CLINICAL TRIAL PROTOCOL

Study Title:	A Randomized, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of a Maintenance Dose of GEN-003 in Subjects with Genital Herpes Infection
Study Number:	GEN-003-005
Study Phase:	2
Test Product:	GEN-003
IND Number:	14910
Indication:	Treatment of chronic genital herpes simplex infection
Sponsor:	Genocea Biosciences, Inc. Cambridge Discovery Park 100 Acorn Park Drive, 5th Floor Cambridge, MA 02140
Medical Monitor:	Thomas Heineman, M.D., Ph.D. Genocea Biosciences, Inc. Phone: 617-715-6670

Version	Date
1.0	06 March 2017
1.1	15 September 2017
2.0	13 October 2017

TABLE OF CONTENTS

SPONSOR SIGNATURE PAGE

GEN-003-005: A Randomized, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of a Maintenance Dose of GEN-003 in Subjects with Genital Herpes Infection

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: THomas C. Heineman
THomas C. Heineman (Oct 16, 2017)

Date: Oct 16, 2017

Thomas Heineman, M.D., Ph.D.
Vice President of Clinical Development
Genocea Biosciences, Inc.

INVESTIGATOR SIGNATURE PAGE

GEN-003-005: A Randomized, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of a Maintenance Dose of GEN-003 in Subjects with Genital Herpes Infection

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Print Name:_____

SYNOPSIS

Sponsor: Genocea Biosciences, Inc.	
Study Title: A Randomized, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of a Maintenance Dose of GEN-003 in Subjects with Genital Herpes Infection	
Test Product: GEN-003	
Name of Active Ingredients: GB208, GB217, Matrix-M2 adjuvant (MM2)	
Study Number: GEN-003-005	**Study Phase:** 2
Study Centers: Up to 9 centers in the United States	

Primary Efficacy Objective:

- To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose in reduction of genital herpes lesion rate

Secondary Efficacy Objectives:

- To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose on genital herpes recurrence through 6 months:
  - Reduction of genital herpes recurrence frequency
  - Increase of proportion of subjects who are genital herpes recurrence-free
  - Increase of time to first genital herpes recurrence
  - Reduction of genital herpes recurrence duration

Safety Objective:

- To evaluate the safety and tolerability of a maintenance dose of GEN-003 versus placebo

Study Design: This study is a randomized, double-blind, placebo-controlled clinical trial of GEN‑003 in subjects who have received previous doses of GEN-003. Subjects who completed Study GEN-003-003 and received all 3 doses of GEN‑003, reported data in daily electronic reporting period on at least 80% of days, and had no important protocol deviation in that trial will be offered enrollment in this study. Subjects who meet all inclusion and no exclusion criteria and provide written informed consent for this study will be randomized within 11 to 18 months after the last active GEN-003 dose in a 1:1 ratio to receive 1 intramuscular (IM) dose (the maintenance dose) of GEN-003 or placebo. Randomization will be stratified on the basis of the GEN-003 dose received by the subject in Study GEN-003-003.

Subjects will use a daily electronic tool for reporting the presence or absence of genital herpes lesions and the severity of genital herpes symptoms from Day 1 until the Month 6 Visit.

Subjects will complete the EuroQol – 5 Domains – 5 Levels (EQ-5D-5L) questionnaire on each day of the first recurrence after the maintenance dose through Month 6.

A serum sample will be collected from each subject for future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1)

At selected investigational sites, a whole blood sample will be collected and processed to isolate peripheral blood mononuclear cells (PBMCs) for future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1).

Local reactions and systemic events will be recorded for the first 7 days after the maintenance

dose on a paper Diary Card; if any event is ongoing after Day 8, it will be followed until resolution. All adverse events (AEs) and concomitant medications will be recorded from Day 1 to Day 29/Month 1. After Day 29/Month 1 to the end of the study, only serious AEs (SAEs), AEs of special interest (AESIs), medically attended AEs (MAAEs), antiviral medications, and vaccines will be recorded. All AEs will be graded in accordance with the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials from Grade 1 (mild) to Grade 4 (life-threatening).

From Month 2 to Month 12, the investigational site will contact each subject by telephone or site visit for review of daily electronic reporting tool data and assessment of SAEs, AESIs, and antiviral medication (through Month 6).

A Data Monitoring Committee (DMC) will review safety data at intervals of a minimum of 3 months until all subjects have completed the GEN-003/placebo dosing period. Any additional meetings and the specific safety monitoring plan will be detailed in the DMC charter.

Efficacy Endpoints:

Primary:

- Genital herpes lesion rate (proportion of days with lesions present) in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

Secondary:

- Frequency of genital herpes recurrences in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool
- Proportion of subjects genital herpes recurrence-free at 6 months after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool
- Time to first genital herpes recurrence in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool
- Duration of genital herpes recurrences in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

Safety Endpoints:

- Reactogenicity
  - Local reactions: Pain, tenderness, swelling, redness
  - Systemic events: Fever, headache, chills, fatigue, nausea, vomiting, diarrhea, muscle aches
- AE, SAEs, AESIs, MAAEs

Number of Subjects Planned: Up to 90 subjects

Diagnosis and Main Criteria for Inclusion: Subjects who completed Study GEN-003-003 (completed all study visits including the Month 12 visit) and received all 3 doses of active GEN-003 (any dose combination), received the last dose of GEN-003 within 11 to 18 months, and reported data in daily electronic reporting period on at least 80% of days, and had no important protocol deviation.

Duration of Treatment: 1 dose

Test Product; Dose; and Mode of Administration: GEN-003 (60 μg of each antigen, GB208

and GB217, 50 µg of MM2, and normal saline), administered as a 0.5 mL IM injection
Control Product; Dose; and Mode of Administration: Normal saline, administered as a 0.5 mL IM injection
Statistical Methods: **Sample Size:** No formal sample size calculations were performed for this study. **Analyses:** Efficacy: Genital herpes lesion rates (the proportion of days with genital lesions present) in the 6-month period after the maintenance dose will be compared between treatment groups using the Wilcoxon rank sum text. The median frequencies of recurrences in the 6-month period will be compared between treatment groups using the Wilcoxon rank sum test. The proportion of subjects in each treatment group who are genital herpes recurrence-free at 6 months after the maintenance dose will be tabulated and compared using a chi-square test for homogeneity of proportions. Time to first recurrence in the 6-month period after the maintenance dose will be tabulated and graphed using the Kaplan-Meier method. The log-rank test will be used to compare the time to first recurrence survival curves between the GEN-003 and placebo groups. Median of individual mean duration of genital herpes recurrences during the 6-month period will be compared using the Wilcoxon rank sum test. Safety: Safety data will be summarized by the number and proportion of subjects with: • Reactogenicity: local reactions and systemic events • AEs, SAEs, AESIs, MAAEs

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CFR	Code of Federal Regulations
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics Committee
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol – 5 Domains – 5 Levels
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gD	glycoprotein D
GH-SSD	Genital Herpes Signs and Symptoms Diary
GLP	Good Laboratory Practice
GMT	geometric mean titer
GrB	granzyme B
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HSV-1	herpes simplex virus type-1
HSV-2	herpes simplex virus type-2
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFN-γ	interferon-gamma
IgG	immunoglobulin G
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MM2	Matrix-M2 adjuvant
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PhRMA	Pharmaceutical Research and Manufacturers of America
RGHQoL	Recurrent Genital Herpes Quality of Life Questionnaire

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SFC	spot-forming cell
TSS	total severity score

1 INTRODUCTION

1.1 HSV-2 Infection

Herpes simplex viruses (HSVs) are the main cause of genital ulcers worldwide (Looker 2008). More than 400 million people worldwide are infected with HSV type 2 (HSV-2), which is primarily sexually transmitted, and an estimated 140 million people have genital HSV type 1 (HSV-1) infection (World Health Organization 2016). Evidence of infection, by serologic studies, is present in 1 out of every 6 people aged 14 to 49 in the United States (http://www.niaid.nih.gov/topics/genitalherpes/Pages/default.aspx; Centers for Disease Control and Prevention 2015). Women are more commonly infected than men, with 1 out of every 5 women in the US having evidence of infection. Certain groups, such as people with human immunodeficiency virus (HIV) and commercial sex workers, have high rates of infection ranging from 60 to 95%, (Kimberlin, Rouse 2004; Gupta et al 2007). HSV-2 infection is associated with a 3-fold increase in risk of acquiring HIV infection and is considered to be a substantial contributor to the worldwide AIDS epidemic (Corey 2007). Most HSV-2 seropositive people are unaware of their infection status, probably because of mild and atypical symptoms and signs, and this lack of awareness contributes to the continued spread of HSV-2 infection among susceptible populations.

In people with recognized genital herpes, the disease is characterized by the development of vesicles at the site of infection, usually the anogenital region (defined as the area covered by boxer shorts). Vesicles persist for days and evolve to ulcers that eventually crust and heal. The initial clinical manifestations occur approximately 4 days after acquisition of infection and are referred to as the primary outbreak or infection (or nonprimary initial, for the first episode of HSV-2 in a patient who is HSV-1 seropositive). In the absence of antiviral therapy, lesions resolve over the course of 1 to 3 weeks. The virus migrates in a retrograde process to become latent in the sensory nerve ganglia. At varying intervals, recurrences (secondary outbreaks or infections) develop when the virus travels anterograde to the skin or mucosal surfaces. During the first year after primary infection, the median recurrence rate in the absence of therapy is 4 per year, and 20% of patients experience more than 10 recurrences (Benedetti et al 1994).

HSV-2 infection is transmitted by contact with the mucosal membranes of an infected person who is shedding the virus. During clinically active recurrences (presence of genital ulcers), HSV-2 can frequently be detected in ulcers and the surrounding skin and mucosa. However, during asymptomatic periods, shedding of HSV-2 from the anogenital regions of an infected person can be detected on approximately 10% to 13% of days (subclinical shedding) by polymerase chain reaction (PCR) (Fife et al 2006; Martens et al 2009). Most transmission occurs during such periods of subclinical shedding. Transmission may also occur from pregnant mother to infant at birth, resulting in a severe form of disseminated infection leading to permanent neurologic damage or death of the infant (Whitley 2004).

1.2 Current Treatment of Recurrent HSV-2 and Transmission

There are no known curative treatments or therapeutic vaccines for HSV-2 infection. Current therapy is directed at reducing the duration of primary disease or reducing the duration or frequency of secondary outbreaks. For these indications, acyclovir, valacyclovir, or famciclovir

can be effective. Both clinical and subclinical shedding of HSV-2 are reduced during periods of therapy (Wald et al 1996; Gupta et al 2004; Fife et al 2006; Martens et al 2009; Johnston et al 2012). However, in a clinical trial valacyclovir reduced transmission of HSV-2 from infected persons to uninfected partners by only 48% (Corey et al 2004). The limitations of antiviral therapy include the requirement for daily treatment, potentially incomplete compliance leading to breakthrough of viral shedding or clinical disease, inability to completely suppress clinical recurrences, and limited prevention of transmission of infection. Consequently, there have been a number of attempts to develop effective vaccines either for prevention or treatment of infection with HSV-2 (Stanberry et al 2002; de Bruyn et al 2006; Awasthi & Friedman 2014), but none is currently available.

1.3 GEN-003

GEN-003 is an HSV-2 protein subunit vaccine consisting of 2 recombinant T-cell antigens (GB208 and GB217) and Matrix-M2 adjuvant (MM2):

- GB208: a T-cell antigen and internal fragment of the immediate early protein ICP4. ICP4 was identified as one of the most frequent proteins recognized by the T-cells of immune seronegative subjects studied by AnTigen Lead Acquisition System (ATLAS™), suggesting its potential role in control of viral replication and utility as a vaccine candidate.

- GB217: a B-cell antigen (also known as glycoprotein D, or gD) that was identified through screening at Genocea to also invoke a T-cell response. This surface glycoprotein is a target of both HSV-2 neutralizing antibodies and of T-cell responses.

- MM2: immune stimulating complexes derived from fractionated *Quillaja saponins*, phosphatidylcholine, and cholesterol

1.4 Nonclinical Pharmacology and Toxicology Studies of GEN-003 Antigens and MM2

Non-GLP (Good Laboratory Practice) and GLP studies of immunogenicity and toxicity in mice, GLP studies of immunogenicity and toxicity in monkeys, non-GLP and GLP studies of efficacy in guinea pigs, and a GLP local tolerance study in rabbits were conducted. Summaries of these nonclinical studies are provided below. Additional details of the studies can be found in the current Investigator Brochure.

1.4.1 Nonclinical Models of Immunogenicity and Efficacy

Immune responses to components of GEN-003 were evaluated in mice and monkeys. The study results indicated that GB208 and GB217 prime potent and functional T-cell and B-cell responses, including HSV-2 neutralizing antibodies, when administered with MM2.

The GLP immunogenicity study results indicated that GB208 and GB217 prime potent and functional T-cell and B-cell responses, including HSV-2 neutralizing antibodies, when administered with MM2. In a guinea pig model of vaginal HSV-2 infection, GEN-003 induced increases in GB208- and GB217-specific IgG titer and HSV-2 neutralizing antibodies (Skoberne

2013). Both the number of days with genital HSV-2 lesions and HSV-2 shedding were reduced in animals that received active vaccine compared to those in the placebo group.

1.4.2 Nonclinical Toxicology Studies

GLP repeat-dose toxicology studies of GEN-003 antigens and MM2 in mice and monkeys and local tolerance study in rabbits showed no safety signals believed to be relevant to potential risks to humans receiving GEN-003.

1.5 Clinical Trials of GEN-003

Three clinical trials of GEN-003 have been completed, and 2 trials are ongoing. Summaries are provided below. Additional details of the studies can be found in the current Investigator Brochure.

1.5.1 GEN-003-001: A Phase I/IIa, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study of the Safety and Immunogenicity of a HSV-2 Vaccine Containing Matrix M-2 Adjuvant in Individuals with Documented HSV-2 Genital Infection

Subjects aged 18 to 50 years with documented diagnosis of genital HSV-2 infection for > 1 year but who were otherwise healthy were enrolled sequentially into 1 of 3 dose cohorts defined by the antigen dose (10, 30, or 100 µg for each of the 2 protein antigens) and randomized within each cohort in a ratio of 3:1:1 to receive 3 intramuscular (IM) doses of GEN-003 antigens with MM2, GEN-003 antigens without MM2, or placebo at intervals of 21 days. Thus, the treatment groups were as follows:

- 10 µg each GEN-003 antigen + 50 µg MM2 (31 subjects)
- 30 µg each GEN-003 antigen + 50 µg MM2 (29 subjects)
- 100 µg each GEN-003 antigen + 50 µg MM2 (27 subjects)
- 10 µg each GEN-003 antigen (9 subjects)
- 30 µg each GEN-003 antigen (10 subjects)
- 100 µg each GEN-003 antigen (9 subjects)
- Placebo (28 subjects)

The study is complete; 143 subjects were enrolled. GEN-003 antigens when combined with MM2 generated a reduction in HSV-2 shedding rates that was maintained for at least 6 months after treatment, and the greatest reduction was achieved in the adjuvanted 30 µg dose group. No reduction in HSV-2 shedding occurred in the absence of MM2. 30 µg GEN-003 antigens combined with MM2 reduced lesion rates (proportion of days with lesions divided by the 28-day duration of the swab collection period) for at least 6 months post-treatment. 100 µg GEN-003 antigens with MM2 also reduced HSV-2 shedding and lesion rates but less durably.

GEN-003 antigens elicited strong and durable antibody and T-cell immune responses to both vaccine-specific antigens and production of HSV-2 neutralizing antibodies at all doses. The addition of MM2 augmented these responses.

GEN-003 antigens with or without MM2 exhibited an acceptable safety and tolerability profile for use as a therapeutic vaccine. Five serious adverse events (SAEs) in 5 subjects (femur fracture, suicide attempt, complicated migraine, myocardial infraction, abortion spontaneous) were reported during the course of the study, and none was considered associated with treatment. No adverse events of special interest (AESIs) were reported.

Three subjects had an adverse event (AE) leading to discontinuation of dosing, and 1 subject discontinued the study because of an AE of attempted suicide 21 days after Dose 3 that was assessed by the Investigator as not likely related to the investigational product (IP). For AEs, incidences were generally higher in the adjuvanted groups than in the unadjuvanted group and higher in the unadjuvanted group than in the placebo group. The severity of AEs tended to be higher in adjuvanted vaccine groups, and were more often related to the IP, than in the unadjuvanted and placebo groups.

The most common solicited local reactions were pain, tenderness, and induration at the administration site, and the most common solicited systemic symptoms were myalgia and fatigue. Three subjects discontinued dosing because of reactogenicity.

1.5.2 GEN-003-002: A Randomized, Double-Blind, Factorial Study to Compare the Safety and Efficacy of Varying Combinations of GEN-003 and Matrix-M2 in Subjects with Genital HSV-2 Infection

Subjects aged 18 to 50 years with documented diagnosis of genital HSV-2 infection for > 1 year were randomized in equal proportions to receive 3 IM doses of 1 of the following doses at intervals of 21 days:

- 30 µg each GEN-003 antigen + 25 µg MM2 (44 subjects)
- 30 µg each GEN-003 antigen + 50 µg MM2 (45 subjects)
- 30 µg each GEN-003 antigen + 75 µg MM2 (44 subjects)
- 60 µg each GEN-003 antigen + 25 µg MM2 (44 subjects)
- 60 µg each GEN-003 antigen + 50 µg MM2 (44 subjects)
- 60 µg each GEN-003 antigen + 75 µg MM2 (44 subjects)
- Placebo (45 subjects)

The study is complete; 310 subjects were enrolled.

Reduction in anogenital HSV-2 shedding was observed in all active treatment groups immediately after the last dose and persisted to 12 months after the last dose. The most effective dose combinations (60 µg each GEN-003 antigen with 50 µg MM2 and 60 µg each GEN-003 antigen with 75 µg MM2) also reduced HSV-2 lesion rates. Rate ratios (95% confidence intervals) for lesion rate at 12 months compared to baseline were 0.35 (0.18, 0.71; $P = 0.0033$) and 0.53 (0.31, 0.89; $P = 0.0165$), respectively. These 2 doses are currently being further evaluated in Study GEN-003-003.

GEN-003 elicited strong and durable humoral and cellular immune responses to the vaccine antigens (GB208 and GB217) including the production of HSV-2 neutralizing antibodies in all active dose groups.

GEN-003 exhibited an acceptable safety and tolerability profile for use as a therapeutic vaccine in all dose combinations. Ten SAEs in 8 subjects (femur facture, myocardial infarction, viral syndrome, post lumbar puncture syndrome, pyelonephritis, diverticulitis, bipolar disorder [exacerbation of existing condition, 2 episodes], cholecystitis, and overdose) were reported during the course of the study, and none was considered associated with treatment. No AESIs were reported.

Five subjects had an AE resulting in discontinuation of dosing. AEs occurred at similar rates and with similar severity in all the treatment groups, including the placebo group except for chills, which occurred about 2.5 times more frequently in the placebo group.

Three subjects discontinued dosing because of reactogenicity. The frequency of Grade 3 local reactions or systemic events within 7 days of any dose was 4.4% for subjects who received placebo and ranged from 20.0% to 43.2% among active dose groups; no Grade 4 local reactions or systemic events occurred.

The most common local reactions were pain and tenderness at the injection site, which occurred within 7 days following 1 or more vaccinations in most subjects who received active vaccine. Swelling occurred in about half of subjects who received active vaccine, and redness in about a quarter. The most common systemic events were fatigue and muscle aches, which occurred within 7 days following 1 or more vaccinations in most subjects who received active vaccine, and nausea, which occurred in 41.1% of subjects who received active vaccine.

1.5.3 GEN-003-002a: Rollover Trial for Placebo Subjects Previously Enrolled into GEN-003-002 - A Randomized, Double-Blind, Factorial Study to Compare the Safety and Efficacy of Varying Combinations of GEN-003 and Matrix-M2 in Subjects with Genital HSV-2 Infection

Subjects who received placebo in Study GEN-003-002 were offered enrollment in this study of the same active dose combinations given in that study.

The study is complete; 37 subjects were enrolled. The low number of subjects per group precluded a meaningful inference about the effect of antigen or adjuvant dose on the clinical efficacy of the different dose combinations.

No AEs leading to discontinuation of dosing, SAEs, AESIs, or deaths occurred during the study. The most common local reactions during the 7 days after vaccination were pain and tenderness at the injection site, which occurred in most subjects. The most common systemic events were fatigue and muscle aches, which also occurred in most subjects. The incidence and severity of overall AEs and treatment-related AEs were similar across all dose groups.

Within the limitations of the small sample size, the safety profile of GEN-003 in this study was similar to previous studies.

1.5.4 GEN-003-002b: A Long-term Follow-up Study of Efficacy and Immunogenicity of GEN-003 in Subjects with Genital Herpes Simplex Virus Type 2 (HSV-2) Infection

Subjects who received at least 1 dose of GEN-003 (any dose combination) and had no important protocol deviations in Study GEN-003-002 were offered enrollment in this follow-up study to evaluate long-term efficacy and immunogenicity up to 48 months postdose. A total of 140 subjects have been enrolled, and the study is ongoing.

1.5.5 GEN-003-003: A Randomized, Double-blind Study to Evaluate a New Formulation of GEN-003 in Subjects with Genital HSV-2 Infection

Subjects aged 18 to 50 with documented diagnosis of genital HSV-2 infection for > 1 year were randomized in a 1:1:1 ratio to receive 3 IM doses of 1 of the following doses of a new GEN-003 formulation at intervals of 21 days:

- GEN-003: 60 µg each antigen + 50 µg MM2 (43 subjects)
- GEN-003: 60 µg each antigen + 75 µg MM2 (44 subjects)
- Placebo: (44 subjects)

A total of 131 subjects were enrolled, and an interim analysis of data through 6 months postdose was conducted in December 2016 and January 2017. In this analysis, the 60 µg each GEN-003 antigen/50 µg MM2 dose reduced the rate of genital HSV-2 lesions during the 6 months after dosing compared to placebo (4.5% of days vs. 7.9%, respectively; 41% reduction vs. placebo, $P < 0.05$). GEN-003 also consistently demonstrated significant benefits compared to placebo for the secondary clinical endpoints (Table 1).

Table 1: Study GEN-003-003: Secondary Clinical Endpoints – Interim Analysis at 6 Months Postdose

Endpoint	Dose		
	Placebo N = 44	60 µg each GEN-003 antigen/50 µg MM2 N = 43	60 µg each GEN-003 antigen /75 µg MM2 N = 44
Mean duration of recurrences (days)	4.8	3.3	4.3
P-value versus placebo[a]	NA	0.01	0.64
Mean number of recurrences over 6 months	2.7	2.1	1.9
P-value versus placebo[a]	NA	0.08	0.02
Proportion of subjects recurrence-free 6 months after first dose (Kaplan-Meier estimate)	10%	29%	31%
P-value versus placebo[b]	NA	0.03	0.02
Proportion of subjects recurrence-free 6 months after last dose (Kaplan-Meier estimate)	13%	22%	36%
P-value versus placebo[b]	NA	0.17	0.02

Abbreviations: NA = not applicable.
a by Wilcoxon rank sum test
b by log-rank test

Overall shedding rates decreased from baseline in both vaccine dose groups. For the 60 µg GEN-003 antigens/50 µg MM2 group, both the decrease from baseline ($P = 0.03$) and the difference from the placebo group ($P = 0.05$) were statistically significant. These differences did not reach statistical significance for the 60 µg GEN-003 antigens/75 µg MM2 group.

IgG geometric mean titers (GMTs) to GB208 and GB217 and HSV-2 neutralizing antibodies increased after dosing in both active vaccine groups, peaking after Dose 1 for GB208 and Dose 3 for GB217 and HSV-2 neutralizing antibody. All post-treatment GMTs in both active vaccine groups were statistically higher than those in the same group at baseline (Day 1) and those in the placebo group at each corresponding time point.

The IFN-γ spot-forming cells (SFCs) peaked after Dose 3 for GB208 and after Dose 1 for GB217 in the 60 µg GEN-003 antigens/50 µg MM2 dose group. The IFN-γ SFCs peaked after Dose 1 for both GB208 and GB217 in the 60 µg GEN-003 antigens/75 µg MM2 dose group and declined by Day 50 (7 Days after Dose 3). The GrB SFCs peaked after Dose 1 for both GB208 and GB217 in both active vaccine groups. However, the GrB response remained steady at Day 50 for the 60 µg GEN-003 antigens/50 µg MM2 dose group but had declined in the 60 µg GEN-003 antigens/75 µg MM2 dose group. All post-treatment IFN-γ and GrB SFCs for both antigens in the both active vaccine groups were statistically higher than those in the same group at baseline and those in the placebo group at each corresponding time point. The observed decrease in the T-cell response in the 60 µg GEN-003 antigens/75 µg MM2 dose group at Day 50 corresponds with the decreased reduction in shedding and lesion rates seen with this dose group, implying that the T-cell response may be exhausted due to overstimulation.

No AESIs occurred during the study. Six SAEs, including 1 death, were reported in 4 subjects:

- Intraductal proliferative breast lesion
- Neck pain and pyrexia (2 SAEs) reported on the same day in a subject hospitalized and treated for culture-negative meningitis
- Post laminectomy syndrome requiring hospitalization; 2 months later, toxicity to various agents resulting in death
- Worsening mitral valve regurgitation requiring hospitalization for mitral valve replacement

None of these SAEs were considered related to vaccination by the Investigator.

Five subjects discontinued dosing for safety reasons (2 in each active group and 1 in the placebo group). Two subjects discontinued dosing due to solicited systemic events.

The frequency of Grade 3 local reactions or systemic events within 7 days of any dose was 13.6% for subjects who received placebo and ranged from 51.2% in the 60 µg GEN-003 antigens/50 µg MM2 group and 68.2% in the 60 µg GEN-003 antigens/75 µg MM2 group; no Grade 4 local reactions or systemic events occurred.

The most common local reactions were pain and tenderness at the injection site, which occurred within 7 days following 1 or more vaccinations in most subjects who received active vaccine. Swelling occurred in 64.4% of subjects who received active vaccine, and redness in 37.9%. The most common systemic events were headache, fatigue, and muscle aches, which each occurred

within 7 days following 1 or more vaccinations in about 80% subjects who received active vaccine.

1.6 Study Rationale

Data to date from clinical trials of GEN-003 administered as a 3-dose regimen have demonstrated an acceptable safety and tolerability profile, strong and durable antibody and T-cell immune responses to both vaccine-specific antigens, production of HSV-2 neutralizing antibodies, reduction in HSV-2 shedding, and clinical benefit. This study will evaluate the effect of an additional dose of GEN-003 administered at approximately 11 to 18 months after the last dose in the primary series.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Efficacy Objective

- To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose in reduction of genital herpes lesion rate

2.1.2 Secondary Efficacy Objectives

- To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose on genital herpes recurrence through 6 months:
  - Reduction of genital herpes recurrence frequency
  - Increase of proportion of subjects who are genital herpes recurrence-free
  - Increase of time to first genital herpes recurrence
  - Reduction of genital herpes recurrence duration

2.1.3 Safety Objective

- To evaluate the safety and tolerability of a maintenance dose of GEN-003 versus placebo

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint

- Genital herpes lesion rate (proportion of days with lesions present) in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

2.2.2 Secondary Efficacy Endpoints

- Frequency of genital herpes recurrences in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

- Proportion of subjects genital herpes recurrence-free at 6 months after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

- Time to first genital herpes recurrence in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

- Duration of genital herpes recurrences in the 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool

2.2.3 Safety Endpoints

- Reactogenicity
  - Local reactions: Pain, tenderness, swelling, redness
  - Systemic events: Fever, headache, chills, fatigue, nausea, vomiting, diarrhea, muscle aches

- AE, SAEs, AESIs, Medically attended AEs (MAAEs)

3 STUDY DESIGN

3.1 Overall Study Design

This study is a randomized, double-blind, placebo-controlled clinical trial of GEN‑003 in subjects who have received previous doses of GEN-003. Subjects who completed Study GEN-003-003 and received all 3 doses of GEN‑003, reported data in daily electronic reporting period on at least 80% of days, and had no important protocol deviation in that trial will be offered enrollment in this study. Subjects who meet all inclusion and no exclusion criteria and provide written informed consent for this study will be randomized within 11 to 18 months after the last active GEN-003 dose in a 1:1 ratio to receive 1 IM dose (the maintenance dose) of GEN-003 or placebo. Randomization will be stratified on the basis of the GEN-003 dose received by the subject in Study GEN-003-003.

Subjects will use a daily electronic tool for reporting the presence or absence of genital herpes lesions and the severity of genital herpes symptoms from Day 1 until the Month 6 Visit.

Subjects will complete the EuroQol – 5 Domains – 5 Levels (EQ-5D-5L) questionnaire on each day of the first recurrence after the maintenance dose through Month 6.

A serum sample will be collected from each subject for future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1).

At selected investigational sites, a whole blood sample will be collected and processed to isolate peripheral blood mononuclear cells (PBMCs) for future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1).

Local reactions and systemic events will be recorded for the first 7 days after the maintenance dose on the paper Diary Card; if any event is ongoing after Day 8, it will be followed until resolution. All AEs and concomitant medications will be recorded from Day 1 to Day 29/Month 1. After Day 29/Month 1 to the end of the study, only SAEs, AESIs, MAAEs, antiviral medications, and vaccines will be recorded. All AEs will be graded in accordance with the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials from Grade 1 (mild) to Grade 4 (life-threatening) (Appendix 2).

From Month 2 to Month 12, the investigational site will contact each subject by telephone or site visit for review of daily electronic reporting tool data and assessment of SAEs, AESIs, and antiviral use (through Month 6).

A Data Monitoring Committee (DMC) will review safety data at intervals of a minimum of 3 months until all subjects have completed the GEN-003/placebo dosing period. Any additional meetings and the specific safety monitoring plan will be detailed in the DMC charter.

3.2 Rationale for Study Design

3.2.1 GEN-003 Dose

The selection of the 60 µg GEN-003 antigens/50 µg MM2 dose was based on a benefit/risk analysis of data from prior GEN-003 clinical trials in which various GEN-003 antigen and adjuvant doses were evaluated. In all GEN-003 clinical trials, the primary biomarker for assessing vaccine effect was anogenital HSV-2 shedding.

In Study GEN-003-001, the 30 µg antigens dose with MM2 yielded the greatest reduction in HSV-2 shedding. No safety concerns arose during this study, and increasing antigen dose did not correlate with an increased incidence or severity of AEs.

In Study GEN-003-002, the 60 µg GEN-003 antigens groups generally outperformed the 30 µg antigen dose groups, regardless of adjuvant dose, in reducing the rate of HSV-2 shedding. Within the 60 µg antigens dose groups, 50 and 75 µg doses of MM2 yielded the greater and more durable reductions in HSV-2 shedding rates than 25 µg MM2. GEN-003 exhibited an acceptable safety and reactogenicity profile in all dose combinations. The rate of Grade 3 solicited symptoms (local reactions and systemic events) appeared to be related to dose and was highest in the 60 µg GEN-003 antigens/75 µg MM2 dose; however, discontinuations due to AEs were rare and did not appear to be related to dose.

In Study GEN-003-003, the 60 µg GEN-003 antigens/50 µg MM2 dose demonstrated a greater reduction in HSV-2 shedding rate than the 60 µg GEN-003 antigens/75 µg MM2 dose. Also, 6-month data demonstrated that both active groups had similar clinical efficacy against recurrent genital herpes. The vaccine containing the higher MM2 dose was associated with a modestly higher frequency of Grade 3 solicited symptoms than the 60 µg GEN-003 antigens/50 µg MM2 dose.

In an open session of a DMC meeting during the conduct of Study GEN-003-003, Genocea requested an opinion as to whether a dose group containing the lower dose of adjuvant (25 µg) should be added. In their written response, they stated: "DSMB is not convinced of a dose response effect on AEs, therefore an additional arm at a lower dose (as proposed by the Sponsor) may not reduce AEs."

On the basis of these results, the 60 µg GEN-003 antigens/50 µg MM2 was selected as the final dose for this and other future GEN-003 studies. This decision was supported by review of the shedding analyses and the modified intent-to-treat efficacy analyses of lesion rate, frequency, and duration of recurrence, which combined with the superior immunology and shedding responses of the 60 µg GEN-003 antigens/50 µg MM2 dose, supported the dose selection decision. Modified intent-to-treat analyses were used for the efficacy data to best represent real-world usage. The per-protocol analyses produced similar results.

3.2.2 Efficacy Endpoints

Genital herpes lesion rate in the 6-month period after the maintenance dose was selected as the primary endpoint because lesion rate is the most comprehensive measure of genital herpes disease burden. It is defined as the proportion of days with genital herpes lesions present.

Therefore, unlike other measures of vaccine efficacy, lesion rate accounts for both the frequency and duration of genital herpes disease. Use of this measure has been facilitated by technological advances in data collection methodology, namely, the development of electronic patient-reported outcomes tools that facilitate real-time daily data collection and encourages compliance through automatic reminders. In addition, assessment of lesion rate mitigates the impact of potential inconsistencies in the dataset. Endpoints related to recurrence frequency may be affected by patterns of lesion reporting that do not accurately reflect disease activity. For example, a subject may report on consecutive days: lesion – no lesion – lesion. This biologically improbable pattern may be counted as 2 recurrences, thereby increasing the estimate of disease frequency in a way that overstates true disease burden. However, this pattern of reporting would have minimal impact on lesion rate because 1 additional lesion day over the year-long follow-up period is unlikely to substantially affect the overall lesion rate.

The secondary efficacy endpoints evaluate other clinically important measures of vaccine effect, such as the frequency and duration of genital herpes recurrences.

3.3 Study Duration

The total duration of enrollment is estimated to be 2 months; the actual duration of enrollment may be longer. The duration of each subject's participation is up to 12 months. Thus, the study is expected to last approximately 14 months.

4 SUBJECT POPULATION

4.1 Inclusion Criteria

1. Completed Study GEN-003-003 (completed all study visits including the Month 12 visit)
2. Received all 3 GEN-003 doses (any dose combination) in Study GEN-003-003
3. Received last dose of GEN-003 within 11 to 18 months before the maintenance dose
4. Reported data in the daily electronic reporting period on at least 80% of days in Study GEN‑003-003
5. Collected at least 45 swabs (of 56 total expected swabs) during the Month 11 to 12 swab collection period in Study GEN-003-003
6. Willing and able to provide written informed consent
7. Willing to perform and comply with all study procedures, including attending clinic visits as scheduled and completion of a daily electronic reporting tool
8. Postmenopausal (≥12 months with no menses without an alternative medical cause) or willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, intrauterine device (IUD), or use of a spermicide combined with a barrier method (e.g., condom, diaphragm) for 28 days before and 90 days after receiving the IP

4.2 Exclusion Criteria

1. Did not meet all eligibility criteria in Study GEN-003-003, or received incorrect treatment (treatment different from that to which they were randomized) in Study GEN-003-003
2. Use of suppressive antiviral medication within 14 days before the maintenance dose
3. Use of topical steroids or antiviral medication in the anogenital region from 14 days before the maintenance dose
4. Use of tenofovir, lysine, or other medication or supplement known or purported to affect HSV recurrence frequency or intensity from 14 days before the maintenance dose
5. History of any form of ocular HSV infection, HSV-related erythema multiforme, or herpes meningitis or encephalitis
6. Immunocompromised individuals, including those receiving any type of systemic immunosuppressive medication within 30 days prior to the maintenance dose

7. Diagnosis or suspicion of an AESI (refer to Appendix 4 for list).
8. Diagnosis or suspicion of any other autoimmune disease not listed in Appendix 4
9. Vaccine-related SAE in GEN-003-003
10. Known current infection with HIV or hepatitis B or C virus
11. History of hypersensitivity to any component of the vaccine
12. Prior receipt of another vaccine containing HSV-2 antigens other than GEN-003
13. Receipt of any IP within 30 days prior to the maintenance dose of GEN-003/placebo
14. Receipt of any blood product within 90 days prior to the maintenance dose
15. Receipt of a live vaccine within 28 days prior to or any other vaccine within 14 days prior to maintenance dose
16. Planned use of any vaccine from the maintenance dose to 28 days after the maintenance dose
17. Pregnant or nursing women
18. History of drug or alcohol abuse that, in the opinion of the Investigator, would interfere with the subject's ability to comply with the requirements of the study
19. Other active, uncontrolled comorbidities that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the study requirements
20. Changes to medication used to manage an underlying comorbidity within 60 days prior to the maintenance dose

4.3 Criteria for Temporary Delay of Dosing

1. Febrile illness (temperature ≥38.0°C) or other acute illness within the past 48 hours

5 INVESTIGATIONAL PRODUCTS

5.1 GEN-003/Placebo

5.1.1 Formulation

GEN-003 consists of 2 recombinant antigens corresponding to 2 distinct HSV-2 proteins (GB208 and GB217) in combination with MM2 and diluent. Placebo is normal saline (diluent). These components are detailed in Table 2.

Table 2: Composition of GEN-003

Ingredient	Description	Dose
GB208	Corresponds to a ~39 kDa internal fragment of the ICP4 protein	60 µg
GB217	A recombinant version of the glycoprotein gD modified by a deletion of the transmembrane region	60 µg
Matrix-M2 Adjuvant	An immune stimulating complex-based adjuvant containing saponin fractions purified from Quillaja saponaria (soapbark tree) bark, phosphatidylcholine, and cholesterol	50 µg
Diluent	0.9% normal saline	Not applicable

5.1.2 Packaging and Labeling

GEN-003/placebo is prepared from the following 3 components before injection:

- GB208 and GB217 antigens in a lyophilized form are supplied in a 3 mL glass vial containing 125 µg, at a concentration of 0.25 mg/mL when reconstituted to a volume of 0.5 mL.
- MM2 is supplied in a second 3 mL glass vial containing 0.75 mL of MM2 at a concentration of 1 mg/mL.
- Normal saline (0.9% sodium chloride in water) from commercially available supply is supplied in a third vial for dilution of MM2 and reconstitution of antigens to the desired concentration and for use as placebo.

The vaccine components are packaged and labeled as IPs in accordance with applicable legal and regulatory requirements.

5.1.3 Storage

The antigens and MM2 are stored at 2°C to 8°C. The site must report excursions above 8°C to the Sponsor for an assessment of product quality.

Normal saline is stored at room temperature.

5.1.4 Preparation and Administration

Preparation of GEN-003/placebo must be performed by a designated unblinded site pharmacist (or otherwise qualified personnel) in accordance with the Pharmacy Manual provided by the Sponsor. It is important to note that preparation requires approximately 30 minutes.

GEN-003/placebo will be administered by trained study personnel. Each injection will consist of a total volume of 0.5 mL administered IM to the deltoid muscle of either arm. Both 1.0-inch and 1.5-inch needles will be provided. For obese subjects, a 1.5-inch needle is recommended.

Administration of GEN-003/placebo will be temporarily delayed if the subject has had a febrile illness (temperature ≥38.0°C) or other acute illness within the past 48 hours.

5.2 Randomization

Eligible subjects will be randomized in a 1:1 ratio to receive 1 IM dose of GEN-003 (60 μg each antigen and 50 μg MM2) or placebo.

Randomization will be stratified on the basis of the GEN-003 dose received by the subject in Study GEN-003-003.

Randomization will be achieved using the randomization component of the electronic case report form (eCRF). After subject eligibility is confirmed on this form, the system will send an e-mail to the unblinded pharmacist (or otherwise qualified personnel) with instructions for accessing the treatment assignment.

5.3 Blinding and Unblinding

Subjects, Investigators, and all study staff with direct subject contact will be blinded to treatment assignment (GEN-003 vs placebo). A designated unblinded pharmacist (or otherwise qualified personnel) at each site will prepare each dose. That individual should have no contact with the subjects and minimize contact with other site study personnel.

Unblinding of treatment assignment is discouraged. In the event of a medical emergency, for which the identity of the treatment assignment is critical to the care of a subject, the Investigator should call the Medical Monitor to discuss. In the event that unblinding is deemed necessary, an unblinded statistician will provide the treatment assignment to the Medical Monitor who will provide the information to the Investigator. A decision to discontinue a subject from further IP administration is not a rationale for unblinding the treatment assignment.

An unblinded statistician will be available to the DMC and Medical Monitor and will review interim analysis.

5.4 Investigational Product Accountability, Dispensing, and Destruction

The Investigator (or designee) will maintain an accurate record of the receipt of the GEN-003 components as shipped by the Sponsor (or designee), including the date received and lot or batch

numbers. In addition, an accurate disposition record will be kept, specifying the date and lot or batch numbers administered of each GEN-003 component or placebo to each subject.

At the completion of the study, all unused IP supplies will be returned to the Sponsor (or designee) or disposed of by the site in accordance with the Sponsor's (or designee's) written instructions.

5.5 Concomitant Medications

All concomitant medications, including over-the-counter medications and supplements, will be recorded in the eCRF from Day 1 to Day 29/Month 1. Use of antiviral medications will be recorded from Day 1 through Month 6.

5.6 Prohibited Medications

5.6.1 Antiviral Medication Use for Suppression or Recurrence of Genital Herpes

5.6.1.1 Suppressive Therapy

Subjects are forbidden from taking suppressive antiviral therapy through the Month 6 Visit.

5.6.1.2 Treatment of Recurrences

Up to 3 days of antiviral treatment is permitted for recurrences.

5.6.2 Medications and Supplements with Anti-HSV Activity

Use of acyclovir, valacyclovir, famciclovir, tenofovir (except for postexposure prophylaxis for HIV-1), lysine, or other medication or supplement known or purported to affect HSV recurrence frequency or intensity is prohibited from 14 days before the maintenance dose through the Month 6 Visit (except as noted in Section 5.6.1.2 for the acute treatment of genital herpes recurrences).

5.6.3 Immunosuppressive Medications

Systemic immunosuppressive medications are prohibited from 30 days before the maintenance dose to the end of the study.

5.6.4 Vaccines

Subjects may not receive a live vaccine within 28 days prior to the maintenance dose or any other vaccine within 14 days prior to the maintenance dose. In addition, subjects may not receive any vaccine from maintenance dose to 28 days after the maintenance dose. It is particularly important to reinforce this information if the subject will be receiving GEN-003/placebo during the influenza season.

5.7 Other Study Restrictions

5.7.1 Fluid and Food Intake

There are no restrictions on fluid or food intake during the study. However, because of the large volume of blood drawn on days when PBMCs are obtained, subjects should be well-hydrated.

5.7.2 Birth Control and Prevention of HSV-2 Transmission

Male and female subjects who are not postmenopausal (≥12 months with no menses without an alternative medical cause) must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, IUD, or use of spermicide combined with barrier method (e.g., condom, diaphragm) for 28 days before the maintenance dose through 90 days after the maintenance dose.

Subjects should be advised that GEN-003 has not been proven to reduce the likelihood of transmission of HSV-2 infection to an uninfected sexual partner.

5.8 Treatment Compliance

To ensure compliance with the dosing regimen, the dose of GEN-003/placebo will be administered by trained study personnel in the clinic who have been delegated that responsibility by the Investigator.

6 STUDY PROCEDURES

Refer to Appendix 1 for the Schedule of Events.

6.1 Definitions and Descriptions of Assessments and Procedures

Serum/urine pregnancy tests – For all women

Daily electronic reporting tool – Each day subjects will report the presence or absence of genital herpes lesions and genital herpes symptoms. In addition, if genital herpes symptoms are present, subjects will also rate the severity of the symptoms using the questions from the Genital Herpes Signs and Symptoms Diary (Appendix 5). Data must be entered daily through Month 6 Visit. Each subject will receive a daily reminder if data have not been entered for that day. The investigational site will receive a weekly e-mail notification if a subject has missed any data, and the site should make contact with the subject to promote compliance. Site staff will also review the data in the tool each week and at each visit.

Genital herpes lesions – Papules, pustules, vesicles, or ulcers, including those that have crusted. Symptoms of prodrome, redness, itchiness, or post-inflammatory hyperpigmentation of re-epithelialized ulcers do not constitute the presence of lesions.

EQ-5D-5L – The subject will complete this questionnaire on each day of the genital herpes first recurrence after the maintenance dose through Month 6. A pad of paper copies of the questionnaire will be provided to each subject after the maintenance dose is administered.

Reactogenicity – Subjects will be interviewed and examined at 1 hour after the maintenance dose and the following items will be entered in the eCRF:

- Local reactions: Pain, tenderness, swelling, redness
- Systemic events: Headache, chills, fatigue, nausea, vomiting, diarrhea, muscle aches
- Oral temperature

The subjects will also record these items on a paper Diary Card for the first 7 days after the maintenance dose, and the information will be entered in the eCRF.

Diary Card – Subjects will be provided a Diary Card to record local reactions, systemic events, and oral temperature for the 7 days after the maintenance dose. If there are any events ongoing after Day 8, these events will be followed until resolution and the stop date recorded. The Investigator (or Subinvestigator) will review Diary Cards with the subject. Any changes or comments to the subject's Diary Card must be made on the Diary Card and initialed and dated by the Investigator (or Subinvestigator). The Diary Card **AND** the Investigator's (or Subinvestigator's) assessment will serve as the source document. A sample of the Diary Card is provided in Appendix 3.

An event recorded on the Diary Card should not be recorded on the AE eCRF unless it meets the criteria of an SAE.

AEs (including SAEs, AESIs, and MAAEs) – refer to Section 7.

AESIs – refer to Appendix 4 for list.

6.2 GEN-003/Placebo Dosing Period

6.2.1 Maintenance Dose (Day 1) – Clinic Visit

The visit will take approximately 2.5 hours, including observation for 1 hour after vaccination.

Dosing must be delayed if the following criterion is met:

- Febrile illness (temperature ≥38.0°C) or other acute illness within the past 48 hours

The subject may be dosed once the criterion has been resolved and the criterion is no longer met.

The following procedures will be performed for screening:

- Written informed consent
- Medical history, including medication and vaccine history
- Weight
- Urine pregnancy test for all women

Eligibility for study enrollment will be checked. If a subject is excluded because of exclusion criteria 1 (important protocol deviation in Study GEN-003-003), 6 (immunocompromise), 7 (AESI), or 8 (autoimmune disease), then the details of the excluding deviation, diagnosis, or medication will be entered in the eCRF.

Upon determination that a subject meets all eligibility criteria, the following blood samples will be collected:

- Serum for future research
- At selected investigational sites: whole blood for PBMC isolation for future research

The subject will then be **randomized** to treatment assignment (as described in Section 5.2) and GEN-003/placebo administered.

The subject will remain at the investigational site for observation for at least 1 hour, and the following procedures will be performed 1 hour after GEN-003/placebo administration:

- Assessment of local reactions, systemic events, and AEs

Before discharge from the clinic, the subject will be given a Diary Card and instructed to record temperature, local reactions, and systemic events (at the same time each day). The subject will also be instructed that, if any event is ongoing after Day 8, to follow the event until resolution and report the stop date. The subject will be instructed to bring the Diary Card back to the clinic at the next visit.

Before discharge from the clinic, the subject will be given a pad of EQ-5D-5L questionnaires and instructed to complete 1 questionnaire each day of the first genital herpes recurrence.

If needed, the subject will be provided with an electronic device for use of the daily electronic reporting tool. The subject will be instructed in use of the daily electronic reporting tool. The subject will be asked to log into the system to ensure access before leaving the site.

6.2.2 Day 8 (± 3 Days) – Clinic Visit

The following procedures will be performed:

- Review of daily electronic reporting tool data
- Collection of completed EQ-5D-5L questionnaires, if completed
- Review of Diary Card
- Sample collection:
  - Serum for future research
  - At selected investigational sites: whole blood for PBMC isolation for future research
- Assessment of AEs (including SAEs, AESIs, and MAAEs)
- Assessment of concomitant medications and vaccines

The subject will be reminded to continue use of the daily electronic reporting tool.

6.2.3 Day 29/Month 1 (± 3 Days) – Clinic Visit

The following procedures will be performed:

- Review of daily electronic reporting tool data
- Collection of completed EQ-5D-5L questionnaires, if completed
- Sample collection:
  - Serum for pregnancy test for all women (unless surgically sterilized)
  - Serum for future research
  - At selected investigational sites: whole blood for PBMC isolation for future research
- Assessment of AEs (including SAEs, AESIs, and MAAEs)
- Assessment of concomitant medications and vaccines

The subject will be reminded to continue use of the daily electronic reporting tool.

6.3 Follow-up Period

6.3.1 Follow-up Telephone Calls

Follow-up telephone calls will be made at each of the following time points:

- Month 2 (Day 57 ± 7 days)
- Month 4 (Day 113 ± 7 days)
- Month 8 (Day 225 ± 14 days)
- Month 10 (Day 281 ± 14 days)

The following procedures will be performed:

- Review of daily reporting tool data (Month 4 only)
- Assessment of SAEs, AESIs, and MAAEs
- Assessment of antiviral medication through Month 6

The subject will be reminded to continue use of the daily electronic reporting tool.

6.3.2 Month 3 (Day 85 ± 7 days) and Month 6 (Day Day 169 ± 14 days) – Clinic Visits

The following procedures will be performed:

- Review of daily electronic reporting tool data
- Collection of completed EQ-5D-5L questionnaires, if completed
- Assessment of SAEs, AESIs, and MAAEs
- Assessment of antiviral medication

6.3.3 Month 9 (Day 253 ± 14 days) and Month 12 (Day 337 ± 14 days) – Clinic Visits

The following procedures will be performed:

- Assessment of SAEs, AESIs, and MAAEs

7 ADVERSE EVENTS

AEs will be reported in a manner consistent with the FDA Guidance for Industry and Investigators, "Safety Reporting Requirements for IND and BA/BE Studies," December 2012 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf).

7.1 Reporting Responsibilities

All AEs (including SAEs, AESIs, and MAAEs) will be recorded from the maintenance dose to Day 29/Month 1. After Day 29/Month 1 to the end of study, only SAEs, AESIs, and MAAEs will be recorded. It is the responsibility of the Investigator or Subinvestigator(s) to perform periodic assessment of AEs. Data describing AEs will be entered in the subject's medical record and eCRF, and as appropriate, an SAE/AESI report form. SAEs and AESIs will be reported to the Sponsor as described in Section 7.6.

7.2 Definitions

7.2.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

7.2.2 Medically Attended Adverse Events

A MAAE is an AE resulting in hospitalization, emergency room visit, or visit to or from medical personnel (other than routine health care visits). If a MAAE is "hospitalization" it should be reported as an SAE as described in Section 7.6 below.

7.2.3 Adverse Event of Special Interest

Refer to Appendix 4 for the list of AESIs.

7.2.4 Serious Adverse Event

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

- Death
- Life-threatening (An AE is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If it is not certain that an event meets the above definitions of an SAE, contact the Medical Monitor to discuss.

7.2.5 Relatedness (Causality)

Causality (relationship to GEN-003/placebo) assessment is required for all AEs that occur during clinical studies. The following terms will be used during this study:

- **Likely** - Reasons to consider an AE likely related to treatment may include, but are not limited, to the following:
  - Timing of the event relative to the administration of the IP
  - Location of the AE relative to the site of IP administration
  - Likelihood based on experience with similar products
  - A biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
  - The AE is repeated on subsequent treatments.
  - No other explanation is likely.

- **Unlikely** - An AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions or subject's known clinical state

7.2.6 Severity

Severity for all AEs, including laboratory abnormalities, will be reported in accordance with Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 2).

If an appropriate listing is not present in this table for an AE, the AE will be graded as follows:

- **Grade 1 (Mild)** - No interference with daily activity

- **Grade 2 (Moderate)** - Some interference with daily activity but medical intervention not required (e.g., doctor visit and/or prescription medicine); over-the-counter medicine permitted

- **Grade 3 (Severe)** - Prevents daily activity and requires medical intervention (e.g., doctor visit and/or prescription medicine)

- **Grade 4 (Potentially Life-threatening)** - Emergency room visit or hospitalization

7.3 Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator should be recorded as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening/baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (e.g., anemia) should be recorded as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

7.4 Physical Exam Abnormalities

Any physical exam abnormality deemed clinically significant by the Investigator at Day 1 should be reported as medical history. Any new physical exam abnormality deemed clinically significant by the Investigator during the study should be reported as an AE.

7.5 Pregnancy

The ICF will include information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy in both subjects and female partners of male subjects. If a female partner becomes pregnant, the Investigator will request consent from the partner to collect this information.

All remaining safety assessments should be performed for a subject who becomes pregnant. All pregnancies that occur during the study–including pregnancies in female partners of male subjects must be reported to the Sponsor on the Pregnancy eCRF and followed to conclusion. The outcome of each pregnancy must also be reported on the Pregnancy eCRF. Pregnancy alone is not an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason. However, an induced therapeutic abortion to terminate a pregnancy due to complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion is always considered an SAE.

7.6 Reporting of Serious Adverse Events and Adverse Events of Special Interest

SAEs and AESIs must be reported to the Sponsor or designee within 1 business day of becoming aware of the event by entering the data on the AE eCRF. If at the time the Investigator submits an initial SAE/AESI report the event has not resolved, the Investigator must provide a follow-up as soon as it resolves (or upon receipt of significant information if the event is still ongoing). All

SAEs/AESIs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Upon checking serious or AESI on the AE eCRF, a notification will be sent to the Medical Monitor and/or designee. Relevant eCRFs (including Medical History, Concomitant Medications, and Adverse Events) must also be completed to provide supporting documentation for the SAE/AESI. If there are additional documents that support the SAE/AESI (e.g., clinic or hospital records or procedure reports), they should be uploaded to the AE eCRF.

After review of the initial SAE/AESI information, the Medical Monitor may request additional documentation.

The Sponsor is responsible for notifying the relevant Regulatory Authorities of certain events. It is the Investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, IP-related events that occur during the clinical trial. Each site is responsible for notifying its IRB/EC of these additional SAEs.

7.7 Follow-Up of Adverse Events

A subject who experiences any AE, whether serious or not serious, will be monitored at appropriate intervals and receive appropriate treatment and medical supervision as clinically indicated. All AEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Clinically significant laboratory abnormalities should be confirmed within 48 hours or as soon as clinically indicated and then followed weekly until resolution.

8 SUBJECT AND STUDY DISCONTINUATION

Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

8.1 Screening Failures

Subjects who sign and date the informed consent form (ICF) but who fail to meet the inclusion and exclusion criteria (Section 4) are defined as screen failures. A screening log, which documents the subject's initials and reason(s) for screen failure, will be maintained by the Investigator for all screen failures. A copy of the log should be retained in the Investigator's study files.

If a subject fails screening because of Exclusion Criteria 1 (important protocol deviation in Study GEN-003-003), 6 (immunocompromise), 7 (AESI), or 8 (other autoimmune disease), then the details of the excluding deviation, diagnosis, or medication will be entered in the eCRF.

8.2 Premature Discontinuation from Study

A subject may be prematurely discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Loss to follow-up
- Death
- Noncompliance or unwillingness to comply with the procedures required by the protocol
- Investigator discretion
- Sponsor request
- Site termination
- Study termination

8.3 Procedures for Premature Discontinuation from Study

If a subject prematurely discontinues the study prior to Day 29/Month 1, then the procedures listed for Day 29/Month 1 (Section 6.2.3) should be performed.

If a subject prematurely discontinues the study after Day 29/Month 1, then the procedures listed for Month 12 (Section 6.3.4) should be performed.

8.4 Study or Site Termination

Conditions may arise during the study that could prompt the study to be halted or the study site to be terminated. Conditions that may prompt such considerations include, but are not limited to, the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study

- A decision on the part of Sponsor to suspend, discontinue, or shorten the study

- Study conduct at the study site may warrant termination under conditions that include, but are not limited to, the following:
  - Failure of Investigator(s) to enroll eligible subjects into the study
  - Failure of Investigator(s) to comply with International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, or national guidelines and regulations
  - Submission of false information from the research facility to the Sponsor, the Clinical Monitor, the United States Food and Drug Administration (FDA), or institutional review board/ethics committee (IRB/EC)
  - Insufficient adherence to protocol requirements
  - A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial
  - Institution or IRB/EC under investigation for cause by a Regulatory Authority

9 DATA MONITORING COMMITTEE

An independent DMC will review this study on an ongoing basis. The DMC will be comprised of 3 physicians with expertise in clinical trials for infectious diseases or of vaccines.

The primary responsibility of the DMC is to safeguard study subjects by reviewing and assessing on a periodic basis the clinical safety data being collected during the study. On the basis of these evaluations of the data, the DMC will make recommendations to the Sponsor to continue the study as planned, or to modify, temporarily suspend, or terminate the study. The DMC will also be responsible for identifying issues and making recommendations regarding the monitoring of subjects for safety, including collection of additional safety data.

The Sponsor will notify the DMC Chair of each SAE, AESI, and MAAE.

The DMC will meet at intervals of a minimum of 3 months until all subjects have completed the GEN-003/placebo dosing period. Any additional meetings and the specific safety monitoring plan will be detailed in the DMC charter.

The Sponsor will be responsible for notifying Investigators and Regulatory Authorities of any DMC recommendations, as appropriate.

10 STATISTICAL CONSIDERATIONS

Details of statistical analyses will be provided in a Statistical Analysis Plan (SAP). Any deviations from the SAP will be described in the Clinical Study Report.

10.1 Sample Size

No formal samples size calculations were performed for this study.

10.2 Analysis Conventions

In general, descriptive statistics for continuous variables will consist of subject count, mean (geometric mean), standard deviation (SD), median, and range. Descriptive statistics for categorical variables will consist of subject counts and percentages.

All analyses will be presented by treatment group. Sensitivity analyses may also be conducted for selected endpoints which incorporate the original treatment group assignments in Study GEN-003-003.

All efficacy, immunogenicity, and safety data will be included in data listings and summaries.

10.3 Analysis Populations

The following populations will be used for analysis of the study data.

- **Per-protocol population**: Subjects who received the maintenance dose, reported data in the daily electronic reporting period on at least 80% of days, and had no important protocol deviations (as defined in Section 11.7). Subjects will be analyzed according to the treatment actually received.
- **Modified intent-to-treat population**: All randomized subjects who received the maintenance dose. Subjects will be analyzed according to the treatment to which they were randomized.
- **Safety population**: All randomized subjects who received at least 1 dose of study vaccine. Subjects will be analyzed according to the treatment actually received.

10.4 Subject Disposition

The number and percentage of subjects enrolled in the study, completing the study, and discontinuing the study will be presented in a tabular format. Reasons for screen failure and for discontinuation will also be summarized.

Important protocol deviations (see Section 11.7) will be listed by subject.

10.5 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Additionally, the number and percent of subjects with past and current medical disorders (i.e., medical history coded using the Medical Dictionary for Regulatory Activities [MedDRA]) at Day 1 will be presented overall and by treatment group. Prior medications will be coded using the most current

WHO Drug Dictionary and summarized by anatomical therapeutic chemical class and preferred term with results presented by treatment group.

10.6 Concomitant Medications

Concomitant medications will be coded using the most current WHO Drug Dictionary and summarized by anatomical therapeutic chemical class and preferred term with results presented by treatment group.

10.7 Primary Efficacy Endpoint – Genital Herpes Lesion Rate

Genital herpes lesion rates (the proportion of days with genital lesions present) in the 6-month period after the maintenance dose will be compared between treatment groups using the Wilcoxon rank sum text.

10.8 Secondary Efficacy Endpoints

10.8.1 Frequency of Genital Herpes Recurrences

The frequency of genital herpes recurrences in the 6-month period after the maintenance dose will be calculated as the number of recurrences reported and summarized by mean, SD, median, and range. The median frequencies of recurrences will be compared between treatment groups using the Wilcoxon rank sum test.

10.8.2 Proportion of Subjects Recurrence-Free

The proportion of subjects in each treatment group who are genital herpes recurrence-free at 6 months after the maintenance dose will be tabulated and compared using a chi-square test for homogeneity of proportions.

10.8.3 Time to First Genital Herpes Recurrence

Time to first recurrence in the 6-month period after the maintenance dose will be tabulated and graphed using the Kaplan-Meier method. The log-rank test will be used to compare the time to first recurrence survival curves between the GEN-003 and placebo groups.

10.8.4 Duration of Genital Herpes Recurrences

Duration of genital herpes recurrences over the 6-month period after the maintenance dose will be calculated and summarized by mean, SD, median, and range. Median of individual mean duration of genital herpes recurrences will be compared using the Wilcoxon rank sum test.

10.8.5 Antiviral Medication Use

Antiviral medications will be coded using the most current WHO Drug Dictionary and summarized by anatomical therapeutic chemical class and preferred term with results presented by treatment group.

10.9 Safety Analysis

10.9.1 Reactogenicity

Local reactions and systemic events within 7 days after the maintenance dose will be summarized by treatment group for frequency and severity.

Antipyretic and analgesic medications taken within 7 days after the maintenance dose will be summarized by treatment group.

10.9.2 Adverse Events

AEs (including SAEs, AESIs, and MAAEs) will be coded using MedDRA and summarized by treatment group for frequency and severity. No formal statistical testing will be performed.

10.10 Interim Analysis

An interim analysis will be conducted after all subjects have completed the Month 6 visit and will include analysis lesion rates. The specific contents of the interim analyses will be detailed in the SAP.

11 ETHICAL AND ADMINISTRATIVE RESPONSIBILITIES

11.1 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized US representative and Investigator abide by GCP as described in ICH Guideline E6, and in US regulations described in 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

11.2 Institutional Review Board/Ethics Committee Approval

This protocol and the ICF and any subsequent modifications will be reviewed and approved by the relevant IRB/EC responsible for oversight of the study. A letter from the IRB/EC indicating approval of the study to be conducted by the Investigator will be provided to the Sponsor prior to initiation of any enrollment at that site. All reviews and approvals by the IRB/EC will be in accordance with 21 CFR Part 56 and ICH-GCP.

11.3 Informed Consent

The ICF document must be signed and dated prior to the initiation of study-related tests, and prior to administration of IP. The original signed ICF for each participating subject shall be filed with records kept by the Investigators. A copy of the ICF must be provided to the subject. If applicable, the ICF will be provided in a certified translation of the local language.

11.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of the Sponsor, the IRB/EC approving this research, and any applicable Regulatory Authorities will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

11.5 Biological Samples

Biological samples collected for this study will become the property of Genocea and may be used for future vaccine and immunology research conducted by or on behalf of Genocea or its affiliates, partners, or collaborators. No identifiable personal information will be associated with these blood samples. Any samples remaining 10 years after the end of the study will be destroyed.

11.6 Protocol Amendments

Any changes to the protocol will be made in writing by the Sponsor in the form of a protocol amendment. All protocol amendments will be sent to the Investigator, who is responsible for submitting the amendment to the IRB/EC for approval.

11.7 Protocol Deviations

There will be no site-specific exceptions or amendments to the written protocol. Strict compliance to the current protocol is required. Any unavoidable deviations must be fully documented and reported to the Sponsor and IRB/EC (as required). The Investigator is responsible for abiding by the IRB/EC rules and regulations for reporting protocol deviations. The Investigator will be requested to address each important protocol deviation with a written corrective and preventive action plan.

The following important protocol deviations will be reported in the eCRF:

- Subject did not meet study eligibility criteria
- Subject did not receive the correct treatment
- Subject received a vaccine in an excluded time period
- Subject used suppressive antiviral therapy

11.8 Case Report Forms

An eCRF will be used to record subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be signed by the Investigator or a Subinvestigator listed on the Form FDA 1572. In addition, patient-reported genital lesion, genital herpes symptom, and antiviral use information will be recorded by the subject in a daily electronic reporting tool. It is the responsibility of the Investigator to ensure that both the eCRFs and the daily electronic reporting tool are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of all electronic data will include an audit trail (to include changes made, reason for change, date of change and person making change).

11.9 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, subject Diary Cards, study progress notes, e-mail correspondences, computer printouts, laboratory data, IP accountability records, and electronic health records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by the Sponsor's representatives, the IRB/EC, and any applicable Regulatory Authorities.

11.10 Retention of Records

US regulations (21 CFR Part 312.62) require that records and documents pertaining to the conduct of this study and the distribution of IPs (including medical records, eCRFs, ICFs, test results, and IP records) be kept on file by the Investigator for 2 years after a marketing

application is approved for the IP for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified.

ICH-GCP requires that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

No study records should be destroyed without prior authorization from the Sponsor.

11.11 Study Monitoring

Site visits will be conducted by an authorized Sponsor representative (the monitor) to inspect study data, subjects' medical records, and eCRFs in accordance with ICH-GCP and national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The Investigator will permit representatives of the Sponsor, the IRB/EC, and any applicable Regulatory Authorities to inspect facilities and records relevant to this study.

11.12 Financial Disclosure

Investigators participating in this study will provide accurate financial disclosure information to the Sponsor, as required by 21 CFR Part 54. Investigators will update the financial information if any relevant changes occur during the study and for 1 year following completion of the study.

11.13 Publication and Disclosure Policy

Investigators and their staff shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Sponsor's products or research programs that is provided to the Investigator. All such persons must be instructed not to further disseminate this information to others. Investigators shall not use the confidential information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by the Investigator shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than disclosure by or through the Investigator; (c) information which, as evidenced by the Investigator's written records, was known by the Investigator prior to Genocea's disclosure; (d) information which is lawfully disclosed to the Investigator by a third party not under any obligation of confidence to Genocea; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Genocea.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Genocea Biosciences, Inc. Genocea reserves the right of prior review of any publication or presentation of information related to the study. Genocea reserves the right of prior review of any publication or presentation of information related to this study. Genocea may use these data now or in the future for presentation or publication at Genocea's discretion or for submission to Regulatory Authorities.

Genocea adheres to the general principles of publication of scientific data as articulated by the International Committee of Medical Journal Editors (ICMJE), the Pharmaceutical Research and Manufacturers of America (PhRMA) Principles of Conduct of Clinical Trials and Communication of Clinical Trial Results, as well as Good Publication Practice as established by the International Society for Medical Publication Professionals, and acknowledges its responsibility to publish results of Genocea-sponsored clinical trials. In all cases, study results must be reported in an objective, accurate, balanced, and complete manner and must contain a discussion of the limitations of the study. Results must be reported regardless of the outcome of the study or the country in which the study was conducted. Persons that fulfill the criteria for authorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) may be authors on publications based on their contributions to the design, conduct, results, and/or analysis of this clinical trial. Consistent with ICMJE and PhRMA guidelines, publications should list those people who made significant contributions to the publication but do not meet the criteria for authorship, for example, study conception and design, conceiving the idea for an article, conducting or managing a study, collecting data, performing statistical analysis, analyzing published literature, drafting or critically reviewing a manuscript. Investigators will have access to the data from this clinical trial for the preparation of scientific presentations and publications, with the understanding that the documents are not to be disclosed without prior written approval of Genocea. All results or analyses from data generated in this study that are intended for public presentation, including scientific meetings, must be shared with Genocea at least 30 days prior to submission (for abstracts and manuscripts) and presentation (posters or oral presentation). Publication of data subsets from individual institutions participating in multicenter trials should not precede the publication of the primary manuscript and—when developed—should always reference the primary publication of the entire trial.

By signing the Investigator Signature Page of this protocol, the Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this statement shall survive the completion of the study.

12 REFERENCES

Awasthi S, Friedman HM. Status of prophylactic and therapeutic genital herpes vaccines. Curr Opin Virol. 2014;6:6-12.

Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med; 1994;121:847–54.

Centers for Disease Control and Prevention. 2015 Sexually transmitted diseases treatment guidelines: genital HSV infections https://www.cdc.gov/std/tg2015/herpes.htm. Updated June 8, 2015. Accessed January 11, 2017.

Corey L. Herpes simplex virus type 2 and HIV-1: the dialogue between the 2 organisms continues. J Infect Dis. 2007;195:1242–4.

Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11–20.

de Bruyn G, Vargas-Cortez M, Vargas T, et al. A randomized controlled trial of a replication defective (gH deletion) herpes simplex virus vaccine for the treatment of recurrent genital herpes among immunocompetent subjects. Vaccine. 2006;24:914–20.

Famvir [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.

Fife KH, Warren TJ, Ferrera RD, et al. Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc. 2006;81:1321–7.

Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. J Infect Dis. 2004;190:1374–81.

Gupta R, Warren T, Wald A. Genital herpes. Lancet. 2007;370:2127–37.

Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. Lancet. 2012;379:641–7.

Kimberlin DW, Rouse DJ. Clinical practice. Genital herpes. New Engl J Med. 2004;350:1970–7.

Looker KJ, Garnett GP, Schmid GP. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. Bull World Health Organ 2008;86:805-12, A.

Martens MG, Fife KH, Leone PA, et al. Once daily valacyclovir for reducing viral shedding in subjects newly diagnosed with genital herpes. Infect Dis Obstet Gynecol 2009;2009:105376.

Skoberne M, Cardin R, Lee A, et al. An adjuvanted herpes simplex virus 2 subunit vaccine elicits a T-cell response in mice and is an effective therapeutic vaccine in Guinea pigs. J Virol. 2013;87:3930–42.

Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. N Engl J Med. 2002;347:1652–61.

Valtrex [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2013.

Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med. 1996;124:8–15.

Whitley R. Neonatal herpes simplex virus infection. Curr Opin Infect Dis. 2004;17:243–6.

World Health Organization. *WHO guidelines for the treatment of Genital Herpes Simplex Virus*. Geneva: World Health Organization, 2016. Available at http://apps.who.int/iris/bitstream/10665/250693/1/9789241549875-eng.pdf?ua=1. Accessed February 20, 2017.

Appendix 1 Schedule of Events

	Study Vaccine (GEN-003/Placebo) Dosing Period		
	Maintenance Dose		
Study Day/Month	**Day 1**	**Day 8**	**Day 29/Month 1**
Window (days)		**± 3**	**± 3**
	Clinic Visit	**Clinic Visit**	**Clinic Visit**
Informed consent	X		
Medical history	X		
Serum (S) / urine (U) pregnancy test	U		S
Concomitant medication and vaccine assessment	X	X	X
Eligibility criteria check	X		
Weight	X		
Serum for research purposes	X	X	X
PBMCs for research purposes [a]	X	X	X
Randomization	X		
GEN-003/placebo dosing [b]	X		
Distribution (D) / review (R) of Diary Card	D	R	
Instruction in daily electronic reporting tool	X		
Daily electronic reporting tool	Subject will report the presence or absence of genital lesions, and severity of genital herpes symptoms on each day from Day 1 through Month 6.		
Review of daily electronic reporting tool data		X	X
EQ-5D-5L	Subject will complete the EQ-5D-5L on each day of the first recurrence after the maintenance dose through Month 6.		
AE (including SAEs, AESIs, MAAEs) assessment	X	X	X

AE = adverse event; AESI = adverse event of special interest; EQ-5D-5L = EuroQol – 5 Domains – 5 Levels; MAAE = medically attended adverse event; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event.

a At selected sites only

b After confirmation of no febrile illness or other acute illness for the past 48 hours

Study Day/Month	Follow-up Period							
	Month 2	**Month 3**	**Month 4**	**Month 6**	**Month 8**	**Month 9**	**Month 10**	**Month 12**
Window (days)	**Day 57 ± 7 days**	**Day 85 ± 7 days**	**Day 113 ± 7 days**	**Day 169 ± 14 days**	**Day 225 ± 14 days**	**Day 253 ± 14 days**	**Day 281 ± 14 days**	**Day 337 ± 14 days**
	Phone Contact	**Clinic Visit**	**Phone Contact**	**Clinic Visit**	**Phone Contact**	**Clinic Visit**	**Phone Contact**	**Clinic Visit**
Daily reporting tool	Subject will report the presence or absence of genital lesions and severity of genital herpes symptoms on each day from Day 1 through Month 6.							
Review of daily electronic reporting tool data	X	X	X	X				
EQ-5D-5L	Subject will complete the EQ-5D-5L on each day of the first recurrence after the maintenance dose through Month 6.							
SAE/AESI/MAAE assessment	X	X	X	X	X	X	X	X
Antiviral and vaccine use assessment	X	X	X	X				

AE = adverse event; AESI = adverse event of special interest; EQ-5D-5L = EuroQol – 5 Domains – 5 Levels; MAAE = medically attended adverse event; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event.

a At selected sites only

b After confirmation of no febrile illness or other acute illness for the past 48 hours and no suspicion of AESI

Appendix 2 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

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

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Tables for Laboratory Abnormalities

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
Phosphorus – 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

Serum	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
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

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/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)

Urine	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

Appendix 3 Sample Diary Card

Please assess your symptoms and complete this form each evening (after 4 pm)

			Systemic Events							Local Reactions (at the Injection Site)				
Day	**Date**	**Oral Temp (°F)**	**Headache (0 to 3)**	**Chills (0 to 3)**	**Fatigue (0 to 3)**	**Nausea (0 to 3)**	**Diarrhea (0 to 3)**	**Vomiting (0 to 3)**	**Muscle Aches (0 to 3)**	**Pain (0 to 3)**	**Tenderness (0 to 3)**	**Swelling (0 to 3)**	**Swelling (size, mm)**	**Redness (size, mm)**
1														
2														
3														
4														
5														
6														
7														
8														

Instructions for Scoring Intensity

Intensity Grading Scale for Systemic Events	Intensity Grading Scale for Pain	Intensity Grading Scale for Tenderness	Intensity Grading Scale for Swelling
0 = None 1 = Mild, no interference with daily activity 2 = Moderate, some interference with daily activity 3 = Severe, significant interference, prevents daily activity	0 = None 1 = Mild, awareness of pain but it does not interfere with daily activity and no pain medication is taken 2 = Moderate, awareness of pain and there is interference with daily activity or requires non-narcotic pain medication 3 = Severe, awareness of pain and it prevents daily activity or requires use of narcotic pain medication	0 = None 1 = Mild, hurts to touch 2 = Moderate, hurts with movement 3 = Severe, significant discomfort at rest	0 = None 1 = Mild, does not interfere with daily activity 2 = Moderate, interferes with daily activity 3 = Severe, prevents daily activity

Instructions for Measuring Size: Use the ruler provided and record the number of millimeters across the widest part of the red/swelling area.

Appendix 4 Adverse Events of Special Interest

Gastrointestinal disorders

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases

- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma (including diffuse systemic form and CREST syndrome)
- Spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis)
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis (including site-specific variants: e.g., noninfectious encephalitis, encephalomyelitis, myelitis, and myeloradiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- Guillain-Barre syndrome (including Miller Fisher syndrome and other variants)
- Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy)

- Multiple sclerosis
- Myasthenia gravis, including Eaton-Lambert syndrome
- Narcolepsy
- Optic neuritis
- Transverse myelitis

Skin disorders

- Alopecia areata
- Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis)
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis)
- Medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and antineutrophil cytoplasmic antibody positive vasculitis [type unspecified], Henoch-Schönlein purpura, Behcet's syndrome, and leukocytoclastic vasculitis)

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including immunoglobulin A nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjogren's syndrome
- Stevens-Johnson syndrome
- Uveitis

Appendix 5 Genital Herpes Signs and Symptoms Diary

Genital Herpes Signs and Symptoms Diary
Version 5.0
January 17, 2017

Instructions to patients:
The following questions ask about signs and symptoms of your genital herpes. Signs of genital herpes may include having genital lesions (bumps, blisters, sores or scabs) that you may see or feel by touch, or drainage or swelling you might have from a genital lesion. These lesions may be on your genitals, genital area, thighs or buttocks.

Some people may experience certain symptoms with genital lesions including pain, itching, or pain with urination. Please read each question carefully and choose the one best answer for each question. Please consider any signs or symptoms due to your genital herpes at their **worst**, **in the last 24 hours**.

Q1: Do you have a genital herpes lesion (bump, blister, sore or scab) that you could see or feel by touch in the last 24 hours?
☐ Yes
☐ No

Q1a: If yes, approximately how many genital herpes lesions can you see or feel?
☐ 1 ☐ 2-4 ☐ 5-7 ☐ 8 or more

Q1b: (if patient answers "Yes" to Q1) Do you have an **open** genital herpes lesion (bump, blister, sore or scab)?
☐ Yes
☐ No

Q2: (if patients answers "No" to Q1) Did you experience any signs or symptoms in the last 24 hours that would indicate you will soon experience a genital herpes recurrence?
☐ Yes
☐ No

[Q3-Q4 asked ONLY if patient answers "YES" to Q1 or "YES" to Q2]
[Q5-Q7 asked ONLY if patient answers "YES" to Q1]

Q3: Rate the severity of any itching you have experienced in the genital area over the last 24 hours

No itch										Worst possible itch
0	1	2	3	4	5	6	7	8	9	10

Q4: Rate the severity of any pain (soreness or tenderness) you have experienced in the genital area over the last 24 hours

No pain										Worst possible pain
0	1	2	3	4	5	6	7	8	9	10

Q5: Rate the severity of any genital lesion pain during urination you have experienced over the last 24 hours

No pain with urination										Worst possible pain with urination
0	1	2	3	4	5	6	7	8	9	10

Q6: Rate the severity of any genital lesion draining or discharge you have experienced over the last 24 hours

No draining or discharge										Worst possible draining or discharge
0	1	2	3	4	5	6	7	8	9	10

Q7: Rate the severity of any genital lesion swelling you have experienced over the last 24 hours

No swelling										Worst possible swelling
0	1	2	3	4	5	6	7	8	9	10

Appendix 6 Protocol Amendments and Summary of Changes

Amendment 1, Protocol Version 1.1, 14 September 2017

The overall purpose of the amendment is to:

- Clarify that prescription medications to treat genital herpes (e.g., antivirals) will not be captured with daily electronic reporting tool
- Added an interim analysis following Month 5 – 6 swab collection period
- Updated safety reporting from study GEN-003-003
- Minor edits for clarity and to correct typographical errors

Summary of Changes

Section	Change	Rationale
Synopsis – Study Design, ¶ 2, and Section 3.1, ¶ 2	Subjects will use a daily electronic tool for reporting the presence or absence of genital herpes lesions~~,~~ severity of genital herpes symptoms ~~**and use of prescription medications to treat genital herpes**~~ from Day 1 until the end of the study.	Information on prescription medications to treat genital herpes will not be captured in electronic tool; only in eCRF.
Synopsis – Exploratory Endpoint and Section 2.2.3	Anogenital HSV-2 shedding rates: Proportion of anogenital swabs positive for HSV-2 DNA by PCR **before and after the maintenance dose using data from GEN-003-003 as subject baseline**	Inadvertently left out of original protocol.
Section 1.5.5 - 003-003: A Randomized, Double-blind Study to Evaluate a New Formulation of GEN-003 in Subjects with Genital HSV-2 Infection, ¶ 6	No AESIs ~~**or deaths**~~ occurred during the study. **Six** ~~Five~~ SAEs, were reported in **4** ~~3~~ subjects: Change to SAE: - Post laminectomy syndrome requiring hospitalization; 2 months later, **toxicity to various agents** ~~**ovarian cyst ruptured**~~ resulting in death New SAE: - Worsening mitral valve regurgitation requiring hospitalization for mitral valve replacement	Typo – death New information about SAE resulting in death and one additional SAE was reported since the original protocol was written.

Section	Change	Rationale
Section 6.1 - Daily electronic reporting tool	Each day subjects will report the presence or absence of genital herpes lesions and genital herpes symptoms ~~**and the use of antivirals**~~.	Electronic diary will not capture daily use of antivirals.
Section 6.2.1 - Maintenance Dose (Day 1) – Clinic Visit, ¶ 5	If a subject is excluded because of exclusion criteria 1 (important protocol deviation in Study GEN-003-003), 6 (immunocompromise), **7 (AESI)**, or **8 (autoimmune disease)**, then the details of the excluding deviation, diagnosis, or medication will be entered in the eCRF.	Correct error in order of exclusion criteria numbers.
Section 7.2.2 - Medically Attended Adverse Events	**A** ~~An~~ MAAE is an AE resulting in hospitalization, emergency room visit, or visit to or from medical personnel (other than routine health care visits). **If a MAAE is "hospitalization" it should be reported as an SAE as described in Section 7.6 below.**	Typo Clarified reporting of MAAE that results in hospitalization.
Section 10.11 – Interim Analysis	Added: **An interim analysis will be conducted after all viral shedding samples from Month 5 to 6 swab collection period have been tested and will include analysis of shedding and lesion rates. The specific contents of the interim analyses will be detailed in the SAP**.	Added an interim analysis to the protocol.
Original 11.12 – Protocol Deviations	Deleted entire section.	Already included in Section 11.7.
Appendix 1	Subjects will report the presence or absence of genital lesions~~,~~ severity of genital herpes symptoms~~, **and the use of prescription medication to treat genital herpes**~~ on each day from Day 1 through Month 12.	Electronic diary will not capture daily use of antivirals.

Amendment 2, Protocol Version 2.0, 13 October 2017

The overall purpose of the amendment is to:

- Change clinical objectives and endpoint observation period from 12 months to 6 months
- Eliminate swab collection and shedding analyses
- Eliminate blood collection for immunology at Months 6 and 12, and eliminate immunology analyses
- Eliminate RGHQoL data collection, and analyses of all quality of life assessments
- Allow for use of suppressive antiviral medication following the Month 6 visit.

Summary of Changes

Section	Change	Rationale
Synopsis and Section 2.1.2 - Secondary Efficacy Objectives	• To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose on genital herpes recurrence **through 6 months**: - Reduction of genital herpes recurrence frequency - Increase of proportion of subjects who are genital herpes recurrence-free ~~**at 12 months after the maintenance dose**~~ - Increase of time to first~~/**next** genital herpes recurrence - Reduction of genital herpes recurrence duration ~~**• To evaluate the efficacy of GEN-003 versus placebo administered as a maintenance dose in reduction of anogenital herpes simplex virus type 2 (HSV-2) shedding rates after the maintenance dose**~~	The Sponsor has stopped development of GEN-003 and therefore reduced collection and analyses of efficacy and viral shedding data
Synopsis and original Section 2.1.3 - Exploratory Objectives	Deleted entire section.	The Sponsor has stopped development of GEN-003 and therefore reduced collection and all analyses of viral shedding, immunogenicity, and quality of life data

Section	Change	Rationale
Synopsis and Section 3.1 - Overall Study Design, ¶2	Subjects will use a daily electronic tool for reporting the presence or absence of genital herpes lesions and the severity of genital herpes symptoms from Day 1 until the ~~end of the study~~ Month 6 Visit.	Modify design and procedures to reflect reduced data collection
¶3	~~Subjects will collect anogenital swabs for measurement of HSV-2 shedding twice a day for 28- day periods during Months 5 to 6 and Months 11 to 12. Samples will be analyzed for HSV-2 DNA by real-time quantitative polymerase chain reaction (PCR) assay.~~	
¶4	Subjects will complete the EuroQol – 5 Domains – 5 Levels (EQ-5D-5L) questionnaire on each day of the first recurrence after the maintenance dose **through Month 6**. ~~and the Recurrent Genital Herpes Quality of Life Questionnaire (RGHQoL) at Month 6 and Month 12.~~	
¶5	A serum sample will be collected from each subject for ~~evaluation of humoral responses~~ future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1). ~~, and at Month 6 and Month 12. Immunoglobulin G (IgG) specific to the vaccine antigens will be measured by enzyme-linked immunosorbent assay (ELISA), and HSV-2 neutralizing antibodies will be measured by a colorimetric assay.~~	
¶6	At selected investigational sites, a whole blood sample will be collected and processed to isolate peripheral blood mononuclear cells (PBMCs) for ~~evaluation of cellular responses~~ future research purposes before the maintenance dose (Day 1), 7 and 28 days after the maintenance dose (Day 8 and Day 29/Month 1). ~~, and at Months 6 and 12. Secretion of granzyme B (GrB) and interferon-gamma (IFN-γ)~~	

Section	Change	Rationale
¶8	~~**specific to the vaccine-specific antigens will be measured by a GrB/IFN-γ FluoroSpot assay.**~~ From Month 2 to Month 12, the investigational site will contact each subject ~~**monthly**~~ by telephone or site visit for review of daily electronic reporting tool data and assessment of SAEs, AESIs, and antiviral medication **(through Month 6)** ~~**and vaccine use**~~.	
Synopsis and Section 2.2.1 – Primary Efficacy Endpoint	• Genital herpes lesion rate (proportion of days with lesions present) in the ~~**12**~~ 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool	The Sponsor has stopped development of GEN-003 and therefore reduced collection and analyses of efficacy data
Synopsis and Section 2.2.2 – Secondary Efficacy Endpoints	• Frequency of genital herpes recurrences in the ~~**12**~~ 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool • Proportion of subjects genital herpes recurrence-free at ~~**12**~~ 6 months after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool • Time to first/next genital herpes recurrence in the **12** 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool • Duration of genital herpes recurrences in the **12** 6-month period after the maintenance dose: Based on subject report of genital lesions via a daily electronic reporting tool ~~**• Anogenital HSV-2 shedding rates: Proportion of anogenital swabs positive for HSV-2 DNA by PCR after the maintenance dose**~~	The Sponsor has stopped development of GEN-003 and therefore reduced collection and analyses of efficacy and viral shedding data
Synopsis and original Section 2.2.3 – Exploratory Endpoints	Deleted entire section.	The Sponsor has stopped development of GEN-003 and therefore reduced collection and all analyses of viral shedding, immunogenicity, and quality of

Section	Change	Rationale
		life data

Section	Change	Rationale
Synopsis – Statistical Methods: Efficacy	Genital herpes lesion rates (the proportion of days with genital lesions present) in the ~~**12**~~ 6-month period after the maintenance dose will be compared between treatment groups using the Wilcoxon rank sum text. ~~**The frequency of genital herpes recurrences in the 12-month period after the maintenance dose will be calculated as the number of recurrences reported and summarized by mean, standard deviation (SD), median, and range**~~. The median frequencies of recurrences **in the 6-month period** will be compared between treatment groups using the Wilcoxon rank sum test. The proportion of subjects in each treatment group who are genital herpes recurrence-free at ~~**12**~~ 6 months after the maintenance dose will be tabulated and compared using a chi-square test for homogeneity of proportions. Time to first recurrence in the ~~**12**~~ 6- month period after the maintenance dose will be tabulated and graphed using the Kaplan-Meier method. The log-rank test will be used to compare the time to first recurrence survival curves between the GEN-003 and placebo groups. ~~**Survival analysis with Cox model will be used to compare the time to next genital herpes recurrence. Duration of genital herpes recurrences over the 12-month period after the maintenance dose will be calculated and summarized by mean, SD, median, and range.**~~ Median of individual mean duration of genital herpes recurrences **during the 6-month period** will be compared using the Wilcoxon rank sum test. Deleted remainder of efficacy analysis methods.	The Sponsor has stopped development of GEN-003 and therefore reduced analyses of efficacy data

Section	Change	Rationale
Section 3.2.2 – Efficacy Endpoints, ¶1, Sentence 1	Genital herpes lesion rate in the ~~12~~ 6-month period after the maintenance dose was selected as the primary endpoint because lesion rate is the most comprehensive measure of genital herpes disease burden.	To reflect change in primary endpoint observation period
¶2	The secondary efficacy endpoints evaluate other clinically important measures of vaccine effect, such as the frequency and duration of genital herpes recurrences. ~~**In addition, the vaccine's ability to lower HSV-2 shedding rate will also be assessed. Viral shedding rate is a direct measurement of antiviral activity that has been used in previous studies of both vaccines and antiviral medications for genital herpes. It is an objective measure of antiviral activity against HSV-2.**~~	To reflect that viral shedding will no longer be analyzed
Section 5.5 – Concomitant Medications, Sentence 2	Use of antiviral medications and vaccines will be recorded from Day 1 through ~~**the end of the study**~~ Month 6.	Collection of lesion data will end at Month 6, therefore subjects will be allowed to use antiviral medications following the Month 6 visit
Section 5.6.1.1 – Suppressive Therapy	Subjects are forbidden from taking suppressive antiviral therapy during ~~**this study**~~ through the Month 6 Visit.	Collection of lesion data will end at Month 6, therefore subjects will be allowed to use antiviral medications following the Month 6 visit
Section 5.6.1.1 – Treatment of Recurrences	~~**Treatment of recurrences is NOT permitted during swab collection periods.**~~ Up to 3 days of antiviral treatment is permitted for recurrences ~~**that occur outside of swab collection periods**~~.	Genital swabbing has been eliminated from the protocol
Section 5.6.2 - Medications and Supplements with Anti-HSV Activity	Use of acyclovir, valacyclovir, famciclovir, tenofovir (except for postexposure prophylaxis for HIV-1), lysine, or other medication or supplement known or purported to affect HSV recurrence frequency or intensity is prohibited from 14 days before the maintenance dose ~~**to the end of the study**~~ through the Month 6 Visit (except as noted in Section 5.6.1.2 for the acute treatment of genital herpes recurrences).	Collection of lesion data will end at Month 6, therefore subjects will be allowed to use antiviral medications following the Month 6 visit

Section	Change	Rationale
Original 5.6.3 – Topical Steroids and Antiviral Medications	Deleted entire section.	Genital swabbing has been eliminated from the protocol; section is irrelevant
Section 6.1 - Definitions and Descriptions of Assessments and Procedures, Daily Electronic Reporting Tool, sentence 3	Data must be entered daily **through Month 6 Visit**.	To reflect amended reporting period
Section 6.1 - Definitions and Descriptions of Assessments and Procedures, Anogenital Swabs and RGHQoL	Deleted	Genital swabbing and RGHQoL have been eliminated from the protocol
Section 6.1 - Definitions and Descriptions of Assessments and Procedures, EQ-5D-5L, sentence 1	The subject will complete this questionnaire on each day of the genital herpes first recurrence after the maintenance dose **through Month 6**.	To reflect amended reporting period
Section 6.2.1 – Day 1, ¶6	Upon determination that a subject meets all eligibility criteria, the following blood samples will be collected: - Serum for ~~**immunogenicity testing**~~ future research - At selected investigational sites: whole blood for PBMC isolation for ~~**immunogenicity testing**~~ future research	Immunogenicity testing has been eliminated from the protocol
Section 6.2.2 (Day 8), 6.2.3 (Day 29), original Section 6.3.4 (Months 6 and 12)	Sample collection: - Serum for ~~**immunogenicity testing**~~ future research - At selected investigational sites: whole blood for PBMC isolation for ~~**immunogenicity testing**~~ future research	Immunogenicity testing has been eliminated from the protocol
Section 6.3.1 – Follow-up Telephone Calls, ¶1 ¶2	Deleted Month 7 call The following procedures will be performed: • Review of daily reporting tool data **(Month 4 only)** • Assessment of SAEs, AESIs, and MAAEs • Assessment of antiviral medication ~~**and vaccine use**~~ t**hrough Month 6**	No longer required Reflect new data collection periods

Section	Change	Rationale
Section 6.3.2 – Months 3 and 6	The following procedures will be performed: • Review of daily electronic reporting tool data • Collection of completed EQ-5D-5L questionnaires, if completed • Assessment of SAEs, AESIs, and MAAEs • Assessment of antiviral medication ~~**and vaccine use**~~ ~~**The subject will be reminded to continue use of the daily electronic reporting tool.**~~	Combined procedures for Months 3 and 6 (changed from 3 and 9) to reflect new data collection periods
Section 6.3.3 – Months 9 and 12	The following procedures will be performed: • Assessment of SAEs, AESIs, and MAAEs	Combined procedures for Months 9 and 12 (changed from 6 and 12) to reflect new data collection periods and elimination of blood sampling
Original Section 6.3.3 – Months 5 and 11	Deleted entire section	No longer required
Original Section 6.3.4 – Months 6 and 12	Deleted entire section and replaced with new section 6.3.3	See above
Section 10.4 – Subject Disposition, ¶3	~~**Analysis populations will be summarized in a tabular format.**~~	Data will be presented in listings only
Section 10.7 – Primary Efficacy Endpoint	Genital herpes lesion rates (the proportion of days with genital lesions present) in the ~~**12**~~ 6-month period after the maintenance dose will be compared between treatment groups using the Wilcoxon rank sum text.	To reflect analysis of new observation period
Section 10.8.1 – Frequency of Genital Herpes Recurrences, sentence 1	The frequency of genital herpes recurrences in the ~~**12**~~ 6-month period after the maintenance dose will be calculated as the number of recurrences reported and summarized by mean, SD, median, and range.	Reflect analysis of new observation period
Section 10.8.2 – Proportion of Subjects Recurrence-Free	The proportion of subjects in each treatment group who are genital herpes recurrence-free at ~~**12**~~ 6 months after the maintenance dose will be tabulated and compared using a chi-square test for homogeneity of proportions.	Reflect analysis of new observation period

Section	Change	Rationale
Section 10.8.3 – Time to First Genital Herpes Recurrence	Time to first recurrence in the ~~12~~ 6-month period after the maintenance dose will be tabulated and graphed using the Kaplan-Meier method. The log-rank test will be used to compare the time to first recurrence survival curves between the GEN 003 and placebo groups. ~~**Survival analysis with Cox model will used to compare the time to next genital herpes recurrence.**~~	Reflect analysis of new observation period; time to "next" recurrence will not be analyzed
Section 10.8.4 – Duration of Genital Herpes Recurrences, sentence 1	Duration of genital herpes recurrences over the ~~12~~ 6-month period after the maintenance dose will be calculated and summarized by mean, SD, median, and range.	Reflect analysis of new observation period
Section 10.8.5 – Anogenital Shedding Rate	Deleted entire section	Genital swabbing has been eliminated from the protocol
Section 10.9 – Exploratory Efficacy Endpoints	Deleted entire section	Data collection and analysis eliminated from the protocol
Original Section 10.9.6 – Quality of Life	Deleted entire section	Data collection and analysis eliminated from the protocol
Section 10.10 – Interim Analysis	An interim analysis **of lesion rates and recurrences** will be conducted ~~**after all viral shedding samples from Month 5 to 6 swab collection period have been tested and will include analysis of shedding and lesion rates**~~ on data collect to Month 6. The specific contents of the interim analyses will be detailed in the SAP.	Genital swabbing has been eliminated from the protocol
Appendix 1 – Schedule of Events, Serum and PBMCs	Serum for ~~**immunogenicity**~~ research purposes PBMCs for ~~**immunogenicity**~~ research purposes Eliminated at Months 6 and 12	Immunogenicity testing has been eliminated from the protocol
Appendix 1 – Schedule of Events, Daily electronic reporting tool	Subject will report the presence or absence of genital lesions, and severity of genital herpes symptoms on each day from Day 1 through Month ~~12~~ 6.	Reflect new data collection period
Appendix 1 – Schedule of Events, **EQ-5D-5L**	Subject will complete the EQ-5D-5L on each day of the first recurrence after the maintenance dose **through Month 6.**	Reflect new data collection period
Appendix 1 – Schedule of Events, Administration of	Eliminated	RGHQoL has been eliminated from the protocol

Section	Change	Rationale
RGHQoL		
Appendix 1 – Schedule of Events, Instruction in anogenital swab collection; Distribution, reconciliations and processing of swabs; Swab collection	Eliminated	Genital swabbing has been eliminated from the protocol