ModernaTX, Inc.

Protocol mRNA-1608-P101

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

Statistical Analysis Plan

SAP Version 1.0
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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
AST	Aspartate aminotransferase
bAb	Binding antibody
BMI	Body mass index
BMP	Blinding maintenance plan
CI	Confidence interval
cm	centimeters
CMI	Cell-mediated immunogenicity
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
DHHS	Department of Health and Human Services
DIC	Disseminated intravascular coagulation
DBL	Database lock
DBP	Data blinding plan
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
eDiary	Electronic diary
ECL	Electrochemiluminescence
EoS	End of Study
FAS	Full analysis set
FDA	Food and Drug Administration
GHSS	Genital Herpes Signs and Symptoms (eDiary)
GLSM	Geometric least squares means
GM	Geometric mean
GMT	Geometric mean titer
GMFR	Geometric mean fold-rise
GMC	Geometric mean concentration
GMR	Geometric mean ratio
HR	Hazard ratio
HSV	Herpes simplex virus
IA	Interim analysis
IP	Investigational product
IST	Internal safety team
kg	kilogram

Abbreviation	Definition
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
max	Maximum
MCF	Mean cumulative function
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
mFAS	Modified full analysis set
MMRM	Mixed model of repeated measurements
mRNA	Messenger RNA
n	number
nAb(s)	Neutralizing antibody(ies)
PCR	Polymerase chain reaction
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PD	Protocol Deviation
PP	Per-protocol
PT	Preferred term
PWP-TT	Prentice, Williams and Peterson Total Time model
RR	rate ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SoA	Schedule of Assessments
SOC	System organ class
SoE	Schedule of events
SMQ	Standardized Medical Dictionary for Regulatory Activities query
µg	Microgram
ULOQ	Upper limit of quantification
USV	Unscheduled Visit
WBC	White blood cell
WHODrug	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1608-P101, is based on the clinical study protocol (CSP) Amendment 1, dated 16Aug-2023 and the electronic case report form (eCRF) effective as of the SAP sign off.

In addition to the information presented in the SAP section of the protocol (Section 9) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

This is a Phase 1/2, randomized, observer-blind, controlled, dose-ranging study to evaluate mRNA-1608, an HSV-2 therapeutic candidate vaccine, in healthy adults 18 to 55 years of age with recurrent HSV-2 genital herpes.

PPD Biostatistics and Statistical Programming team, designee of Moderna Biostatistics and Statistical Programming department, will perform the statistical analysis of the safety, reactogenicity, immunogenicity, and clinical endpoints data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the interim analysis clinical database lock/snapshot. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail and will be described in Section 7.

In this document, study vaccination, injection of investigational product (IP)/ investigational vaccine, and injection are used interchangeably; study arm, treatment arm, vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objective

The primary objective is the following:

- 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.

2.2. Secondary Objectives

The secondary objectives are the following:

- 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.
- 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.
- 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.
- To evaluate the humoral immunogenicity of mRNA-1608 (2 doses: 3 dose levels [25, 50 and 100 µg]) at baseline, 1 month and 6 months after the second study injection.

2.3. Exploratory Objectives

The exploratory objectives (may be performed) are the following:

- 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.
- To evaluate the humoral immunogenicity of mRNA-1608 (2 doses: 3 dose levels [25, 50, and 100 µg]) at all evaluable time points.
- To further characterize antibody responses to mRNA-1608.
- To evaluate the antigen-specific cellular immunogenicity of mRNA1608 in a subset of participants.
- 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).

3. Study Endpoints

3.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- 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.

3.2. Secondary Endpoints

The secondary objectives will be evaluated by the following endpoints:

- 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.
- 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.
- 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.
- GMT of mRNA-1608 antigen-specific bAbs at baseline, 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 equal to or above the LLOQ or ≥ 4 × LLOQ if baseline bAb level is < LLOQ prior to study injection.

3.3. Exploratory Endpoints

The exploratory endpoints (may be performed) are the following:

- 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.
- Proportion of recurrence-free participants starting 14 days after the second study injection to 6 and 12 months after the second study injection as measured by participant report 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.
- 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).
- Neutralizing antibody levels at additional time points, antibody frequency, specificities, effector functions, avidity, or other endpoints to be determined.
- Frequency, magnitude, and phenotype of vaccine specific T-cell responses measured by flow cytometry or other methods.

- 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.

4. Study Design

4.1. Overall Study Design

This first-in-human study 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.

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).

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.

The study injection groups/study arms are described in Table 1.

Table 1: 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

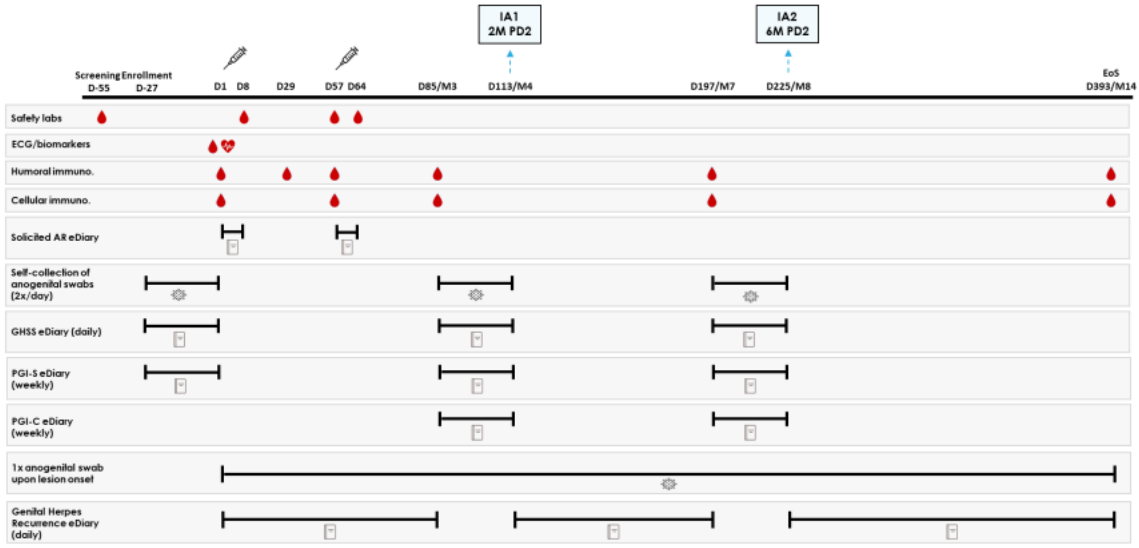
Abbreviations: mRNA = messenger ribonucleic acid; M = month; N = number; N/A = not applicable.

[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.

There are 2 planned IAs (IA1 and IA2). The study schema is displayed in Figure 1.

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.

4.2. Statistical Hypotheses

No formal hypotheses will be tested for this study.

4.3. Sample Size and Power

The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. 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.

Approximately 225 participants will receive mRNA-1608. Details regarding the number of participants in each vaccination group and the randomization ratio are presented in Table 1. 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.

Details are included in Appendix J

4.4. Randomization

Randomization will be performed using an interactive response technology system.

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, 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.

4.5. Blinding and Unblinding

This study is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the study database is locked and unblinded, with certain exceptions; please refer to Data Blinding Plan (DBP) for details. The official final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

5. Analysis Populations

5.1. Randomization Set

The Randomization Set consists of all participants who are randomly assigned.

5.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomly assigned participants who receive the study intervention. Participants will be analyzed according to the group to which they were randomized.

5.3. Modified Full Analysis Set

The modified FAS (mFAS) consists of all participants in the FAS who receive 2 doses of the study intervention. 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.

5.4. Per-Protocol Set

The Per-Protocol (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 important protocol deviations that impact the immune response. 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.

For analysis purposes, the second injection date is expected between study day 50 and 78 inclusive to define PP set.

5.5. Safety Set

The safety set consists of all participants who receive the study intervention. 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.

5.6. Solicited Safety Set

The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for analyses of solicited ARs, and participants will be included in study intervention group corresponding to what they actually received.

In addition, a subset of the Solicited Safety Set is defined for each injection. First Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the first injection and have contributed any solicited AR data on the day of first study injection through the following 6 days.

Second Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the second injection and have contributed any solicited AR data on the day of second study injection through the following 6 days.

5.7. Cell-mediated immunogenicity (CMI) Subset

The CMI subset consists of all participants in the Randomization Set that have evaluable CMI data. The CMI subset will be used for all CMI related analyses.

6. Statistical Analysis

6.1. General Considerations

The SoA are provided in Table 1 of the protocol Section 1.3.

All analyses will be performed by treatment arm unless otherwise specified. Statistical outputs (tables, figures, listings, and datasets) will refer to study participants as participants and will use vaccination, injection of IP and injection interchangeably. All analyses will be conducted using SAS Version 9.4 or higher. All table data will have a corresponding listing.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that vaccination group within the analysis set of interest, unless otherwise specified.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using frequencies and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non- missing measurement (scheduled or unscheduled) collected before the first injection.

For immunogenicity tests, the baseline is defined as the most recent non- missing measurement (scheduled or unscheduled) collected before or on the date of first injection.

For safety laboratory tests, the study baseline is defined as the most recent non- missing measurement (scheduled or unscheduled) collected before the first injection; the period baseline for Day 8 and Day 57 is the same as the study baseline, and the period baseline for Day 64 is the non-missing Day 57 measurement collected before the second injection.

For vital sign tests, the study baseline is defined as the most recent non- missing measurement (scheduled or unscheduled) collected before the first injection; the period baseline for Day 1 is the scheduled measurement collected at Day 1 pre-dose, and the period baseline for Day 57 is the scheduled measurement collected at Day 57 pre-dose.

Study day relative to the first injection will be calculated as below:

a. study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b. study day on or after the date of the first injection will be calculated as: date of assessment/event – date of the first injection + 1.

Study day relative to the most recent injection will be calculated as below:

1. study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;
2. study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;
3. study day on or after the date of the second injection will be calculated as: date of assessment/event – date of the second injection + 1; if study day is on the same day as the second injection, date and time will be compared with the second injection date and time.

The following **analysis periods for safety analyses** will be used in this study:

- 7 days following each vaccination: this period includes the day of vaccination and 6 subsequent days. This analysis period will be used for solicited local and systemic ARs that occur during this time.
- 28 days following each vaccination: this period includes the day of vaccination and 27 subsequent days. This analysis period will be used for unsolicited AEs, unless specified otherwise.
- Overall period: this analysis period starts on Day 1 and continues through the earliest of the following: study completion, discontinuation from the study, or death. This analysis period will be used for analyses of unsolicited AEs including any SAEs, MAAEs, AEs leading to discontinuation of study vaccine and/or study participation, and AESIs.

The durations in months or years will be calculated using the following conversion factors:

- 1 week = 7 days
- 1 month = 28 days
- 1 year = 365.25 days

Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline

- In the derivation of maximum/minimum values and maximum/minimum change from baseline values for safety analyses.
- In individual participant data listings as appropriate.

The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing Data:

- Imputation rules for missing or partial missing dates of prior/concomitant medications and procedures are provided in Appendix D.
- Imputation rules for missing or partial missing AE dates are provided in Appendix E.
- If the immunogenicity results are reported as below the LLOQ (eg, < 0.1), the numeric values will be replaced by 0.5 × LLOQ in the summary. If the laboratory results are reported as greater than the upper limit of quantification (ULOQ) (eg, > 3000), the numeric values will be replaced by ULOQ in the summary if actual values are not available.
- For safety hematology/chemistry laboratory results containing '<' or '>' sign,

  '<x' case: for each lab test, set to x/2;

  '>x' case: for each lab test, set to be x + 1/10^y, where y is the decimal place number of x. For example, > 4.01, display as 4.02.
- Additional considerations are provided in Section 6.5 for analysis of clinical endpoints.

Other incomplete/missing data will not be imputed, unless otherwise specified.

Treatment Groups

Vaccination groups:

The following vaccination groups will be used for summary purposes:

- Control (BEXSERO),
- mRNA-1608 25 µg,
- mRNA-1608 50 µg,
- mRNA-1608 100 µg,
- mRNA-1608 Total (optional),
- Total (optional).

All analyses and data summaries/displays will be provided by vaccination group using appropriate analysis population, unless otherwise specified. Different mRNA dose arms will be analyzed separately without pooling in the analysis of clinical endpoints or immunogenicity endpoints.

6.2. Background Characteristics

6.2.1 Participant Disposition

The number of participants enrolled (collected on CRF) will be provided. For enrolled participants who are not randomized and discontinued study, the reason for study discontinuation will be summarized based on enrolled but not randomized participants.

The number and percentage of participants in the following categories will be summarized based on Randomization Set:

- Randomization Set,
- Full Analysis Set,
- Modified Full Analysis Set,
- Safety Set,
- Solicited Safety Set,
- Per-Protocol Set.

A summary of reasons for participants who are in the Randomization Set but excluded from PP Set will also be provided. A listing of analysis sets will be provided based on the Randomization Set.

The number and percentage of participants in each of the following disposition categories will be summarized by treatment group based on the Randomization Set:

- Received injection (received first injection, received second injection)
- Completed injection based on the Randomization Set
- Discontinued injection and the reason for treatment discontinuation
- Completed study
- Discontinued from the study and the reason for study discontinuation

A participant disposition listing will be provided, including informed consent, participants who completed the study injection schedule, participants who completed study, participants who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation.

The number of participants in the following categories will be summarized:

- Number of participants screened,
- Number and percentage of screen failure participants and the reason for screen failure.

The percentage of participants who screen failed will be based on the number of participants screened. The percentage of participants reporting each reason for screen failure will be based on the number of participants who screen failed. For screened failure participants, age (years), as well as sex, race, ethnicity, and reasons for screen failure will be presented in a listing.

6.2.2 Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (BMI) (kg/m2), and Time from initial genital herpes diagnosis to randomization (years), which is defined as (randomization date - date of initial genital herpes diagnosis + 1)/365.25.

Number and percentage of participants will be provided for categorical variables such as sex, race, ethnicity, HSV-1 antibody status at screening (seropositive, seronegative), HSV-2 antibody status at screening (seropositive, seronegative), both HSV-1 and HSV-2 seropositive, baseline oral herpes (Yes, No), received therapy before study entry (suppressive therapy, episodic therapy). The summaries will be presented based on the Safety Set and mFAS.

Listing of demographics and baseline characteristics will be provided based on the Randomization Set.

6.2.3 Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version used for coding medical history diseases will be included in footnote of analysis output.

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PTs will be displayed in descending order of frequency in the mRNA-1608 Total group and then alphabetically within SOC.

For calculation of time from initial disease diagnosis to randomization, the Imputation rules for missing/partial dates of medical history is included in Appendix D.

All medical history data will be presented in a listing.

6.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODrug Global). WHODrug Global version used will be included in footnote of analysis output. The summary of concomitant medications will be based on the Safety Set, unless otherwise specified. Imputation rules for missing/partial dates of medications, and categorization of prior, concomitant and post medications are detailed in Appendix D.

The number and percentage of participants using concomitant medications during the 7-day follow-up period (ie, on the day of injection and the 6 subsequent days), during the 28 days follow-up period after the injection (ie, on the day of injection and the 27 subsequent days) and throughout the study, using non-study vaccination during the 28 days follow-up period after the injection and throughout the study will be summarized based on the Safety Set.

A summary table of concomitant medications that continued or newly received within 28 days post-injection will be provided by anatomic class (ATC) level 2 and preferred term.

Medications taken to prevent and/or treat pain/fever collected on electronic diary (eDiary) will be summarized based on the Solicited Safety Set for each injection (first, second and any injection).

Prior, concomitant, post medications will be presented in a listing. Study procedures will be presented in a listing only.

6.2.5 Study Exposure and Time on Study

Number and percentage of participants received first injection and second injection will be summarized based on the Safety Set.

Time on study from injection (in days) will be calculated as:

- Study completion date or discontinuation date – injection date +1 day, for participants who completed or discontinued from study;
- Cutoff date – injection date +1 day, otherwise.

Study IP administration data including reasons for IP injection not administered will be listed. Dosing error data will also be presented in a listing.

6.2.6 Important Protocol Deviations

Important protocol deviations (PDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Important protocol deviations rules will be developed and finalized before DBL.

The number and percentage of the participants with each important PD type will be provided based on the Randomization Set.

Important PDs may impact immune response corresponding to the immunogenicity objective, and participants with such deviations will be excluded from the PP Set for immunogenicity analyses; these important PDs will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from the PP Set will be summarized and listed.

6.3. Safety Analysis

Safety and reactogenicity assessments will include monitoring and recording of solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to withdrawal from study vaccine and/or study participation, safety laboratory test results, vital signs, and physical examination findings. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials [DHHS 2007] will be used to categorize unsolicited AEs, safety laboratory test results observed during this study, and vital sign measurements.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set(s). All safety analyses will be provided by vaccination group unless otherwise specified. Participants will be included in the vaccination group corresponding to what they received.

For Safety Set and Solicited Safety Set(s), the following rule will be used to determine participant's actual vaccination group when dosing error occurs:

If a participant only received one injection:

- Participant who received BEXSERO (control) will be summarized under BEXSERO (control) if the planned treatment arm is also BEXSERO (control),
- Participant who received mRNA-1608 will be summarized under mRNA-1608 as 2-dose regimen which is determined by actual dose received according to the dose range mapping rule below.

If a participant received both injections:

- Participant who received BEXSERO (control) for both injections, regardless of dosage, will be summarized under BEXSERO (control).
- Participant who received mRNA-1608 for at least one injection will be summarized under mRNA-1608 2-dose regimen with dose level determined by higher actual dose received according to the dose range mapping rule below.

If non-protocol mRNA-1608 dose level occurs, below dosing range mapping rule will be used:

- mRNA-1608 25 µg: If the received dose of mRNA-1608 is > 0 µg and ≤ 37.5 µg.
- mRNA-1608 50 µg: If the received dose of mRNA-1608 is > 37.5 µg and ≤ 75 µg.
- mRNA-1608 100 µg: If the received dose of mRNA-1608 is > 75 µg.

6.3.1. Unsolicited Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans whether it is considered drug related or not. Adverse events will also be evaluated by the investigator for the coexistence of AESI and/or MAAE. MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner. Unsolicited AEs will be collected for up to 28 days after each injection; SAEs, AESIs, and AEs leading to discontinuation of study vaccine and/or study participation will be collected throughout the study; MAAEs will be collected up to 6 months after the second dose. All AEs started after the first injection will be reported in summary tables.

Unsolicited AEs will be coded by SOC and PT according to MedDRA.

Unsolicited AEs will be summarized separately for the following analysis periods when applicable: within 28 days of any injection, and during the overall period throughout the study.

All summary tables (except for the overall summary of AEs) will be presented by SOC and PT for AEs with counts of participants included. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE within SOC or PT group will be counted once. Participants will be presented according to the highest severity in the summaries by severity, if participants reported multiple events under the same SOC and/or PT. Percentages will be based upon the number of participants in the Safety Set within each vaccination group.

In addition, the number of participants with occurrences of selected AEs of clinical interest identified by standardized MedDRA queries (SMQs) will be summarized. SMQs will be summarized by PT, if applicable. Percentages will be based upon the number of participants in the Safety Set within each vaccination group. Detailed descriptions of SMQs are presented in Appendix I.

6.3.1.1. Incidence of Unsolicited Adverse Events

An overall summary of unsolicited AEs including the number and percentage of participants who experience the following will be presented:

- Any unsolicited AEs,
- Any serious AEs,
- Any fatal AEs,
- Any unsolicited medically attended AEs (MAAEs),
- Any unsolicited AEs leading to discontinuation from study vaccine,
- Any unsolicited AEs leading to discontinuation from participation in the study,
- Any unsolicited severe AEs,
- Any AESI.

The overall summary will be provided for unsolicited AEs up to 28 days after any injection and those throughout the study, respectively. Detailed layouts are included in TLF shells.

In addition, separate listings containing individual participant AE data for unsolicited AEs, unsolicited treatment-related AEs, unsolicited severe AEs, unsolicited treatment-related severe AEs, serious AEs, treatment-related serious AEs, unsolicited AEs leading to discontinuation from study vaccine, unsolicited AEs leading to discontinuation from participation in the study, unsolicited medically-attended AEs and AESI will be provided. Unsolicited AEs started after the first injection will be included in the listing(s).

6.3.1.2. AEs by System Organ Class and Preferred Term

The following summary tables of AEs will be provided by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event):

- All unsolicited AEs,
- All unsolicited AEs that are treatment-related,
- All serious AEs,
- All serious AEs that are treatment-related,
- All unsolicited AEs leading to discontinuation from study vaccine,
- All unsolicited AEs leading to discontinuation from participation in the study,
- All unsolicited severe AEs,
- All unsolicited severe AEs that are treatment-related,
- All unsolicited medically attended AEs,
- All unsolicited medically attended AEs that are treatment-related,
- All unsolicited AESIs.

The above summary tables by SOC and PT will be provided for unsolicited AEs up to 28 days after any injection and then separately throughout the study.

6.3.1.3. AEs by Preferred Term

A summary table by PT will be provided for all unsolicited AEs up to 28 days after any injection and then separately throughout the study.

6.3.1.4. AEs by System Organ Class, Preferred Term and Severity

The following summary tables will be provided by SOC, PT, and maximum severity (mild <moderate <severe) using frequency counts and percentages on all unsolicited AEs.

- All unsolicited AEs
- All treatment-related unsolicited AEs

6.3.2. Serious Adverse Events

The following summary tables of unsolicited serious AEs within 28 days after any injection and overall period will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event) on all unsolicited serious AEs.

- All serious AEs
- All serious treatment-related AEs

Death events will be provided in a separate listing.

6.3.3. Solicited Adverse Reactions

The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the participant in an eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist in the eDiary (i.e., solicited ARs). Any solicited ARs occurring within 7 days after each injection, if not entered in the eDiary in the required input time window, should be reported in the Reactogenicity eCRF form. Solicited ARs reported in either the eCRF and eDiary will be included in the evaluation of solicited ARs.

The following local ARs will be solicited: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, chills, and fever.

The solicited ARs will be reported in the eCRF based on the grading scales presented in Table 6 in the protocol.

All solicited ARs (local and systemic) will be considered causally related to injection.

All solicited ARs analyses will be based on Solicited Safety Set. All solicited ARs analyses will be provided by treatment group for each injection (first and second) and any injection, unless otherwise specified.

An overall summary of solicited ARs including the number and percentage of participants who reported any solicited AR, any solicited local AR, and any solicited systemic AR within 60 minutes after each injection, 7 days after each injection, grade 3 or grade 4 Solicited AR after any injection will also be summarized.

The number and percentage of participants who reported any solicited AR, any solicited local AR, and any systemic solicited AR within 7 days after each injection will be tabulated with a two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method.

The number and percentage of participants experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral or temporal route) by severity grade and the number and percentage of participants experiencing a fever of Grade 3 or higher temperature (a temperature greater than or equal to 39.0°C/102.1°F by the oral or temporal route) in cumulative half-degree (°F) increments will be provided.

The onset day of an individual solicited AR after each injection is defined as the time point at which the solicited AR first occurred. The number and percentage of participants who reported any solicited AR, any solicited local AR, systemic solicited AR and individual solicited ARs (has a severity grade of Grade 1 or greater) within 7 days after first/second injection will be summarized by onset day.

The duration (days) of each type of solicited AR will be summarized. Duration will be calculated as end date of solicited AR – onset date of solicited AR + 1, no matter it is intermittent or continued or if the solicited AR continues beyond 7 days.

6.3.4. Clinical Laboratory Evaluations

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 hematology, chemistry and coagulation such as white blood cell (WBC) count, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase (ALP), platelets, and total bilirubin.

The safety laboratory test results for chemistry and hematology parameters will be summarized based on Safety Laboratory Subset. The Safety Laboratory Subset consists of all participants who have hematology or chemistry measurements of study baseline and at least one post-study baseline of scheduled visits at Day 8, Day 57, or Day 64.

Unscheduled visits may contribute to summaries on worst case values in shift from study/period baseline in hematology toxicity grades and shift from study/period baseline in chemistry toxicity grades.

For continuous hematology and serum chemistry parameters, the observed values and change from period baseline by visit will be summarized at each scheduled visit.

Toxicity grading criteria based on the US Food and Drug Administration (FDA) Guidance for Industry will be presented using period baseline and study baseline respectively.

Shift from the period baseline in toxicity grade will be summarized by visit:

- Day 8 change from baseline,
- Day 57 change from baseline,
- Day 64 change from Day 57 dose (ie, period baseline).

Shift from the study baseline in toxicity grade will be summarized by visit and overall:

- Day 8 change from study baseline,
- Day 57 change from study baseline,
- Day 64 change from study baseline,
- Maximum change over study from study baseline.

All laboratory test results, including pregnancy tests, will be presented in the data listings based on the Safety Set. The results that are outside the reference ranges will be flagged in the data listings.

6.3.5. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing by visit. The values that are outside the reference ranges will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 3 or higher) in Appendix G in any vital sign measurement will be listed separately.

The observed values and change from pre-injection to post-injection will be summarized for all vital sign measurements. The toxicity grades at each visit and worst grade post-study-baseline will also be summarized by treatment group.

6.3.6. Physical Examination

Physical examination will be performed at scheduled time points per protocol.

Summary tables or listings will not be provided for physical examinations, any finding will be part of the medical history or AE analysis.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Set and summarized by treatment group unless otherwise specified.

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. The supportive analysis is required if the condition is met at the end of study; it is optional for interim analyses.

6.4.1. Immunogenicity Assessments

Serum bAb levels against vaccine glycoprotein antigens are measured by a multiplex ligand binding assay using ECL detection for secondary endpoint.

In addition, nAb levels and cell-mediated immunogenicity are collected for exploratory endpoints.

6.4.2. Analysis of Binding Antibody

The geometric mean concentration (GMC) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n} log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity levels.

The geometric mean fold-rise (GMFR) measures the changes in antibody concentration within participants. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n} log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n} log_{10}(v_{ij}) - log_{10}(v_{ik})}{n}\right\}}$$

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity concentration levels for participant i at time points j and k, $j \neq k$ and k is baseline.

For calculation of GMCs, missing results will not be imputed. Concentration levels reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the ULOQ will be converted to the ULOQ if actual values are not available.

The analysis of mRNA-1608 antigen-specific bAbs at 1 month and 6 months after full vaccination (Days 85 and 197) are considered as analysis of secondary endpoints, and analyses at other timepoints are considered exploratory analysis. The following analyses will be performed:

- GMC of bAb levels with corresponding 95% CI will be provided at Days 1, 29, 57, 85, 197 and 393. The 95% CIs will be calculated based on the t distribution of the log-transformed values and then back transformed to the original scale for presentation. The following descriptive statistics will also be provided at Days 1, 29, 57, 85, 197 and 393: the number of participants (n), median, minimum, and maximum.
- GMFR of bAb with corresponding 95% CI will be provided at Days 29, 57, 85, 197 and 393 over baseline. The 95% CIs will be calculated based on the t distribution of the difference in the log-transformed values (post-baseline time point – baseline) and then back transformed to the original scale for presentation.
- Proportion of participants with seroresponse in bAb at Days 29, 57, 85, 197 and 393 will be provided with 2-sided 95% CI using the Clopper-Pearson method. Vaccine seroresponse is defined as an antigen-specific bAb concentration ≥4-fold if Baseline bAb concentration is equal to or above the LLOQ or ≥4 × LLOQ if

Baseline bAb concentration is <LLOQ. The difference of the seroresponse rates between each mRNA-1608 group and BEXSERO (control) group will be provided with 2-sided 95% CIs using the Miettinen-Nurminen method.

- Proportion of participants with a ≥ 2-fold and ≥ 3-fold rise in bAb levels from baseline to Days 29, 57, 85, 197 and 393 will be provided with 2-sided 95% CI using the Clopper-Pearson method. A ≥ z-fold rise from baseline is defined as a ≥ z x LLOQ if baseline bAb concentration <LLOQ, and a ≥ z x ratio of antibody levels if baseline bAb concentration ≥LLOQ.
- For bAb levels, the GMC at Days 29, 57, 85, 197 and 393 for each treatment group, and the geometric mean ratio (GMR) of mRNA-1608 25 µg, mRNA-1608 50 µg, mRNA-1608 100 µg vs. BEXSERO (control), will be estimated based on an analysis of covariance (ANCOVA) model using the PP Set. The dependent variables will be the log-transformed bAb levels at Days 29, 57, 85, 197 and 393 with the treatment group and sex (per CRF) a factor. Additional covariates such as log-transformed baseline GMC may be included. The geometric least square means (GLSM) for each treatment group at each visit and its corresponding 95% CI on a log-transformed scale estimated from the model will be back-transformed to obtain the estimates in the original scale as an estimate of the GMC. The GMR of mRNA-1608 25 µg, mRNA-1608 50 µg, mRNA-1608 100 µg vs. BEXSERO (control), respectively, will be estimated by the ratio of the corresponding GLSMs and 2-si ded 95% CI to assess the treatment difference. The modeling approach will also be applied to subgroup analysis by sex, without including the sex group variable as the covariate.
- Reverse cumulative curves will be provided for bAb assessments at each timepoint.

6.4.3. Sensitivity Analysis of Binding Antibody

As a sensitivity analysis, when there are more than 10% difference between PP set and FAS set, the immunogenicity endpoints may be also analyzed using a mixed model of repeated measurements (MMRM) based on the FAS using all available data from post-baseline scheduled visits.

The model will include the log-transformed antibody level as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects and sex group (per CRF) as a covariate. Additional covariates such as log-transformed baseline concentration

may be included. A term for visit will be included in the repeated statement (in SAS PROC MIXED) and an unstructured covariance matrix will be used thus allowing adjustment for correlations between time points within participants. The Kenward-Roger adjustment of degrees of freedom will be used. If the model does not converge, a simpler covariance structure of compound symmetry may be implemented. The model may be applied for subgroup analysis by sex, without including the sex group variable as the covariate.

The GLSM and corresponding 2-sided 95% CI for the antibody concentrations for each treatment group will be provided by visit. The GLSM and corresponding 95% CI and 90% CI results in log-transformed scale estimated from the model will be back-transformed to obtain these estimates in the original scale. The GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI will be provided to assess the treatment difference between mRNA-1608 groups vs. BEXSERO (control) at each visit.

6.4.4. Exploratory Analysis of Neutralizing Antibody

Neutralizing antibody levels will be analyzed similarly to bAbs. Seroresponse of nAbs will be defined as an antigen-specific nAb titer ≥ 4-fold if Baseline nAb titer is equal to or above the LLOQ or ≥ 4 × LLOQ if Baseline nAb titer is < LLOQ.

6.4.5. Exploratory Analysis of CMI Endpoints

Descriptive summary statistics will be provided at each scheduled visit and vaccination group for CMI parameters, based on CMI Subset. Selected parameters will be plotted over time.

6.5. Clinical Endpoint Analyses

The analyses of clinical endpoints will be based on the mFAS by treatment arm. 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.

Data handling rules for GHSS/GHR data (for recurrence rate and lesion rate) and swabbing data (for shedding rate) are included in Appendix L.

6.5.1. Genital Herpes Recurrences

The analysis of frequency of genital herpes recurrences counted starting 14 days after the second study injection to 6 months and 12 months after the second study injection as measured by participant report of genital recurrences via GHSS eDiary and daily genital herpes recurrence eDiary are considered as analysis of secondary endpoints, and other analyses such as frequency of genital herpes recurrence measured by PCR result and time to first genital herpes recurrence are considered exploratory analysis.

Handling of missing test results: for the purposes of determining number of recurrences, a diary entry of missing will be treated the same as a diary entry of 'No', except for the following case: if 1 or 2 consecutive instances of missing is flanked by 'yes' values on both sides, those consecutive missing values will be imputed as 'Yes' value.

An **episode of recurrence** is defined as one or more consecutive "yes" to the "Do you have genital herpes lesion?" question either from GHSS or daily recurrence eDiary within a 14-day period from the first "yes" response regardless of "no" or missing entries in between. The start date of an episode is the first date of "yes" response, and the end date of an episode is the last date of "yes" within the episode. Duration of each episode is defined as the end date – the start date +1.

As a sensitivity analysis, an episode of recurrence is defined as one or more consecutive "yes" entries followed by at least one "no" entry. For example, two "yes" responses separated by at least one "no" is classified as two distinct recurrences.

The **recurrence analysis period** up to 6 months will include the time from 14 days of the second injection until the last GHSS or daily recurrence eDiary collected up to the 1) the Day 225 visit date or 2) if Day 225 visit date is not available, the earliest of study day 225, study discontinuation date, or cutoff date. The recurrence analysis period up to 12 months will be defined similarly using Visit Day 393.

An episode of recurrence in its entirety will be determined first before considering the analysis period. If the start date of the episode precedes the analysis period, then the entire episode will be excluded. For example, an episode that starts 2 days after the second injection and ends 20 days after will be excluded from the analysis period that starts 14 days after the second injection.

Descriptive summary will be provided for genital herpes recurrences starting 14 days after the second study injection to 6 months and 12 months after the second study injection (participants who discontinued before the analysis start date will be excluded):

- Number of genital herpes recurrence episodes per participant.
- Duration of recurrence analysis period in days per participant.
- Duration of episodes in days. Note that participants with multiple episodes will be counted multiple times.

Annualized recurrence rate in number per person-year, defined as total number of recurrence episodes divided by total analysis period (in year, ie 365.25 days) per arm will also be provided.

With a modeling approach, the recurrence rates will be analyzed in a negative binomial regression model, which includes the number of recurrence episode as the dependent variable, sex per CRF and treatment arms as factors, and the logarithm of observation period (in year, ie 365.25 days) as the offset. The model adjusted rate ratio between mRNA-1608 arms versus the control arm and 95% CI will be provided.

Time to first genital herpes recurrence (events counted starting 14 days after the second study injection) will be analyzed by a stratified Cox proportional hazards model with Efron's method for ties, including treatment as a factor, stratified by sex per CRF. The hazard ratio and its 95% CI comparing mRNA-1608 arms versus the control arm will be provided. A participant without any recurrence will be censored at the 12-month analysis period end date, and a participant who discontinued earlier than the analysis start date will be censored at Day 1. In addition, the Kaplan-Meier method will be used to estimate the median time to first recurrence and recurrence-free probability at 6 months and 12 months after the second study injection, with 2-sided 95% CIs. The Kaplan-Meier plots will be provided. Time to first genital herpes recurrence (events counted starting after the first study injection) will be analyzed similarly.

In addition, an episode of recurrence confirmed by PCR is defined as a recurrence episode accompanied by at least one HSV-2 positive PCR result measured during the extended episode window, defined from the episode start date -3 to episode end date +3, inclusively. A similar descriptive summary will be provided.

The number and percentage of participants who have first recurrence starting after the second study injection and starting 14 days after the second study injection will be presented as the following categories corresponding to the extended episode window:

- With clinical assessments of genital herpes symptoms (yes, no)
- With valid HSV-2 PCR results (positive, negative)
- With valid HSV-1 PCR results (positive, negative)
- With valid culture results (positive for HSV-2, negative for HSV-2 and positive for HSV-1, negative for HSV-1 and HSV-2)
- With both valid HSV-2 PCR and culture results (both HSV-2 positive)
- With both valid HSV-1 PCR and culture results (both HSV-1 positive)

If the mFAS and FAS differs by more than 10%, then in the FAS analysis, the episodes will be defined to start from the first injection instead of 14 days after the second injection. A similar descriptive summary will be provided.

6.5.2. Genital Shedding Rates

The analyses of reduction in HSV-2 genital shedding rate are considered as analysis of secondary endpoints, and analyses of reduction in HSV-1 genital herpes lesion rate are considered exploratory analysis.

Genital shedding rate is defined on the individual level per participant as well as on the group level per arm. Genital shedding rate **per participant** is defined for each 28-day swabbing period as the number of anogenital swabs with HSV-2 DNA positive results (ie positive results per PCR) divided by the number of swabs during the swabbing period. The genital shedding rate **per arm** is defined as total number of positive swabs per arm divided by the total number of swabs during each swabbing period per arm.

Handling of missing test results: for the purposes of determining shedding rate, only swab samples analyzed with a valid result (Detected, Not detected) will be included in

denominators for shedding rate calculation. If a sample is not analyzed or missing results, the sample is considered as missing at random and thus no imputation will be performed.

Descriptive summary will be provided during each period (Baseline, month 2 and month 6 after dose 2):

- Genital shedding rate per participant
- Genital shedding rate per arm
- Absolute change from baseline (ie post baseline minus baseline) per participant

With a modeling approach, the genital shedding rate will be analyzed using the longitudinal Poisson mixed model (Bernstein et al 2017), which includes the number of positive swabs during each swabbing period as the dependent variable, treatment arms, period, treatment arms by period interaction as fixed effects, log of the number of swabs per period as offset, a random intercept for participant and an empirical variance structure (Magaret 2016). The rate ratio and 95% CI between each post baseline period versus baseline will be provided for each treatment arm. In addition, the rate ratios (post baseline over baseline) will be compared for mRNA-1608 arms versus control arm at each post baseline period in terms of ratio of rate ratios. If the model fails to converge (e.g. due to limited sample size), then a descriptive summary based on the rates per arm will be provided instead.

As exploratory analysis, HSV-1 genital shedding rate will be analyzed similarly by descriptive summary.

6.5.3. Genital Herpes Lesion Rate

Genital herpes lesion rate is defined on the individual level per participant as well as on the group level per arm. Genital herpes lesion rate **per participant** is defined for each 28-day swabbing period as the number of days with lesion present (“yes” to the question "Do you have genital herpes lesion?" according to the GHSS eDiary) divided by the number of days with GHSS eDiary during the 28-day swabbing period (The window for participants who have been discontinued from the study will be determined based on their date of discontinuation). The genital herpes lesion rate per arm is defined as total number of days with lesion present (“yes” to the question "Do you have genital herpes lesion?" according to the GHSS eDiary) per arm divided by the total number of days during each swabbing period per arm.

Handling of missing diary entry: referring to the statistical analysis plan of Genocea (2018), for the purposes of determining days with lesions, a missing diary entry will be treated the same as a diary entry of 'No', except for the following case: if 1 or 2 consecutive instances of missing is flanked by 'yes' values on both sides, those consecutive missing values will be imputed as 'Yes' value.

Descriptive summary will be provided during each period (Baseline, month 2 and month 6 after dose 2):

- Genital herpes lesion rate per participant
- Genital herpes lesion rate per arm
- Absolute change from baseline (ie post baseline minus baseline) per participant

With a modeling approach, the genital herpes lesion rate will be analyzed using the longitudinal Poisson mixed model (Bernstein et al 2017), which includes the number days of lesions present during each swabbing period as the dependent variable, treatment arms, period, treatment arms by period interaction as fixed effects, log of the number of eDairies per period as offset, a random intercept for participant, using an empirical variance structure (Magaret 2016). The rate ratio and 95% CI between each post baseline period versus baseline will be provided for each treatment arm. In addition, the rate ratios (post baseline over baseline) will be compared for mRNA-1608 arms versus control arm at each post baseline period in terms of ratio of rate ratios. If the model fails to converge (e.g. due to limited sample size), then a descriptive summary based on the rates per arm will be provided instead.

6.5.4. Antiviral Medication Use

As an exploratory analysis, antiviral medication use (Y/N) within the 6 months and 12 months after the second injection will be summarized by treatment arms. Selected antiviral medications will also be summarized by preferred terms.

6.6. Quality of Life (QoL) Endpoint Analyses

The QoL analysis will include GHSS severity scores, PGI-S and PGI-C. The analysis details, including psychometrics, will be documented in a separate Psychometric and supplemental statistical analysis plan.

6.7. 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.

6.8. Subgroup Analyses

The following analysis will be performed within each Sex subgroup (per CRF collection), and by HSV-1 status at screening to explore potential differences in clinical endpoints, safety/reactogenicity or immune responses across subgroups:

- Overview of solicited adverse reactions
- Overview of unsolicited AEs
- ANCOVA and MMRM analysis of binding antibodies
- Analysis of binding antibody and seroresponse rate
- Analysis of neutralizing antibody and seroresponse rate
- Main analysis of recurrence, shedding rate and lesion rate

6.9. Final Analyses

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final clinical study report (CSR), including individual listings.

7. Changes from Planned Analyses in Protocol

Not applicable.

8. References

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9. List of Appendices

9.1. Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to 2 decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 2 below.

If a participant has multiple assessments for the same analysis visit, the following rule will be used:

- If multiple assessments occur for both scheduled visit and unscheduled visit, the assessment collected at scheduled visit will be used.
- If multiple assessments occur for an analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments with equal distance to the target study day, the last assessment will be used.

Table 2 Visit Window

Visit	Target Study Day	Visit Window in Study Day
Labs		
Screening	-28	< 1
Day 8	8	[1, 32]
Day 57	57	[33, 60]
Day 64	64	[61, 80]
Humoral Immunogenicity		
Day 1	1 (Date of First Injection)	≤ 1
Day 29	29	[2, 43]
Day 57	57	[44, 71]
Day 85	85	[72, 141]
Day 197	197	[142, 295]
Day 393	393	≥ 296
Cellular Immunogenicity		
Day 1	1	≤ 1
Day 57	57	[2, 71]

Visit	Target Study Day	Visit Window in Study Day
Day 85	85	[72, 141]
Day 197	197	[142, 295]
Day 393	393	≥ 296

9.3. Appendix C Schedule of Assessments for mRNA-1608 Treatment Regimen

Refer to Table 1: Schedule of Assessments (SoA) in the protocol.

9.4. Appendix D Imputation Rules for Missing Dates of Prior/Concomitant Medications and Medical History

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:

- If only Day is missing, use the first day of the month, unless:
    - The medication end date is after the date of injection or is missing AND the start month and year of the medication coincide with the start month and year of injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of injection.
- If Day and Month are both missing, use the first day of the year, unless:
    - The medication end date is after the date of injection or is missing AND the start year of the medication coincides with the start year of injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of injection.
- If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining status as prior or concomitant. If the medication is known to be not taken prior to study vaccine administration (e.g. answer to the question of "Was the medication taken prior to study treatment administration?" in CRF is No), the medication will be treated as though it began after the injection for purposes of determining status as prior or concomitant.

2. Missing or partial medication stop date:
    a. If only DAY is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
    b. If DAY and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
    c. If DAY, Month and year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 3 Prior, Concomitant, and Post Categorization of a Medication (Vaccine studies)

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ Each Dose Date and ≤ 28 days Post Each Dose**	**> 28 days Post Each Dose**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ 28 days post each dose	-	C	CA
> 28 days post each dose	-	-	A

A: Post; C: Concomitant; P: Prior

Medical history of disease diagnosis will be used to calculate time from initial diagnosis to randomization. If there are partially missing start date, the date will be imputed as follows:

a. If only DAY is missing, use the first day of the month.
b. If DAY and Month are both missing, use the first day of the year.
c. If DAY, Month and year are all missing, the date will not be imputed.

9.5. Appendix E Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:
    - If only Day is missing, use the first day of the month, unless:
        - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if AE start time is collected.
    - If Day and Month are both missing, use the first day of the year, unless:
        - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date and time of first injection, when time is available.
    - If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment -emergent.
2. Missing or partial AE end dates will not be imputed.

9.6. Appendix F Severity Grading of Laboratory Abnormalities (When Applicable)

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** ULN is the upper limit of the normal range.

9.7. Appendix G Severity Grading of Vital Sign Abnormalities

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
For analysis purpose, the grades will be calculated using the numerical portion only.

9.8. Appendix H Severity Grading of Reactogenicity

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Local					
Injection site pain	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Prevents daily activity	Requires emergency room visit or hospitalization

Reaction	**Grade 0 (None)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-Threatening)**
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical interventio n	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

9.9. Appendix I Definition of AE of Clinical Interest by SMQ

SMQ/CMQ Name*	Type of MedDRA Query	SMQ Level*	SMQ Code*	Search Criteria
Anaphylactic Reaction	SMQ	1	20000021	Algorithm A or (B and C) or (D and (B or C))
Angioedema	SMQ	1	20000024	Narrow/Broad
Arthritis	SMQ	1	20000216	Narrow/Broad
Cardiac Arrhythmias	SMQ	1	20000049	Narrow/Broad
Arrhythmia Related Investigations, Signs and Symptoms	SMQ	2	20000051	Narrow/Broad
Cardiac Arrhythmia Terms (including bradyarrhythmias and tachyarrhythmias)	SMQ	2	20000050	Narrow/Broad
Cardiac Failure	SMQ	1	20000004	Narrow/Broad
Cardiomyopathy	SMQ	1	20000150	Narrow/Broad
Central Nervous System Vascular Disorders	SMQ	1	20000060	Narrow/Broad
Central Nervous System Haemorrhages and Cerebrovascular Conditions	SMQ	2	20000061	Narrow/Broad
Central Nervous System Vascular Disorders, not Specified as Haemorrhagic or Ischaemic	SMQ	2	20000165	Narrow/Broad
Convulsions	SMQ	1	20000079	Narrow/Broad
Demyelination	SMQ	1	20000154	Narrow/Broad
Embolic and Thrombotic Events	SMQ	1	20000081	Narrow/Broad
Embolic and Thrombotic Events, Arterial	SMQ	2	20000082	Narrow/Broad
Embolic and Thrombotic Events, Venous	SMQ	2	20000084	Narrow/Broad

Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous	SMQ	2	20000083	Narrow/Broad
Guillain-Barre Syndrome	SMQ	1	20000131	Narrow/Broad
Haematopoietic Cytopenias	SMQ	1	20000027	Narrow/Broad
Haematopoietic Cytopenias Affecting More Than One Type Of Blood Cell	SMQ	2	20000028	Narrow/Broad
Haematopoietic Erythropenia	SMQ	2	20000029	Narrow/Broad
Haematopoietic Leukopenia	SMQ	2	20000030	Narrow/Broad
Haematopoietic Thrombocytopenia	SMQ	2	20000031	Narrow/Broad
Hearing and Vestibular Disorders	SMQ	1	20000170	Narrow/Broad
Hearing Impairment	SMQ	2	20000171	Narrow/Broad
Vestibular Disorders	SMQ	2	20000172	Narrow/Broad
Hypersensitivity	SMQ	1	20000214	Narrow/Broad
Immune-mediated/Autoimmune Disorders	SMQ	1	20000236	Narrow/Broad
Ischaemic Heart Disease	SMQ	1	20000043	Narrow/Broad
Myocardial Infarction	SMQ	2	20000047	Narrow/Broad
Other Ischaemic Heart Disease	SMQ	2	20000168	Narrow/Broad
Noninfectious Myocarditis/Pericarditis	SMQ	1	20000239	Narrow/Broad
Peripheral Neuropathy	SMQ	1	20000034	Narrow/Broad
Thrombophlebitis	SMQ	1	20000115	Narrow/Broad
Vasculitis	SMQ	1	20000174	Narrow/Broad
*Based on MedDRA 27.0.				

The list is included for illustration purpose and may be updated for each analysis milestones following the sponsor's standard update across programs.

Any of the following three scenarios would qualify as an anaphylactic reaction based on the SMQ analysis:
One event from Category A, **or**
One event from Category B **AND** one event from Category C, **or**
One event from Category D **AND** one event from Category B **OR** Category C

Category A	Category B	Category C	Category D
-Anaphylactic reaction -Anaphylactic shock -Anaphylactic transfusion reaction -Anaphylactoid reaction -Anaphylactoid shock -Circulatory collapse -Dialysis membrane reaction -Kounis syndrome -Procedural shock -Shock -Shock symptom -Type I hypersensitivity	-Acute respiratory failure -Asthma -Bronchial oedema -Bronchospasm -Cardio-respiratory distress -Chest discomfort -Choking -Choking sensation -Circumoral oedema -Cough -Cough variant asthma -Cyanosis -Dyspnoea -Hyperventilation -Irregular breathing -Laryngeal dyspnoea -Laryngeal oedema -Laryngospasm -Laryngotracheal oedema -Mouth swelling -Nasal obstruction -Oedema mouth -Oropharyngeal oedema -Oropharyngeal spasm	-Allergic oedema -Angioedema -Circumoral swelling -Erythema -Eye oedema -Eye pruritus -Eye swelling -Eyelid oedema -Face oedema -Flushing -Injection site urticaria -Lip oedema -Lip swelling -Nodular rash -Ocular hyperaemia -Oedema -Oedema blister -Periorbital oedema -Periorbital swelling -Pruritus -Pruritus allergic -Rash -Rash erythematous -Rash pruritic -Skin swelling -Swelling -Swelling face -Swelling of eyelid -Urticaria	-Blood pressure decreased -Blood pressure diastolic decreased -Blood pressure systolic decreased -Cardiac arrest -Cardio-respiratory arrest -Cardiovascular insufficiency -Diastolic hypotension -Hypotension -Hypotensive crisis -Post procedural hypotension

	-Oropharyngeal swelling -Pharyngeal oedema -Pharyngeal swelling -Respiratory arrest -Respiratory distress -Respiratory failure -Reversible airways obstruction -Sensation of foreign body -Sneezing -Stridor -Swollen tongue -Tachypnoea -Throat tightness -Tongue oedema -Tracheal obstruction -Tracheal oedema -Upper airway obstruction -Vaccine associated enhanced respiratory disease -Wheezing	-Urticaria papular	

9.10. Appendix J Note to File of MEMO of sample size calculation in mRNA-1608-P101

Note to File

Protocol: mRNA-1608-P101

Subject: MEMO of sample size calculation in mRNA-1608-P101

Date: 23 June 2023

Description: This memo documents the detailed assumptions and statistical methods to supplement the sample size determination under protocol mRNA-1608-P101, version 1.0

In the protocol, the sample size determination was provided as follows:

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 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 2011) in the repeated binary measurements model (Magaret 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.*

Recurrence rate

The recurrence rate was modeled by a negative binomial distribution. The following assumptions were used:

- Annual mean = 5, or equivalent semi-annual mean = 2.5; 60% reduction
- Annual standard deviation = 4.75
- 10% dropout rate

These assumptions were made referring Benedetti 1994 and Benedetti 1999. With the assumptions, the power and sample size are included in Table 4 below based on normal approximation to difference in rates.

Table 4 sample size calculation for recurrence rate

Recurrence rate in control	Recurrence rate in vaccine	Reduction (1-K)	Power: Pr(K>0)	n per arm Assuming equal SD
2.5	1	60%	80%	54
2.5	1	60%	>90%	75/arm as planned

Viral shedding rate

The viral shedding rates are modeled by the repeated binary measurements model of Magraret 2011:

- Baseline and post baseline data (A and B) with viral shedding rates p_A, p_B
  $p_B = Kp_A$ (that means 1-K is the reduction rate)
- For subject i taking treatment T, m specimens are collected and tested
  $X_{ijT} \sim Bernoulli(p_{iT})$ with AR(1) coefficient ϕ_i
  $Y_{iT} = \sum_{j=1}^{m} X_{ijT}$
  $p_{iA} \sim Beta(\boldsymbol{\alpha}, \boldsymbol{\beta})$
  $\phi_i \sim \text{Beta}(\boldsymbol{\epsilon}, \boldsymbol{\zeta})$
- Compute Var$(\frac{Y_{iA}}{m} - \frac{Y_{iB}}{m})$
- Sample size calculation based on change from baseline within a treatment arm using one-sample Z-test; This corresponds to the cross over method in Magaret 2011.

The following assumptions were made in the sample size calculation by referring to Magaret 2011 and Tronstein 2011:

- $\boldsymbol{\alpha = 0.5, \beta = 4.7}$ so that the baseline shedding rate is 10% based on Tronstein 2011
- $\boldsymbol{\epsilon = 2.1, \zeta = 1.8}$ to allow moderate autocorrelation of 0.54 following Magaret 2011
- **10**% dropout rate
- 56 samples (2 times per day during the 28 day windows)

The power and sample size calculation are included in Table 5 below.

Table 5 sample size calculation for shedding rate

Shedding rate in Baseline	Shedding rate in Post-baseline	Auto correlation (r)	Reduction (1-K)	# of Samples per participant (m)	Power	n per arm
10%	4%	0.54	60%	56	80%	39
10%	4%	0.54	60%	56	90%	52
10%	**4%**	**0.54**	**60%**	**56**	**>90%**	**75/arm**

Lesion rate

The lesion rates are also modeled by the repeated binary measurements model of Magraret 2011 as for shedding rate above. The following assumptions were made in the sample size calculation:

- $\boldsymbol{\alpha = 0.64, \beta = 5.16}$ so that the baseline shedding rate is 11% based on clinical team's input
- $\boldsymbol{\epsilon = 2.24, \zeta = 1.49}$ to allow moderate autocorrelation of 0.6
- **10**% dropout rate
- 28 readings from the eDiary during the 28-day windows

The power and sample size calculation are included in Table 6 below.

Table 6 sample size calculation for lesion rate

Lesion rate in baseline	Lesion rate in post-baseline	Auto correlation (r)	Reduction (1-K)	# of readings per participant (m)	Power	n per arm
11%	3.85%	0.6	65%	28	80%	52
11%	3.85%	0.6	65%	28	90%	69
11%	**3.85%**	**0.6**	**65%**	**28**	**>90%**	**75/arm**

The following codes were used and stored on CDR at K:\biometrics\infectious_disease\mRNA-1608\p101\docs\sample size memo\

- Recurrence rate.R
- Viral shedding rate.R
- Lesion rate.R
- formbbinom.R

9.11. Appendix K Internationally Agreed Order for Display of System Organ Class

1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

9.12. Appendix L Data Handling Rules for GHSS/GHR Data and Swabbing Data

For GHSS/GHR data, there can be a gap where the eDairy data collection is not triggered. The following data handling rules will be implemented.

- For subjects with GHR data overlapping with GHSS data, the GHSS data will be kept and the overlapping GHR data will be removed.
- For subjects with multiple GHR records on the same day, only the record with higher priority will be kept (Yes has higher priority than No).
- For subjects with gaps in the GHSS/GHR data, the gaps will not be filled, and thus not counted in the duration of analysis period. However, a gap of 1 or 2 days flanked by two 'yes' will be handled as one continuous episode in the episode definition.
- eDiary data reported after the date of study discontinuation will be excluded from analysis.

For analysis of shedding rate using swab samples, the following data handling rules will be implemented.

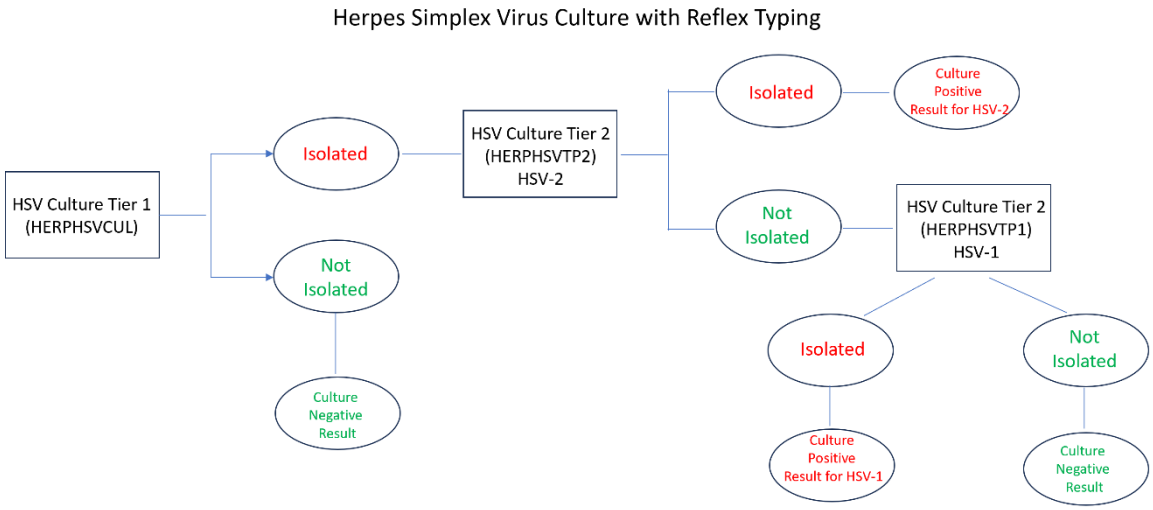
1. Collection time will not be used in the analysis. The analysis is primarily based on the label (eg Day 12 AM, Day 12 PM)
2. The following rules are applied to ensure there is only one record for each type of test at each analysis timepoint within a swabbing period:
    a. Identify the planned samples (ie those labeled as HSV Self Collected Day xx AM/PM for planned visits) and backup samples (ie those labeled as HSV Self Collected xx and not for symptom onset visit) in each period.
    b. In case of duplicated backup samples with the same test results at the same timepoint, the sample with the smallest sample ID is kept.
    c. Only when planned swab samples are missing at a timepoint, the backup samples on the same collection date will be used to supplement the missing planned samples. When there are multiple backup samples at the same timepoint with different results, sample with positive results (ie detected) will be prioritized over negative samples (ie not detected).

For analysis of recurrence confirmed by PCR results, the following rules are applied:

- Only swab samples for Symptom Onset will be used to confirm the recurrence

- A recurrence episode is confirmed by positive PCR result, if the PCR collection date falls in the extended episode window, defined by [episode start date -3 days, episode end date +3 days]

The culture samples follow a two-tier testing, and the results will be determined by the following diagram:



There are three categories for the test results:

- Positive for HSV-2 (through tier 2 test, top red)
- Positive for HSV-1 (through tier 2 tests, bottom red)
- Negative for both (this can be from tier 1, or from tier 2 bottom right green circle from the diagram above)

DocuSign

Certificate Of Completion

Envelope Id: PPD
Subject: mRNA-1608-P101 sap v1 Docusign
Source Envelope:
Document Pages: 62
Certificate Pages: 5
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Signatures: 4
Initials: 0

Status: Completed

Envelope Originator:
PPD
325 Binney St
Cambridge, MA 02141
PPD
IP Address: PPD

Record Tracking

Status: Original
04-Sep-2024 | 18:39

Holder: PPD

Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 04-Sep-2024 | 18:49 Viewed: 04-Sep-2024 | 20:31 Signed: 04-Sep-2024 | 20:31
Electronic Record and Signature Disclosure: Accepted: 21-Mar-2022 | 16:49 ID: PPD		
PPD Security Level: Email, Account Authentication (Required), Logged in	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 04-Sep-2024 | 18:49 Viewed: 04-Sep-2024 | 20:36 Signed: 04-Sep-2024 | 20:37
Electronic Record and Signature Disclosure: Accepted: 11-May-2023 | 14:35 ID: PPD		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 04-Sep-2024 | 18:49 Viewed: 05-Sep-2024 | 13:22 Signed: 05-Sep-2024 | 13:22
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Drawn on Device Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 04-Sep-2024 | 18:49 Viewed: 05-Sep-2024 | 10:58 Signed: 05-Sep-2024 | 10:59
Electronic Record and Signature Disclosure: Accepted: 05-Sep-2024 | 10:58 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	04-Sep-2024 | 18:49
Certified Delivered	Security Checked	05-Sep-2024 | 10:58
Signing Complete	Security Checked	05-Sep-2024 | 10:59
Completed	Security Checked	05-Sep-2024 | 13:22

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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