccine program teams will provide additional safety oversight. Refer to Section 8.11.1 for further details on IST.

4.2. Scientific Rationale for Study Design

The mRNA-1608-P101 study will provide data on the safety, reactogenicity, immunogenicity and proof-of-concept of clinical benefit of mRNA-1608 in participants 18-55 years of age to enable the selection of an appropriate dose level for the initiation of a Phase 3 program.

This study is designed as an observer-blind, controlled, dose-ranging study. Participants will receive 1 of the 3 dose levels (25, 50, and 100µg) of mRNA-1608 administered as 2 doses at 0 and 2 months, or control (BEXSERO). BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals aged 10 through 25 years (BEXSERO Package Insert 2023). The rationale to include a control vaccine in this study, which includes endpoints dependent on participant self-report of genital herpes lesions and self-collection of anogenital swabs, is to reduce the risk of potential bias among participants associated with the use of a placebo control with likely lower reactogenicity. BEXSERO was selected as the control because the dosing schedule is compatible with that of mRNA-1608. BEXSERO has an established safety record in adults and a reactogenicity profile that is expected to be more similar to mRNA-1608 than a saline placebo control.

The accumulated safety experience with the Sponsor's mRNA platform across multiple distinct antigens (Section 4.3) has informed upon the study design of initial FIH clinical studies, including mRNA-1608-P101. Safety oversight in the Sponsor's mRNA FIH studies involve both continuous real-time medical monitoring as well as an independent IST, consisting of Sponsor physicians not involved in the program (Section 8.11.1). Parallel dose escalation of a sentinel

cohort followed through Day 8 (approximately the first 25 participants per study arm in this study), with a pause for IST review before expansion to full enrollment, has been accepted by FDA and used in numerous prior Phase 1 clinical studies using the Sponsor's mRNA platform: mRNA-1283, IND #27196 (COVID-19); mRNA-1010, IND #27460 (Flu); mRNA-1189, IND #27738 (EBV); mRNA-1195, IND #29331 (EBV Tx); and mRNA-1468, IND #29026 (VZV). These prior Phase 1 studies included diverse novel antigen targets and enrolled healthy adult study populations, including older adults (mRNA-1468 & mRNA-1010) within parallel dosed sentinel groups.

In this observer-blind study, participants, clinic staff involved in participant assessment, and Sponsor personnel (or its designees) will be blinded to participant vaccine allocation. Unblinded study personnel, who will not participate in any other aspect of the study, will perform study intervention accountability, dose preparation, and administration of study intervention.

4.3. Justification for Dose

No clinical studies of mRNA-1608 have been conducted to date.

As described in other INDs for mRNA vaccine candidates based on the same technology, the safety and tolerability of similar mRNA-based vaccines formulated in a SM-102-containing LNP matrix encapsulating mRNA constructs, that encode for various antigens, have been evaluated in multiple GLP-compliant repeat-dose toxicity studies using up to 6 distinct mRNA construct sequences in Sprague-Dawley rats followed by a 2-week recovery period. The Sponsor considers the toxicity associated with mRNA vaccines formulated in LNP formulations to be driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the consistency of the aggregate rat repeat-dose toxicity profile observed in these GLP studies using mRNA vaccines with IM doses ranging from 8.9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same SM-102 LNP matrix, differing only by the encapsulated mRNA sequence(s).

Previous studies of the Sponsor's mRNA/LNP SM-102 platform have assessed dose levels as high as 250 µg for mRNA-1273, a SARS-CoV-2 vaccine (Jackson et al 2020, NCT04283461), and mRNA-1893, a Zika vaccine (unpublished data, NCT04917861). Additionally, doses of up to 300 µg of the multivalent mRNA-1647, a cytomegalovirus vaccine (unpublished data, NCT03382405), and the multivalent mRNA-1653, a combination vaccine against human metapneumovirus and parainfluenza virus type 3 (unpublished data, NCT03392389), have been tested in Phase 1 studies. The vaccines were generally well tolerated at these dose levels.

The Sponsor has conducted pharmacology studies in mice demonstrating that mRNA-1608 elicits dose-dependent binding antibody, neutralizing antibody, and T-cell responses. The dose levels and schedule were selected based on extrapolation from the mRNA-1608 non-clinical data package as well as significant data from previous and ongoing clinical studies demonstrating the safety and immunogenicity of mRNA vaccines at similar dose levels.

4.4. End of Study Definition

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

The end of study is defined as completion of the last visit of the last participant in the study or last scheduled procedure(s) as shown in the SoE (Table 1) for the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Is an adult 18 to 55 years of age at the time of consent (Screening Visit).
2. Is in good health, in the opinion of the Investigator, based on review of medical history and physical examination performed at screening.
3. Has a diagnosis of genital HSV-2 infection for at least 1 year before the Screening Visit.
4. Seropositive for HSV-2 as determined by Western Blot.
5. Has a history of recurrent genital herpes defined as at least 3 and no more than 9 reported genital herpes recurrences in the 12 months preceding the Screening Visit, or if currently on suppressive therapy, prior to initiation of suppressive therapy.
6. Willing to refrain from taking suppressive antiviral therapy from the Screening Visit until the end of the study.
7. Willing to refrain from the use of episodic antiviral therapy during the three 28-day anogenital swabbing periods. Episodic therapy may be used outside the three 28-day swabbing periods.
8. Provides written informed consent for participation in this study, and willing to perform and comply with all study visits and procedures in this protocol including:
   - Completion of a daily eDiary for 7 days after study injection.
   - Completion of daily and weekly eDiaries for three 28-day periods (1 prior to and 2 after study injections) and every day after the first study injection (excluding two 28-day periods).
   - Collection of two swab samples per day from the anorectal and genital areas for three 28-day periods (1 prior to and 2 after study injections) and swab 1-2 samples from the anorectal and genital areas upon onset of genital herpes symptoms after the first study injection.
9. Understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures, in the opinion of the Investigator.
10. Has a BMI of 18 kg/m^2 to <35 kg/m^2 at the Screening Visit.
11. Female participants:
    - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
      – Is a woman of nonchildbearing potential (WONCBP) as defined in Section 10.2 (Contraceptive and Barrier Guidance).

OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.2, during the study intervention period and for at least 3 months after the last dose of study injection. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study injection.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 28 days before the first dose of study injection, see Section 8.8.1 (Pregnancy Testing).
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study injection are located in Section 8.8.1 (Pregnancy Testing).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

5.2. Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Prior immunization with a vaccine containing HSV antigens.
2. History of any form of ocular HSV infection, HSV-related erythema multiforme, or HSV-related neurological complications.
3. History of genital HSV-1 infection.
4. Acutely ill or febrile (body temperature ≥38.0°C/100.4°F) 72 hours prior to or at the Screening Visit or on Day 1. Participants meeting this criterion may be rescheduled within the allowed window and will retain their initially assigned participant number. Afebrile participants with minor illnesses can be randomized at the discretion of the Investigator.
5. Clinical screening laboratory values (total WBC count, hemoglobin, ALT, AST, creatinine, alkaline phosphatase, platelets and total bilirubin) with a toxicity score ≥Grade 2 at Screening. The inclusion of participants with Grade 1 laboratory abnormalities considered not clinically important is allowed based on Investigator's discretion (DHHS 2007).
6. History of hepatitis B, hepatitis C, or HIV types 1 or 2 (HIV-1, HIV-2).
7. 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 2 months prior to screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

- Asymptomatic conditions are not exclusionary, provided that they are being appropriately managed and 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).
- Participants who have undergone surgical procedures within 7 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study injection are excluded. However, minor surgical procedures under local anesthesia (eg, excision of skin lesion) or diagnostic procedures (eg, colonoscopy) are allowed.

8. Current or previous diagnosis of congenital or acquired immunodeficiency, immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. Certain immune-mediated conditions that are well-controlled and stable (eg, Hashimoto's thyroiditis) as well as those that do not require systemic immunosuppressants per exclusion criterion #17 (eg, asthma, psoriasis, hypothyroidism or vitiligo) may be permitted at the discretion of the Investigator.
9. A dermatologic condition that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas) at the discretion of the Investigator.
10. Any medical, psychiatric, or occupational condition, including reported history of substance (drug or alcohol) abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
11. Diagnosed with a malignancy within previous 5 years (excluding nonmelanoma skin cancer).
12. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA vaccine(s) or any components of the mRNA vaccines.
13. History of myocarditis, pericarditis, or myopericarditis.
14. Previously received BEXSERO or other vaccine to prevent serogroup B meningococcal disease (also known as meningitis B).
15. History of allergic disease or reactions likely to be exacerbated by any component of BEXSERO vaccine.
16. History of bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
17. Received systemic immunosuppressants for >14 days in total within 180 days prior to Screening Visit (for glucocorticoids ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study (including intra-articular steroid injections). Inhaled, nasal and topical steroids are allowed.

18. 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.
19. Donated ≥450 mL of blood products within 28 days prior to the Screening Visit or plans to donate blood products during the study.
20. 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. Interventions such as counseling, biofeedback, and cognitive therapy are not exclusionary.
21. Has received or plans to receive any licensed or authorized vaccine, including COVID-19 vaccines, ≤ 28 days prior to the first study injection (Day 1), or plans to receive a licensed or authorized vaccine within 28 days before or after study injection with the exception of licensed influenza vaccines, which may be received more than 14 days before or after any study injection.
22. Working or has worked as study personnel or is an immediate family member or house member of study personnel, study site staff, or Sponsor personnel.

5.3. Lifestyle Restrictions

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

Participants in the study are asked to refrain from the use of episodic antiviral therapy to treat genital herpes symptoms during the three 28-day anogenital swabbing periods. Episodic therapy may be used outside the three 28-day swabbing periods. Participants in the study should defer vaccination with licensed or authorized vaccines, including COVID-19 vaccines, 28 days before or after the study injection with the exception of licensed influenza vaccines, which may be received more than 14 days before or after any study injection.

Although preclinical studies support the clinical evaluation of mRNA-1608, it is unknown if mRNA-1608 will increase, decrease, or not change symptoms of genital herpes or HSV-2 viral shedding. Participants will be informed on the risks of transmitting HSV to a sexual partner, provided male latex condoms, and encouraged to talk to sexual partners about their risk.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure eligibility criteria and any SAE.

Individuals who do not meet the criteria for enrollment in this study (screen failures) may be rescreened once if confirmed eligible upon rescreening. Rescreened participants should be assigned a new participant number for every screening/rescreening event. The definition of enrollment is provided in Section 4.1.

6. STUDY INTERVENTIONS

6.1. Study Interventions Administered

mRNA-1608 (drug product) consists of 5 different mRNAs encoding 3 HSV-2 glycoprotein antigens (gB, gC, and gD) and 2 HSV-2 immediate early proteins [ICP0 and ICP4] formulated in LNPs composed of 4 lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; 1,2-distearoyl-sn-glycero-3-phosphocholine; and cholesterol. mRNA-1608 is provided as a sterile white-to-off white liquid dispersion. Refer to IB for additional details on mRNA-1608.

mRNA-1608 is administered as an IM injection. Participants will receive 2 injections of mRNA-1608 at 1 of the 3 dose levels of 25, 50, or 100 µg (Study Arms #1-3) (Table 3), administered as 2 doses at 0 and 2 months.

The control (Study Arm #4) (Table 3) that will be used in the study is BEXSERO, a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. Administration of BEXSERO will be off-label for study participants who have previously received vaccine to prevent serogroup B meningococcal disease vaccine or are over 25 years of age (BEXSERO package insert 2023).

6.2. Randomization

Randomization will be performed using an IRT system.

The Sponsor's Biostatistics Department or designee will generate the randomized allocation schedule(s) for study intervention group assignment. Approximately 300 participants with a history of recurrent genital herpes will be randomly assigned in a 1:1:1:1 ratio to receive 1 of 3 dose levels of mRNA-1608 (25, 50, and 100 µg) administered as 2 doses at 0 and 2 months, (Table 3) or control (BEXSERO) administered as 2 doses at 0 and 2 months. Randomization in study arms will proceed in parallel and will be stratified by sex. Study intervention grouping will be performed on the Randomization Visit (Day 1). The confirmation for study injection must be recorded on the Injection eCRF page.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination and ideally the need for unblinding should be discussed with the Sponsor before unblinding. If the Investigator determines that there is an urgent need to know the treatment assignment to provide medical care for the study participant, they may proceed to unblind without permission from the Sponsor. However, if unblinding has occurred, the Sponsor must be notified within 24 hours. The date and reason for unblinding must be recorded.

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Preparation of Study Intervention

The study interventions will be prepared for each participant based on the study intervention group assignment. Specific instructions for the preparation of mRNA-1608 are detailed in the Pharmacy Manual. Instructions for the preparation of BEXSERO are detailed in the package insert (Bexsero Package insert 2023).

6.3.2. Study Intervention Administration

The study intervention will be administered as a single IM injection into the deltoid muscle on Day 1 and Day 57. Preferably, the study intervention should be administered into the nondominant arm.

Participants will be monitored for a minimum of 60 minutes after study injection. Assessments will include vital sign measurements and monitoring for local or systemic reactions as shown in the SoE (Table 1).

The study site will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either onsite resuscitation equipment and personnel or appropriate protocols for the rapid transport of a participant to a resuscitation area or facility are required.

Further instructions for the preparation and administration of mRNA-1608 and BEXSERO control are described in the Pharmacy Manual and the Bexsero Package insert 2023.

6.3.3. Study Intervention Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the study interventions.
- Confirming the appropriate labeling of the study interventions for clinical study use so that it complies with the US legal requirements.

The Investigator is responsible for acknowledging receipt of the study interventions by a designated staff member at the site, which includes the following:

- Confirming that the study interventions were received in good condition.
- Confirming that the temperature during shipment of mRNA-1608 from the Sponsor to the Investigator's designated storage location was appropriate.
- Confirming that the Sponsor has authorized the mRNA-1608 study intervention for use.
- Ensuring the appropriate dose level of the study intervention is properly prepared using aseptic technique.

Further description of the study interventions and corresponding instructions for the receipt, storage, preparation, administration, accountability, and destruction are described in the Pharmacy Manual.

6.3.4. Study Intervention Packaging and Labeling

The Sponsor will provide the Investigator (via the study site pharmacy) with adequate quantities of the study interventions. The study interventions will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

All study interventions used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, CFR Title 21 GMP

guidelines, ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

6.3.5. Study Intervention Storage

All study interventions must be stored in a secure area with limited access and must be protected from moisture and light until it is prepared for administration in accordance with the instructions in the Pharmacy Manual.

6.3.6. Study Intervention Accountability

The Investigator is responsible for ensuring the study intervention accountability staff maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study intervention, and the return to the Sponsor or alternative disposition of used/unused product(s) in a drug accountability log. Drug accountability will be reviewed by the site monitor during site visits and at the completion of the study. For further direction, refer to the Pharmacy Manual.

6.3.7. Study Intervention Handling and Disposal

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

Study intervention may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A document for destruction (ie, Certificate of Destruction) must be obtained and sent to the Sponsor or designee. Refer to Pharmacy Manual for further directions.

6.4. Study Intervention Compliance

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

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window specified in the SoE (Table 1). 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). 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. The site must 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.

6.5. Dose Modification

No dose modifications are allowed.

6.6. Continued Access to Study Intervention after the End of the Study

There will be no access to mRNA-1608 following the end of the study.

6.7. Prior and Concomitant Therapy

At each visit, the study site staff should question the participant regarding any medications taken and vaccinations received and record the information as specified in Section 6.7.1 and Section 6.7.2.

6.7.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

6.7.2. Concomitant Medications and Therapies

At each study visit or safety call, study site staff must question the participant regarding any medications taken and non-study interventions received by the participant and record the following information in the eCRF:

- All concomitant medications, except vitamins and dietary supplements, administered through 28 days (the day of each study injection and the subsequent 27 days) after each study intervention.
- Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Antiviral therapy to treat genital herpes recurrences.
- Systemic steroids (≥10 mg/day of prednisone or equivalent), immunosuppressants, immune-modifying drugs, immunoglobulins, and/or blood products administered from Screening through Day 393/EoS.
- All non-study vaccinations administered from Screening through Day 393/EoS.
- Any concomitant medications or vaccines relevant to or for the treatment of an AESI (Section 8.10.5), a MAAE (Section 8.10.4), or an AE leading to withdrawal from the first dose on Day 1 through Day 393/EoS.
- Any concomitant medications or vaccines relevant to or for the treatment of a SAE will be recorded from the signing of the ICF through Day 393/EoS.

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

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

If a participant takes a prohibited drug therapy, the Investigator and the Medical Monitor will make a joint decision about continuing or withholding the administration of study intervention to the participant based on the time the medication was administered, the drug's pharmacology and PK, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the Investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

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

Use of Antiviral Therapy to Prevent or Treat Genital Herpes

Participants will be asked to refrain from taking suppressive antiviral therapy from the Screening Visit until the EoS and from the use of episodic antiviral therapy to treat genital herpes recurrences during the three 28-day anogenital swabbing periods (Section 5.1). Episodic therapy may be used outside the three 28-day swabbing periods. For the purposes of this study, the recommended therapy for genital herpes recurrences is valacyclovir (500 mg) twice daily for 3 days which may be provided to participants at the discretion of the Investigator. Use of episodic antiviral therapy should be recorded in the participant's eCRF.

6.7.3. Concomitant Medications and Vaccines that may Lead to the Elimination of a Participant from Per-Protocol Analyses

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

- Any investigational or nonregistered product (drug or vaccine) other than the study interventions used during the study period.
- Systemic immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For glucocorticosteroids, this will mean that ≥10 mg/day of prednisone or equivalent is not permitted. Inhaled, nasal, 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.
- An authorized or licensed vaccine administered from Screening through 28 days after the first study injection and 28 days before and 28 days after the second study injection.

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

7.1. Pause Rules

Study pause rules will be continuously monitored by the study Investigators, study team, and Sponsor's IST (Section 8.11.1). The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the IST of potential safety signal events or the triggering of pause rules.

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 a review of the AE(s).

If the study team or IST request that the study be paused due to a safety concern, further randomization and injection in all study injection groups will be suspended regardless of dose level. The Sponsor will notify the CBER within 48 hours in the event of a study pause.

7.1.1. Pause Rule Criteria, Events, and Thresholds - Single Event

The specific type and frequency of single safety events that will result in a pause in further randomization and administration of study injection are summarized in Table 4.

Table 4: Pause Rule Criteria, Events, and Thresholds - Single Event

Pause Rule	Event	Number of Participants
1	Any SAE 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: AE = adverse event; 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 clinical trials" (DHHS 2007).

7.1.1.1. Pause Rules Based on the Occurrence of Events in a Proportion of Participants

The specific type and frequency of safety events that will result in a pause in randomization and study injection administration based on defined threshold levels which are aggregate incidences relative to the number of exposed participants within a study injection group are summarized in Table 5.

Table 5: Pause Rule Criteria, Events, and Thresholds – Proportion of Participants

Pause Rule	Event	Number or Percentage of Participants[a]
4	Any severe unsolicited non-serious AE [b] for which there is a reasonable possibility of a causal relationship to the study injection.	≥2 of the initial 10 participants within the same study injection group or ≥20% of participants within the same study injection group after the initial 10 participants have received study injection
5	Any Grade 3 or higher[c] solicited local AR, starting within the 7-day post dosing 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 within the same study injection group or ≥20% of participants within the same study injection group after the initial 10 participants have received study injection[d]
6	Any Grade 3 or higher[c] solicited systemic AR, starting within the 7-day post dosing 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 within the same study injection group or ≥20% of participants within the same study injection group after the initial 10 participants have received study injection[d]

Abbreviations: AE = adverse event; AR = adverse reaction; FDA = Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory Activities; US = United States.

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

b. Includes Grade 3 laboratory abnormality as described in Section 8.10.13.

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 during the study conduct an Investigator or the study 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 randomization and study injection in all study arms 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 randomization and injection will be paused as follows:

- For pause rule criteria 1, 2, 3, and 4, study randomization, and injection will be paused for all study arms.
- For pause rule criteria 5 and 6 (tolerability criteria based on defined threshold levels for solicited ARs, which are either absolute numbers of events or aggregate incidences relative to the number of exposed participants within a study injection group), study randomization and injection will be paused for all study injection groups assigned to the same or higher dose level (in the case of mRNA-1608) as the study arm in which the pause rule criterion was met. Study randomization and injection may resume for study injection 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, if the Investigator confirms a data entry error), then the IST may recommend resuming dosing as appropriate.

All study Investigators will be informed of any pauses, and the IRT system will prevent additional study injections as appropriate. The Sponsor will comply with local/regional/national requirements for notification of regulatory authorities upon institution of an official study pause. In all cases of a study pause, randomization and injection will not resume until Investigators have been informed of the basis for resuming 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 enrolled but not randomized for more than 56 days as the result of a study pause, the participant will maintain enrolled status and may still be randomized in the study as long as the participant continues to provide consent and is still eligible to participate in the study. If before or during the pause, the participant collected at least 45 out of 56 anogenital swabs during the 28-day swabbing period prior to study injection (Day -27 to Day 0), those data may be used as baseline values for that participant and further collection of baseline anogenital swabs and eDiary entries will not be required.

7.2. Criteria for Delay or Withholding of Study Injection

Body temperature must be measured at the dosing visit before study injection. The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may be injected at a later date within the time window specified in the SoE (Table 1):

- Acute moderate or severe infection with or without fever at the time of dosing.
- Fever, defined as body temperature ≥38.0°C (100.4 F) at the time of dosing.
- Symptomatic genital herpes recurrence at the time of dosing.
- Receipt of any licensed or authorized vaccine within 28 days of any study injection.

Participants with a minor illness without fever, as assessed by the Investigator, can be administered the study injection. Participants with a fever ≥38.0°C (100.4°F) or a symptomatic genital herpes recurrence will be contacted within the time window acceptable for participation and reevaluated for eligibility. If the Investigator determines that the participant's health on the day of administration temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

The Investigator, in consultation with the Medical Monitor, should withhold the study injection if the participant meets any of the following criteria:

- Becomes pregnant.

- Develops symptoms or conditions listed in the exclusion criteria (Section 5.2).
- Experiences a clinically significant change in clinical laboratory test results, vital sign measurements, or general condition that, in the judgment of the Investigator, requires withholding of study injection.

Participants who report a SAE assessed as related to study intervention will be discontinued from further study injection.

The reason(s) for withholding the study injection will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the Investigator could delay the study injection within the visit window or withhold study injection based on a joint decision of the Investigator and the Medical Monitor.

7.3. Participant Discontinuation/Withdrawal from the Study

A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The Investigator will request the participant to complete all study procedures pending at the time of withdrawal.

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

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

- AE (specify)
- SAE (specify)
- Solicited AR or reactogenicity event (specify)
- AESI (specify)
- Death
- LTFU
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants discontinued from the study because of AEs (including SAEs, AESIs, SARs, or reactogenicity events) must be clearly distinguished from participants who are discontinued for other reasons. Investigators will follow-up with participants who are withdrawn from the study as a result of an AE, AESI, SAE, SAR, or reactogenicity event until resolution of the event.

A participant discontinuing from the study may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 10.1.6).

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

7.4. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone/telehealth visit calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone/telehealth visit calls and registered letters) should be documented in the participant's medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence, as described above, has been completed.

If a participant does not complete a visit within the defined study visit window specified in the SoE (Table 1), every effort should still be made to complete the assessments for that visit (even though outside of the defined visit window). 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 (ie, relative to their Day 1 or Day 57 visit).

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an informed consent form (ICF; Section 10.1.6). Participants will undergo study procedures at the time points specified in the SoE (Table 1).

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), Investigators may convert study site visits to home visits or telehealth visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of participants and study site staff or to comply with state or municipal mandates.

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, symptoms of genital herpes, or new or ongoing AEs. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in the SoE (Table 1). Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log and record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Screening

Following the Screening Visit (up to 56 days before the Day 1 visit), all screening requirements, including the Screening Status eCRF to indicate if a participant is either a screen failure or not, must be completed.

The Screening Visit and Day 1 Visit will not be performed on the same day. The Medical Monitor should be contacted if screening cannot be completed in 1 day.

8.2. Confirm Inclusion and Exclusion Criteria

All inclusion and exclusion criteria described in Section 5.1 and Section 5.2 must be met before randomization (Day 1 Visit). Any changes to participant health or medications that could affect eligibility for the second injection (Day 57) will be reviewed prior to study injection. A full review of inclusion and exclusion criteria is not required on Day 57.

8.3. Demographic and Baseline Data

Demographic information relating to the participant's sex, age, ethnicity, and race will be recorded at Screening on the appropriate eCRF page.

8.4. Medical History

Medical history (including verbal history) from each participant will be collected and recorded on the appropriate eCRF page. Significant findings that were present prior to study injection must be included in the Medical History eCRF page.

8.5. Safety Assessments

8.5.1. Physical Examination

A full physical examination will be performed (according to standard medical practice, including assessment of height and weight) at the Screening Visit and on Day 1. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, musculoskeletal system, and extremities. At screening, BMI will be calculated using the formula weight (kg)/(height [m])^2.

Treatment of any abnormality observed during physical examination should be performed according to local medical practice outside the study or by referral to an appropriate healthcare provider at the discretion of the Investigator.

8.5.2. Vital Signs

Vital sign measurements will include the assessment of body temperature (oral being the preferred route), systolic and diastolic blood pressures, pulse rate, and respiratory rate. The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the SoE (Table 1). On the days of study injection, vital sign measurements will be collected once before injection and approximately 60 minutes after injection (before participants are discharged from the study site). Participants who are febrile (fever is defined as a body temperature ≥38.0°C/100.4°F) or experiencing a symptomatic genital herpes recurrence before administration of the study injection on the scheduled injection days must be rescheduled within the relevant window period to receive the study injection. Afebrile participants with minor illnesses may be injected at the discretion of the Investigator.

Vital signs may be collected at other study visits in conjunction with a symptom-directed physical examination. When applicable, vital sign measurements should be performed before blood collection. The information collected will be recorded in the eCRF.

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

8.5.3. Electrocardiograms

A 12-lead ECG will be obtained after 10 minutes of supine rest at Visit 1/Day 1 prior to administration of study injection. Skin preparation should be thorough and electrode placement should be according to standard 12-lead ECG procedure. The purpose of the ECG is to have a baseline comparison for possible subsequent clinical evaluations of suspected myocarditis/pericarditis. Interpretation of the ECG is not required prior to administration of study injection. 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, as per the inclusion and exclusion criteria (Section 5.1 and Section 5.2).

8.5.4. Use of Electronic Diaries

During the course of the study, participants will be asked to use an eDiary to report ARs and genital herpes signs and symptoms/recurrences. At the time of consent, the participants must confirm that they will be willing to complete:

- Daily Solicited AR eDiary for 7 days after each study injection to report ARs.
- Daily GHSS eDiary and weekly PGI-S and PGI-C eDiaries for 28-day periods (as shown in SoE, Table 1.) to report genital herpes signs and symptoms.
- Daily Genital Herpes Recurrence eDiary after the first study injection (excluding 28-day periods) to report genital herpes recurrences.

eDiaries will be completed using either an application downloaded to their own device or using a device that is provided at the time of enrollment and developed for ease of use. Details regarding the use of eDiaries and timing of self-collected anogenital swabs are provided in Section 8.5.4 and Section 8.8.5.

Reporting ARs

At the Enrollment Visit (Day -27), the participants will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 8.10.3).

Participants will be instructed on Day 1 on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each dosing visit, participants will be instructed (Day 1) and reminded (Day 57) on how to document and report solicited ARs within a provided eDiary. Participants will record data into the eDiary starting approximately 60 minutes after administration of study injection under supervision of the study site staff to ensure successful entry of assessments. Participants will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of study injection and for 6 days after study injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as described in Section 8.10.3.

- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration) will be performed using the ruler and instructions provided by the study site.
- Any medications taken to treat or prevent pain or fever on the day of study injection or for the next 6 days.

The eDiary will be the only source document allowed for solicited systemic or local ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. Quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the next day may be excluded from the analyses of solicited ARs.

Study site staff will review eDiary data with participants at a visit 7 days after the study injection.

Reporting Genital Herpes Signs and Symptoms/Recurrences

Participants will use eDiaries during the study to report information on genital herpes recurrences. A daily GHSS eDiary will be used to report the presence or absence of genital herpes lesions and severity of genital herpes symptoms during the following 28-day periods:

- Prior to randomization and study injection (approximately Day -27 to Day 0).
- During Month 3 to Month 4 (approximately Day 85 to Day 112).
- During Month 7 to Month 8 (approximately Day 197 to Day 224).

Participants will be trained/retrained on daily use of the GHSS eDiary on Day -27, Day 85, and Day 197. Information collected during these 3 periods will be used to determine the genital herpes lesion rate (proportion of days with lesions present) and associated symptoms before and after study injection.

Participants will also use a weekly PGI-S eDiary during the three 28-day periods and a PGI-C eDiary during the two 28-day periods post injection (PGI-C) to contextualize data obtained from the GHSS eDiary. Participants will receive training/retraining on use of PGI-S and PGI-C eDiaries together with training on the use of the GHSS eDiary.

At approximately 14 days (±3 days) after the start of each 28-day period (approximately Day -13, Day 99, Day 211), trained study site staff will conduct an anogenital swab and eDiary follow-up call via telephone or telehealth visit to discuss participant progress and with use of the GHSS, PGI-S and PGI-C eDiaries as relevant (Section 8.7).

Beginning after the first study injection (Day 1), but excluding the 28-day periods described above, all participants in the study will use a Daily Genital Herpes Recurrence eDiary for reporting the presence or absence of genital herpes lesions (without severity of symptoms):

- During Month 0 to Month 3 (approximately Day 1 to Day 84).

- During Month 4 to Month 7 (approximately Day 113 to Day 196).
- During Month 8 to Month 14/EoS (approximately Day 225 to Day 393).

Participants will receive training on the use of the Daily Genital Herpes Recurrence eDiary on Day 1 and retraining on subsequent visits. Information collected from the GHSS eDiary and the Daily Genital Herpes Recurrence eDiary will be used to determine the frequency of genital herpes recurrences and the time to first genital herpes recurrence beginning after the second study injection.

8.6. Study Intervention

After completing all prerequisite procedures prior to study intervention, the study intervention will be administered via a single IM injection into the deltoid muscle. Two doses of mRNA-1608 or control (BEXSERO) will be administered to all participants at 0 and 2 months.

A detailed description of the study intervention procedure is provided in Section 6.3.2.

8.7. Safety Calls

A safety call is a telephone or telehealth visit call made to the participant by trained study site staff. This call will follow a script, which will facilitate the collection of relevant safety information. Safety calls will follow a schedule for each participant, as shown in the SoE (Table 1). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation of study intervention or withdrawal from the study; information on concomitant medications associated with those events; receipt of any non-study vaccinations; receipt of any systemic steroids (≥10 mg/day of prednisone or equivalent), immunosuppressants, immune-modifying drugs, immunoglobulins, and/or blood products (Section 8.10.7). All safety information collected from the telephone/telehealth visit contact must be documented in source documents as described by the participant and not documented on the script used for the safety call contact. An unscheduled follow-up safety call may be triggered if an eDiary record results in identification of a relevant safety event.

At approximately 14 days (±3 days) after the start of each 28-day anogenital swab collection period (approximately Day -13, Day 99, Day 211), trained study site staff will conduct an anogenital swab and eDiary follow-up call via telephone or telehealth visit to discuss participant progress with daily self-collection of anogenital swabs and use of the GHSS, PGI-S and PGI-C eDiaries (as relevant). A reported safety event and/or concomitant medication will be documented appropriately in source documents. An unscheduled follow-up call may be triggered in the case of a safety event or if the participant has questions about anogenital swabbing or eDiary use that cannot be immediately answered.

8.8. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoE (Table 1):

- Solicited local and systemic ARs (Section 8.10.3) that occur during the 7 days after the study injection (ie, the day of study injection [Day 1] and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.

- Unsolicited AEs observed or reported within 28 days after the study injection, with the day of study injection as Day 1 (Section 8.10.1).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 393/EoS.
- MAAEs from Day 1 through 6 months after the final study injection or withdrawal from the study (Section 8.10.4).
- AESIs from Day 1 through Day 393/EoS or withdrawal from the study (Section 8.10.5).
- SAEs from the signing of ICF through Day 393/EoS or withdrawal from the study (Section 8.10.2).
- Abnormal results of safety laboratory tests (Section 8.8.2).
- Vital sign measurements (Section 8.5.2).
- Physical examination findings (Section 8.5.1).
- Details of all pregnancies in female participants will be collected from Day 1 through Day 393/EoS. All pregnancies must be followed to determine the outcome (Section 8.8.1); however, pregnancy related data received after the end of the study may not be collected in the clinical database.

8.8.1. Pregnancy Screen and Testing

The effects of the study interventions on the unborn child and/or newborn baby are not known. Therefore, is important that study participants are not pregnant or and do not become pregnant during the study. A point-of-care urine pregnancy test will be performed for all female participants of childbearing potential at the Screening Visit and before study injection on Day 1 and Day 57. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. Additional pregnancy testing during the study may also be performed if required by local regulatory requirements. The participant's FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status (Section 10.2).

Further details on reporting and follow-up of pregnancy are provided in Section 8.10.6.

8.8.2. Safety Laboratory Assessments

Blood samples for safety testing will be taken for all participants at the Screening Visit. Additional blood samples for safety testing will be collected on Days 8, 57, and 64 for the first approximately 100 participants randomized in the study (approximately 25 participants per study arm) as indicated in the SoE (Table 1). Tests will include WBC count, hemoglobin, platelets, ALT, AST, total bilirubin, alkaline phosphatase, and creatinine. Laboratory tests will be performed by the central laboratory, unless otherwise specified.

8.8.3. Blood Sampling Volumes

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 in

the ICF. 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 Manual.

8.8.4. Ancillary Supplies for Participant Use

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

Participants will be provided kits for the collection of swabs from the anorectal and genital area (2 individual swabs per day) during the three 28-days periods as described in Section 8.8.5. Participants will be provided additional kits for collecting samples (1 swab from genital and rectal areas) upon onset of genital herpes symptoms.

8.8.5. Clinical Assessments

The following outcomes will be measured for each participant:

- Frequency of genital herpes recurrences starting 14 days after the second study injection.
- Genital herpes lesion rate (proportion of days with lesions present during the three 28-day swabbing periods).
- HSV-2 genital shedding rate (proportion of HSV-2 DNA positive anogenital swabs during three 28-day swabbing periods).
- Frequency of virologically-confirmed genital herpes recurrences after the second study injection.

Participants will use an eDiary to report the presence or absence of genital herpes lesions and severity of genital herpes symptoms as described in Section 8.5.4.

Participants will self-collect swabs from the anorectal and genital areas twice a day (2 individual swabs per day) for measurement of HSV-2 viral shedding (any HSV-1 shedding will also be measured but analyzed separately from HSV-2 shedding) during the following 28-day periods:

- Prior to randomization and study injection (approximately Day -27 to Day 0).
- During Month 3 to Month 4 (approximately Day 85 to Day 112).
- During Month 7 to Month 8 (approximately Day 197 to Day 224).

Participants will receive materials and training/retraining on how to collect and store swabs using provided kits as specified in the SoE (Table 1). On the first day of each 28-day swabbing period (Day -27, Day 85 and Day 197), participants will collect the first swab in the clinic and the second swab at home, preferably in the evening. Participants who collect less than 45 of the anticipated 56 anogenital swabs between Enrollment visit (Day -27) and Day 1 will not be randomized to receive study injection.

At approximately 14 days (± 3 days) after the start of each 28-day period (approximately Day -13, Day 99, Day 211), trained study site staff will conduct a an anogenital swab and eDiary

follow-up call via telephone or telehealth visit to discuss participant progress with daily self-collection of anogenital swabs (Section 8.7).

Participants experiencing symptoms consistent with genital herpes should have an anogenital swab(s) collected as soon as possible (within 24 hours) but no later than 72 hours after the onset of symptoms, for detection of HSV. Expectations for USV and self-collection are as follows:

- After the first study injection (Day 1), but before the second study injection (Day 57), participants will have the option to:
  - Report for a USV for clinical evaluation of genital herpes including collection of a swab sample for detection of HSV DNA; or
  - Self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA.
- Participants experiencing symptoms consistent with genital herpes for the first time starting after the second study injection (Day 57), should report for a USV for clinical evaluation of genital herpes including collection of swabs after onset of symptoms for detection of HSV DNA and HSV culturable virus.
- Thereafter, participants experiencing symptoms consistent with genital herpes will have the option to:
  - Report for a USV for clinical evaluation of genital herpes including collection of a swab sample for detection of HSV DNA; or
  - Self-collect 1 anogenital swab after onset of symptoms for detection of HSV DNA.

Participants should self-collect the anogenital swab or report for a USV as soon as possible (within 24 hours), but no later than 72 hours after the onset of symptoms. During the three scheduled 28-day swabbing periods, participants experiencing symptoms of genital herpes will continue to self-collect anogenital swabs in addition to completing the unscheduled swab collection.

Genital recurrences will not be reported as AEs or MAAEs. Additional details on the self-collection of anogenital swabs for PCR testing will be provided in the Laboratory Manual. Details regarding use of eDiaries and timing of self-collected anogenital swabs are provided in the Study Schema (Section 1.2) and SoE (Table 1).

8.9. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoE. The following analytes will be measured:

- Serum bAb levels against vaccine glycoprotein antigens as measured by a multiplex ligand binding assay using ECL detection.
- Serum nAb levels against HSV-2 as measured by a cell-based assay using green fluorescent protein detection.
- Cell-mediated immunogenicity in a subset of participants (up to 40 per arm).

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual date and time of each sample will be collected. Unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate laboratory manual. Measurement of humoral and cell-mediated immunogenicity will be performed in a laboratory(ies) designated by the Sponsor. 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 Manual.

8.10. Safety Definitions and Related Procedures

The definitions of AEs, SAEs, unsolicited and solicited ARs, AESIs, MAAEs, are described in this section.

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 AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue the study (see Section 7.3). 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 8.10.7 and Section 8.10.11.

8.10.1. Adverse Event

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

A TEAE is defined as any event not present before exposure to the study intervention or any event already present that worsens in intensity or frequency after exposure.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition, after study injection.
- New conditions detected or diagnosed after administration of study injection even though they may have been present before the start of the study.

Events NOT Meeting the Adverse Event Definition

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

An AR is any AE for which there is a reasonable possibility that the study intervention caused the AE (Section 8.10.3). 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 (Section 8.10.3) in the protocol; or is specified as a solicited AR in the protocol, but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after each dose of the study intervention).

8.10.2. Serious Adverse Events

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

- **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 the study intervention.
- **Is life-threatening**
  - An AE is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  - In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least 1 overnight stay as an inpatient 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.

8.10.3. Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that participants are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms occurring after the study injection. An eDiary will prompt daily participant reporting of solicited ARs. Participants will record such occurrences in the eDiary on the days of administration of study injection and on each of the 6 days after dosing.

Severity grading of reactogenicity events will be automatically assigned upon participant entry into the eDiary based on the grading scales presented in Table 6, which are modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All ARs (local and systemic) will be considered causally related to dosing.

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

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

If the participant reported an event that started 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 EDC:

- Solicited local or systemic AR that results in a visit to an HCP (MAAE).
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days post study 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 6: Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4[a] (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	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

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

Note: Events listed above but starting >7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event reported on the AE page will be determined per assessment by the Investigator.

[a.] Grading of Grade 4 events will be determined per Investigator and assessment is recorded in the EDC.

Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

8.10.4. Medically Attended Adverse Events

A MAAE is an AE (serious or nonserious) that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments not required per protocol (eg, rash assessment, abnormal laboratory follow-up) and visits to HCPs 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 the EDC.

8.10.5. 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 described in Section 10.3.

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in (Section 8.10.11).

8.10.5.1. Anaphylaxis

All suspected cases of anaphylaxis associated with study injection administration should be recorded as MAAEs and AESIs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an AESI and/or SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, per Section 8.10.11. The Investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as 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 hypersensitive reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

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

8.10.5.2. Myocarditis/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 Working Case Definitions. The event should also be reported as an SAE if it meets seriousness criteria (see Section 8.10.11).

As an AESI/SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 8.10.12 and Section 8.10.11. The Investigator will submit any updated myocarditis, pericarditis, or myopericarditis case data to the Sponsor within 24 hours of it being available.

For reporting purposes, any events suspicious for myocarditis, pericarditis, or myopericarditis should be reported as an AESI. The CDC case definition is displayed in Section 10.4 as CDC guidance (Gargano et al, 2021). However, any suspected case should be reported, even if it does not meet all criteria. These definitions are intended to serve as a guide to help reporting of suspected cases of myocarditis, pericarditis, or myopericarditis, but the diagnosis of suspected cases is left to the Investigator's clinical judgment.

The Investigator's medical judgment must be applied when assessing participants reporting symptoms concerning for myocarditis, pericarditis, or myopericarditis contained within the CDC case definition. Diagnostic evaluation (eg, ECG, echocardiogram) and laboratory testing (eg, troponin) included in the CDC definition (Section 10.4) should promptly be obtained if considered clinically indicated in any participant with concerning signs/symptoms. Referral to a cardiologist should be considered in those with positive test results or clinically significant symptoms without other identifiable causes. Additional testing and evaluation may be indicated.

Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis, pericarditis, or myopericarditis will be discontinued from further study injection 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 which are reported in ongoing interventional clinical trials per the CEAC charter to determine if they meet CDC criteria for "probable" or "confirmed" events (Section 10.4).

8.10.6. Recording and Follow-up of Pregnancy

The effects of the mRNA-1608 or BEXSERO control on the unborn child and on the newborn baby are not known. It is important that participants are not pregnant and do not become pregnant during the course of the study.

Female individuals who have a positive pregnancy test at the Screening Visit should not be enrolled; participants who have a positive pregnancy test at any time during the study should receive no further dosing with study injection but should be asked to remain in the study and be monitored for safety. Pregnancy testing is scheduled to occur at the Screening Visit, Day 1, and Day 57 (Table 1). Additional pregnancy testing during the study may also be performed if required by local regulatory requirements.

Details of all pregnancies reported in female participants will be collected after the first study injection and until Day 393/EoS.

- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 8.10.11).

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.

8.10.7. Eliciting and Documenting Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

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 study injection through 28 days (the day of each study injection and the subsequent 27 days) after study injection. Serious AEs will be collected from the time of consent until the last day of study participation.

SAEs, AESIs, AEs leading to discontinuation of study injection, and AEs leading to withdrawal from the study will be collected from participants until the end of their participation in the study. MAAEs will be collected from Day 1 through 6 months after the final study injection.

With the exception of SAEs (will be collected from the signing of ICF), any other clinically significant finding identified by a healthcare professional before the first study injection will be captured as medical history. Any AEs occurring before administration of the study injection will be analyzed separately from the AEs occurring after administration of the study injection.

At every study site visit or telephone/telehealth visit contact, participants will be asked a standard question to elicit any medically related changes in their well-being 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 non-study 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.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, AESIs, and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.4). All contacts or contact attempts concerning the follow-up of AEs and SAEs should be recorded in the participant's source documentation.

8.10.8. 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 8.10.11), 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 Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), clinical laboratory test results, and vital sign

measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 8.10.3.

The determination of severity for all unsolicited AEs should be made by the Investigator based upon medical judgment and the definitions 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 site 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.

8.10.9. Assessment of Causality

The Investigator's assessment of an AE's relationship to the study intervention 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 study intervention [mRNA-1608 or BEXSERO control]) caused the event for all AEs and SAEs. The relationship will be characterized using the following classification:

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

8.10.10. Reporting Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study intervention 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, Investigator specified assessment of severity (Section 8.10.8, impact on activities of daily living) and relationship to the study intervention (Section 8.10.9), time of resolution of the event, seriousness, as well as

any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the Investigator to be not clinically significant. The MedDRA will be used to code all unsolicited AEs.

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. Refer to Section 8.10.13 for reporting of medical occurrences that begin before study injection but after obtaining informed consent.

8.10.11. Reporting Serious Adverse Events

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

Any AE considered serious by the Investigator or that meets SAE criteria (Section 8.10.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The Investigator will assess whether there is a reasonable possibility that the study intervention caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The Investigator is responsible for notifying the IRB or IEC 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.

Regulatory reporting requirements for SAEs are described in Section 8.10.16.

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 study intervention or study procedures, or that caused the participant to discontinue the study.

8.10.12. Reporting Adverse Events of Special Interest

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.

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

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

All AESIs, AEs leading to study discontinuation from the study injection or AEs leading to discontinuation from the study will be collected from the first study injection until the last day of

study participation. MAAEs will be collected from the first study injection through 6 months after the final study injection (Table 1).

All other (unsolicited) AEs will be collected from the time of the first study injection through 28 days (the day of each study injection and the subsequent 27 days) after study injection.

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

With the exception of SAEs, medical occurrences that begin before study injection but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

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

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

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

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

8.10.14. Method of Detecting AEs and SAEs

The eDiary has specifically been designed for this study by the Sponsor to collect solicited ARs. Refer to Section 8.5.4 for further details on the use of eDiary. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations. Details on recording of solicited ARs in an eDiary are included in Section 8.10.3.

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

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

8.10.15. Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs, SAEs, and AESIs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 7.4. In addition, follow-up on SAEs and AESIs should continue, even if the intended duration of the safety follow-up for the study has ended, until the event is considered resolved, otherwise explained, or the participant is LTFU.

8.10.16. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARS) according to local regulatory requirements and Sponsor policy and will be forwarded to Investigators, as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.11. Safety Oversight

In addition to the safety oversight provided by the study team, safety monitoring for this study will include IST and the study team members, inclusive of at a minimum, the Sponsor Medical Monitor and a CRO Medical Monitor.

8.11.1. Internal Safety team

An IST composed of at least 3 Sponsor physicians who are independent from the study team will provide additional safety oversight. The study team will conduct ongoing blinded safety reviews during the study and will be responsible for notifying the IST of potential safety signal events or the triggering of pause rules. The IST will perform an unblinded review of all safety data after all participants undergoing safety laboratory testing (approximately 100 participants) have completed the Day 8 visit. Randomization will be paused while this review is conducted. Randomization of the full cohort will resume following IST review if it does not reveal any safety signals of concern and if study pause rules are not met. The IST may perform additional

safety data reviews due to safety concerns that arise during the course of the study or as requested on ad hoc basis by the study team.

An unblinded statistician may support the determination if study pause rules have 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 a review of the AE(s).

If the study team or IST request that the study be paused due to a safety concern, further enrollment and injection in all study injection groups will be suspended regardless of dose level (Section 7.1). The Sponsor will notify the CBER within 48 hours in the event of a study pause.

8.12. Treatment of Overdose

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

However, in the event of an overdose, the Investigator should:

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

Dosage deviations will be tracked as protocol deviations.

8.13. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.14. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.15. Biomarkers

Immunogenicity assessments are described in Section 8.9. Biomarker assessments (to be determined) will be evaluated in this study.

8.16. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Blinding and Responsibility for Analyses

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

- Unblinded personnel (of limited number) will be assigned to study intervention accountability procedures and will prepare the study intervention for all participants. These personnel will have no study functions other than study intervention management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the study intervention to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded medically qualified study site personnel will administer the study intervention. They will not be involved in assessments of any study endpoints.
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.

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

Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results to the blinded Investigators, study site staff, clinical monitors, or participants. Details will be included in the data blinding plan.

The IST may independently review unblinded statistical outputs of safety data on an ad hoc basis if pause rules are triggered and/or at the request of the study team or the IST. Section 8.11.1 provides additional information on IST and safety review.

9.2. Statistical Hypotheses

No formal hypotheses will be tested. The number of proposed participants is considered sufficient to provide a descriptive summary of the safety and immunogenicity of different dose levels of mRNA-1608.

9.3. Sample Size Determination

Approximately 225 participants will receive mRNA-1608. With at least 75 participants in each of 3 dose levels, there is at least 98% probability to observe at least 1 participant with an AE at a true AE rate of 5% for each dose.

For evaluation of recurrence rate, lesion rate, and viral shedding rate, the sample size will provide adequate power based on the following assumptions:

- For the recurrence rate, based on Benedetti et al, 1994 and Benedetti et al, 1999 assume the semi-annual rate is 2.5 in the negative binomial distribution; with 75 participants per arm, it will provide >90% power at one-sided significance level of 2.5% if there is a reduction of 60% in the frequency of recurrence in the first 6 months after study injection comparing an mRNA-1608 arm with the control arm.
- For genital lesion rate, assume the rate is 11% at baseline in the repeated binary measurements model (Magaret et al 2011); with 75 participants per arm, it will provide >90% power at one-sided significance level of 2.5%, if there is a 65% reduction in lesion rate at Month 6 after study injection administration comparing to the baseline lesion rate.
- For viral shedding rate, assume the baseline shedding rate (Day -27 to Day 0) is 10% (Tronstein et al 2011) in the repeated binary measurements model (Magaret et al 2011); with 75 participants per arm, it will provide >90% power at one-sided significance level of 2.5%, if there is a 60% reduction in viral shedding rate at Month 6 after study injection administration comparing to the baseline shedding rate.

9.4. Analysis Populations

Table 7 describes the analysis populations.

Table 7: Analysis Sets

Set	Description
Randomization Set	The Randomization Set consists of all participants who are randomly assigned.
FAS[a]	The FAS consists of all randomly assigned participants who receive the study intervention.
mFAS[a]	The modified FAS consists of all participants in the FAS who receive 2 doses of the study intervention.
PP Set[b]	The PP Set consists of all participants in the FAS who comply with the vaccination schedule, comply with the timings of immunogenicity blood sampling to have a baseline and at least 1 post-injection assessment, and have no major protocol deviations that impact the immune response.
Safety Set[c]	The Safety Set consists of all participants who receive the study intervention.
Solicited Safety Set[d]	The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data.

Abbreviations: AR = adverse reaction; FAS = Full Analysis Set; mFAS = modified Full Analysis Set; PP = Per-Protocol.

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

9.5. Statistical Methods

General Considerations: All analyses will be performed by treatment arm, unless otherwise specified. 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). Additional analyses, as well as exploratory analyses will be described in the SAP.

9.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, gender, race, ethnicity, height, weight, and BMI) and baseline characteristics will be summarized by study intervention group and overall.

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

9.5.2. 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 intervention group unless otherwise specified. Participants will be included in the study intervention 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 (including any clinical safety laboratory abnormalities), treatment-related AEs, severe AEs, SAEs, AESIs, MAAEs, AEs leading to withdrawal from study participation, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR, solicited systemic AR, and solicited AR during the 7-day follow-up period after the study injection will be summarized. A 2-sided 95% 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 clinical trials 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 intervention group and visit at each timepoint; in general, Day 7 will be compared with Screening Visit, and Day 64 will be compared with Day 57.

9.5.3. 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.

For the immunogenicity endpoints, geometric mean of mRNA-1608 antigen-specific bAb and nAb titers with corresponding 95% CI at each timepoint and GMFR of specific antibody titers with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided by 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.

For calculation of GMTs, antibody titers reported as below the LLOQ will be replaced by 0.5 × LLOQ. Further details will be described in the SAP.

9.5.4. Clinical Endpoint Analyses

The analyses of clinical endpoints will be based on the mFAS. If the number of participants in the FAS and mFAS differ (defined as the difference divided by the total number of participants in the mFAS set) by more than 10%, supportive analyses of clinical endpoints may be conducted using the FAS.

Frequency of genital herpes recurrences will be summarized descriptively during 6 months and 12 months after the second study injection, respectively for each arm. As supportive analyses, model-based analytical approaches will be applied to compare the mRNA-1608 arms with the control arm at each timepoint.

Genital herpes lesion rate (proportion of days with lesion present during the 28-day swabbing periods) and HSV-2 genital shedding rates (proportion of HSV-2 DNA positive anogenital swabs during the 28-day swabbing periods) will be summarized descriptively for the 28 days prior to first study injection (baseline shedding rate), and at 2 months and 6 months after the second study injection, respectively for each arm. The rate change from baseline will also be summarized for each arm. As supportive analyses, model-based analytical approaches will be

applied to evaluate the change from baseline for the mRNA-1608 arms at each timepoint, as well as comparison between the mRNA-1608 arms with the control arm at each timepoint.

The time to the first genital herpes recurrence (starting after the second study injection) will be estimated by Kaplan-Meier method for each arm. Recurrence-free probability at 6 months and 12 months after the second study injection will be provided. A stratified Cox proportional hazards model will be used to estimate the hazard ratio of mRNA-1608 arms versus the control arm.

9.5.5. Exploratory Analyses

Exploratory analyses will be described in the SAP.

9.5.6. Subgroup Analyses

Subgroup analyses of the clinical endpoints and immunogenicity endpoints will be described in the SAP.

9.6. Planned Analyses

9.6.1. Interim Analyses

There are 2 planned IAs (IA1 and IA2) of safety, immunogenicity, and clinical endpoint data. IA1 will occur after all participants complete the 28-day swabbing period 2 months after the second study injection (approximately Day 112). IA2 will occur after all participants complete the 28-day swabbing period, 6 months after the second study injection (approximately Day 224). Data from IA2 will be used to inform dose selection for the Phase 3 study.

The IAs will be performed by a separate team of unblinded programmers and statisticians. Except for a limited number of Sponsor and CRO personnel who will be unblinded to perform the IA, the study site staff, Investigators, study monitors, and participants will remain blinded until after the final database lock for final analysis. Details will be included in a study data blinding plan.

The SAP will describe the planned interim and final analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Study Governance Considerations

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB, and all other applicable local regulations.

10.1.2. Study Monitoring

Before an investigational study site can enter a participant into the study, the Sponsor or its representatives will visit the study site for the following:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor, the designated CRO, and the Investigator.

According to ICH GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the Investigator and the Sponsor in the

maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the Investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data and/or documents. In addition, the study monitor will explain to and interpret for the Investigator all regulations applicable to the clinical evaluation of the study intervention as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the study site, for the following purposes:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that study intervention accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the Sponsor and that those SAEs that meet criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.1.3. Audits and Inspections

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

Authorized representatives of the Sponsor, a regulatory authority, and the IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and whether data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 [R2],

and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

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

10.1.4. Financial Disclosure

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

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

10.1.5. Recruitment Strategy

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

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

10.1.6. Informed Consent Process

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

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

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

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

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

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

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

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

A participant who is rescreened is not required to sign another ICF if the rescreening and Day 1 occurs within 56 days from the previous ICF signature date and the participant is able to complete the 28-day baseline self-collection of anogenital swabs and daily reporting of genital herpes signs and symptoms using the GHSS eDiary prior to Day 1.

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

10.1.7. Data Protection

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

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

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

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being.

Each participant will be asked to complete a form allowing the Investigator to notify the participant's primary HCP of his/her/their participation in this study.

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

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

- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.8. Sample Retention and Future Biomedical Research

Samples may be used for purposes related to this research.

The Sponsor may store laboratory samples for the time frame specified in the ICF to address study objectives or further scientific questions related to the mRNA-1608 vaccine or infection-related immune responses. Identifiable samples can be destroyed at any time at the request of the participant. During the study or the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other measures of adaptive immunity to viruses to include humoral and cellular immune assay methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently randomized. A decision to perform such exploratory research may arise from new scientific findings related to vaccine class, as well as reagents for biomarker assay development.

10.1.9. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), etc., as well as some national registries.

10.1.10. Data Quality Assurance

Data collection is the responsibility of the clinical study site staff at the site under the supervision of the 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 the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the clinical monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site staff 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be transferred to another location or party without written notification to the Sponsor.

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

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

10.1.11. Source Documents

Source documents are original documents or certified copies and include, but are not limited to, eDiaries, medical and hospital records, screening logs, ICFs, telephone/telehealth visit contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the case report form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

10.1.12. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.13. Study and Site Closure

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

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.

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 the following:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or ICH GCP guidelines.

- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further mRNA-1608 development.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

10.1.14. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

10.2. Appendix 2: Contraceptive and Barrier Guidance

Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (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 follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - Documented bilateral oophorectomy.
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

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

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[a] 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[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[a] 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[b] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[b] – 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. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

b. Male 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 (LAM) are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure from friction).

10.3. Appendix 3: Adverse Events of Special Interest Terms

Investigators should report all events that fall into the categories presented in Table 8 as an AESI per the reporting processes in Section 8.10.11. 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 8: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts $<125\times10^9$. • 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 (GBS). • 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 investigational product (IMP) administration as defined per protocol (Section 8.10.5.1). • Follow reporting procedures in Section 8.10.11.
Myocarditis/Pericarditis	• Myocarditis. • Pericarditis. • Myopericarditis.

Abbreviation: HELLP = hemolysis, elevated liver enzymes, and low platelet count.

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

Table 9: 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. cMRI findings consistent with myocarditis.	**AND** ≥ 1 new finding of Histopathologic confirmation of myocarditis†. cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin).
	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 participants who meet criteria for both myocarditis and pericarditis.

Abbreviations: 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 Center for Disease Control and Prevention criteria for "probable" or "confirmed" events, (Gargano et al 2021), and provide the assessment to the Sponsor. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

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

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

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

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

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

Reference: (Gargano et al 2021).

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