Protocol

Study ID: 218459

Official Title of the Study: A Phase 1, observer-blind, randomized, placebo-controlled study to evaluate reactogenecity, safety and immune response of an HSV-targeted immunotherapy in HSV-2 seronegative Japanese participants aged 18-40 years

NCT Number: NCT05989672

Date of Document: 20 Mar 2023

Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals SA (GSK)

Rue de l'Institut, 89
1330 Rixensart, Belgium

Primary study intervention	GSK investigational HSV-targeted immunotherapy (GSK3943104A)
Other study intervention	Placebo (sodium chloride)
Study number and abbreviated title	218459 (TH HSV REC-004)
Date of protocol	Final: 16 March 2023
Title	A Phase 1, observer-blind, randomized, placebo-controlled study to evaluate reactogenicity, safety and immune response of an HSV-targeted immunotherapy in HSV-2 seronegative Japanese participants aged 18-40 years.
Brief title	A study on the reactogenicity, safety and immune response of a targeted immunotherapy against HSV in healthy Japanese participants aged 18-40 years.
Sponsor signatory	Lan Lin, Clinical Project Lead, Vaccines Clinical Science

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.3

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Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the investigational intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study number and abbreviated title	218459 (TH HSV REC-004)
Date of protocol	Final: 16 March 2023
Title	A Phase 1, observer-blind, randomized, placebo-controlled study to evaluate reactogenicity, safety and immune response of an HSV-targeted immunotherapy in HSV-2 seronegative Japanese participants aged 18-40 years.
Investigator name	_____
Signature	_____
Date	_____
GSK Japan study representative, function and title	PPD PPD, Clinical Development (Vaccine), Vaccine Medical and Development, Japan Medical & Development, GlaxoSmithKline K. K.
Signature	_____
Date of signature	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of SAEs

GSK central back-up study contact for reporting SAEs: refer to Section 8.3.3.1.

Study contact for reporting SAEs: refer to the local study contact information document.

5. GSK Helpdesk for emergency unblinding

Refer to Section 6.3.4.1.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

Infections caused by HSV types 1 and 2 (HSV-1 and HSV-2) are frequent and affect people of every race, sex, age, and social status [Berger, 2008; Looker, 2008]. Using a pooled analysis, James *et al*. estimated that approximately 491.5 million people worldwide aged 15 to 49 years were infected with HSV-2 (which is equivalent to a global prevalence of 13.2% in this age population) and an estimated 23.9 million are new infections each year (which is equivalent to a global incidence of 0.6%) [James, 2020]. More women are infected than men, probably due to their greater biological susceptibility to HSV-2. Prevalence increases also with age, as infection is lifelong [Wald, 2004]. In the Fukuoka prefecture, the sera of 1244 subjects (574 men and 670 women) in the general population were screened for IgG antibodies against HSV by ELISA [Doi, 2009]. The seroprevalence of HSV-1 and HSV-2 were 59.7% and 8.4%, respectively. By sex, the seroprevalence of HSV-1 and HSV-2 was 55.4% and 7.4% in men and 63.3% and 9.3% in women, respectively. Of note, the study was conducted on a geographically limited population and may not be representative of the entire Japanese population. An international comparison of HSV-1 and HSV-2 seroprevalences revealed that the seroprevalence of HSV-1 in Japan is similar to those reported in other industrialized countries; whilst the seroprevalence of HSV-2 in Japan (4.4-11.1%) was comparable with the one reported in some European countries (4%–14%), but lower than in the United States (22%) [Doi, 2009].

HSV-1 and HSV-2 infections manifest in various forms, from asymptomatic to clinical presentations such as oral herpes or herpes labialis (‘cold sores’) and genital herpes. Both viruses infect epithelial cells at skin or mucosal surfaces (e.g., orolabial mucosa, genital mucosa) and then infect nerve endings, traveling via retrograde transport to the nerve axon, where they establish persistent infection in the trigeminal or lumbosacral ganglia. Reactivation can occur throughout a person’s life: the virus returns to epithelial surfaces via the axon to cause either oral or genital ulcers/lesions or asymptomatic viral shedding [Belshe, 2012]. In addition, it is known that infections with HSV-1 and HSV-2 may result in blindness, encephalitis and neonatal infections. The ability of the virus to be transmitted in the absence of symptoms, or when lesions are unnoticed, contributes to the spread throughout the population.

With the burden of the disease as described above and the limitations of antiviral therapies (e.g., daily intake in case of suppressive therapy, antiviral resistance in immunocompromised patients, limited impact on transmission [Corey, 2004] and no benefit in terms of the risk of acquisition or transmission of HIV-1 [Freeman, 2006]), there is still a high medical need globally for an improved treatment. HSV-2 infections are lifelong, incurable, stigmatizing and no existing interventions can effectively prevent them at population level [Gottlieb, 2019]. CCI [redacted]

GSK is developing a new investigational HSVTI CCI [redacted]. In the ongoing Phase 1/2 study (TH HSV REC-003), 2 formulations have been selected based on the safety, reactogenicity and immunogenicity data 1 month post-Dose 2 for proof-of-concept evaluation.

The purpose of the current study is to assess the safety, reactogenicity and immunogenicity of the 2 selected formulations in ethnic Japanese adults aged 18-40 years. CCI [redacted]

Objectives, endpoints and estimands:

Refer to Table 3.

1.2. Schema

Refer to Figure 1.

1.3. Schedule of Activities

Table 1 Schedule of Activities

Type of Contact	Screening	Study Intervention Administration Phase					Follow-up Phase
	Screening*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Phone call
Timepoints	Day -56	Day 1	Day 8	Day 29	Day 36	Day 57	Day 209
Obtain informed consent (Section 10.1.3)	●						
Check inclusion/exclusion criteria (Sections 5.1 and 5.2)	●	●					
Collect demographic data (Section 8.2.1.1)	●						
Measure and record height and weight (Section 8.2.1.2)	●						
Record medical and vaccination history (Section 8.2.1.3)	●						
Perform physical examination (Section 8.2.1.4)	●	●	○	●	○	○	
Perform pregnancy test (Section 8.2.1.5)	●	●**		●**			
Record pre-study intervention administration body temperature***		●		●			
Study group randomization (Section 6.3.2)		○					
Study intervention number allocation (Section 6.3.3)		●		●			
Check contraindications to subsequent study intervention administration (Section 7.1.1)				●			
Study intervention administration and recording of administered study intervention number (Section 6.1)		●		●			
Blood sampling for HSV testing (~3.5 mL) (Section 8.1.1)	○						
Blood sampling for hematology analysis (~2.0 mL) (Section 8.1.1)	●	●**	●	●**	●	●	
Blood sampling for biochemical analysis (~3.5 mL) (Section 8.1.1)	●	●**	●	●**	●	●	
Blood sampling for antibody determination (humoral immune response) (~8.5 mL) (Section 8.1.1)		○**		○**		○	
Blood sampling (PBMC) for CMI response analysis (~30.0 mL) (see Section 8.1.1)		○**		○**		○	
CCI [redacted]							

Type of Contact	Screening	Study Intervention Administration Phase					Follow-up Phase
	Screening*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Phone call
Timepoints	Day -56	Day 1	Day 8	Day 29	Day 36	Day 57	Day 209
CCI [redacted]							
Distribution of 'Participant card' (Section 8.3.5)	○						
Distribution of paper diary cards (Section 10.3.9)		○		○			
Return of paper diary cards (Section 10.3.9)			○	○	○	○	
Diary card transcription by investigator or delegate (Section 10.3.9)			●	●	●	●	
Record any concomitant medications/vaccinations (Section 6.8)	●	●	●	●	●	●	●
Record intercurrent medical conditions leading to elimination from analysis (Section 9.2.1)	●	●	●	●	●	●	●
Recording of solicited AEs (Days 1 to 7 post-each study intervention administration) (Section 10.3.9)		●	●	●	●		
Recording of unsolicited AEs (Days 1 to 28 post-each study intervention administration) (Section 10.3.9)		●	●	●	●	●	
Recording of MAEs (Section 8.3)		●	●	●	●	●	●
Recording of SAEs (Section 8.3)		●	●	●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (Section 8.3)	●	●	●	●	●	●	●
Recording of pIMDs (Section 8.3)		●	●	●	●	●	●
Recording of AEs leading to withdrawal from the study intervention or withdrawal from study (Section 7)		●	●	●	●	●	●
Recording of pregnancies and pregnancy outcome (Section 8.3)		●	●	●	●	●	●
Study conclusion (Section 4.4)							●

AE: adverse event; **CMI**: cell-mediated immunity; CCI [redacted] **MAE:** medically attended event; **PBMC**: peripheral blood mononuclear cell**; pIMD:** potential immune-mediated disease; **SAE:** serious adverse event.

Note: The double-line borders indicate the analyses which will be performed on all data obtained up to these timepoints (refer to Section 9.3.5).

● is used to indicate a study procedure that requires documentation in the individual electronic Case Report Form (eCRF).

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Screening evaluations may be completed up to 56 days before Visit 1 (Day 1). Study staff should allow sufficient time between the Screening visit and Visit 1 to receive and review HSV testing results, and hematology/biochemical results. If deemed necessary by the investigator, **re-testing** can be performed within the allowed interval. Only data from the re-sampling testing, if done, will be taken into consideration.

** Blood sampling and pregnancy test to be performed before each study intervention administration.

*** The preferred location for measuring temperature will be the oral cavity. Study intervention administration should not occur in case of fever (defined as temperature≥ 38.0°C, regardless of the location of measurement).
# Optional blood sampling. A separate informed consent form (ICF) will be signed by participants who agree to give their blood sample for this optional blood sampling.

Table 2 Intervals Between Study Visits

Interval	Reference Visits	Planned Visit Interval	Allowed Interval Range
Screening (Day -56) → Visit 1 (Day 1)	Screening visit	Up to 56 days*	
Visit 1 (Day 1) → Visit 2 (Day 8)	Study intervention administration Dose 1	7 days	7 – 9 days
Visit 1 (Day 1) → Visit 3 (Day 29)		28 days	28 – 33 days**
Visit 3 (Day 29) → Visit 4 (Day 36)	Study intervention administration Dose 2	7 days	7 – 9 days
Visit 3 (Day 29) → Visit 5 (Day 57)		28 days	28 – 33 days**
Visit 3 (Day 29) → Phone call (Day 209)		180 days	173 – 187 days

* Screening evaluations may be completed up to 56 days before Visit 1 (Day 1). Study staff should allow sufficient time between the Screening visit and Visit 1 to receive and review HSV testing results and hematology/biochemical results.
** Visits out of the allowed interval can lead to elimination from the Per Protocol set for analysis of immunogenicity.

2. INTRODUCTION

2.1. Background

Infections caused by HSV types 1 and 2 (HSV-1 and HSV-2) are frequent and affect people of every race, sex, age, and social status [Berger, 2008; Looker, 2008]. Using a pooled analysis, James *et al*. estimated that approximately 491.5 million people worldwide aged 15 to 49 years were infected with HSV-2 (which is equivalent to a global prevalence of 13.2% in this age population) and an estimated 23.9 million are new infections each year (which is equivalent to a global incidence of 0.6%) [James, 2020]. More women are infected than men, probably due to their greater biological susceptibility to HSV-2. Prevalence increases also with age, as infection is lifelong [Wald, 2004]. In the Fukuoka prefecture, the sera of 1244 subjects (574 men and 670 women) in the general population were screened for IgG antibodies against HSV by ELISA [Doi, 2009]. The seroprevalence of HSV-1 and HSV-2 were 59.7% and 8.4%, respectively. By sex, the seroprevalence of HSV-1 and HSV-2 was 55.4% and 7.4% in men and 63.3% and 9.3% in women, respectively. Of note, the study was conducted on a geographically limited population and may not be representative of the entire Japanese population. An international comparison of HSV-1 and HSV-2 seroprevalences revealed that the seroprevalence of HSV-1 in Japan is similar to those reported in other industrialized countries; whilst the seroprevalence of HSV-2 in Japan (4.4-11.1%) was comparable with the one reported in some European countries (4%–14%), but lower than in the United States (22%) [Doi, 2009].

HSV-1 and HSV-2 infections manifest in various forms, from asymptomatic to clinical presentations such as oral herpes or herpes labialis (‘cold sores’) and genital herpes. Both viruses infect epithelial cells at skin or mucosal surfaces (e.g., orolabial mucosa, genital mucosa) and then infect nerve endings, traveling via retrograde transport to the nerve axon, where they establish persistent infection in the trigeminal or lumbosacral ganglia. Reactivation can occur throughout a person’s life: the virus returns to epithelial surfaces via the axon to cause either oral or genital ulcers/lesions or asymptomatic viral shedding [Belshe, 2012]. In addition, it is known that infections with HSV-1 and HSV-2 may result in blindness, encephalitis and neonatal infections. The ability of the virus to be transmitted in the absence of symptoms, or when lesions are unnoticed, contributes to the spread throughout the population.

The affected age groups and severity of infection are influenced by the infecting virus type, the site of infection, host immune status, and whether the infection is initial or recurrent. Most recurrent genital herpes are caused by HSV-2, while HSV-1 infections are typically orolabial and acquired during childhood [Bradley, 2014; Johnston, 2016]. However, in industrialized countries, HSV-1 genital infections appear to be the leading cause of primary episode genital herpes among young adults [Roberts, 2003; Ryder, 2009; Bernstein, 2013; Johnston, 2016].

With the burden of the disease as described above and the limitations of antiviral therapies (e.g., daily intake in case of suppressive therapy, antiviral resistance in immunocompromised patients, limited impact on transmission [Corey, 2004] and no benefit in terms of the risk of acquisition or transmission of HIV-1 [Freeman, 2006]),

there is still a high medical need globally for an improved treatment. HSV-2 infections are lifelong, incurable, stigmatizing and no existing interventions can effectively prevent them at population level [Gottlieb, 2019]. CCI [redacted]

GSK is developing a new investigational HSVTI CCI [redacted] In the ongoing Phase 1/2 study (TH HSV REC-003), 2 formulations have been selected based on the safety, reactogenicity and immunogenicity data 1 month post-Dose 2 for proof-of-concept evaluation.

The purpose of the current study is to assess the safety, reactogenicity and immunogenicity of the 2 selected formulations in ethnic Japanese adults aged 18-40 years. CCI [redacted].

2.2. Study rationale

Please refer to the current IB for information regarding pre-clinical, clinical and studies of the HSVTI.

The intention of this study is to enable Japanese population to participate in the global Phase 3 study. The purpose of this study in Japan is to evaluate the safety, reactogenicity, and immunogenicity of 2 formulations of HSVTI (CCI [redacted]) in HSV-2 seronegative ethnic Japanese adults aged 18-40 years.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks, and expected AEs of CCI [redacted] can be found in the IB.

2.3.1. Risk assessment

The risk assessment and mitigation strategy for this study are outlined in the table below:

Important / Potential / Identified / Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
CCI		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences are estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Ruggerberg, 2007].	Participants with known hypersensitivity to any component of the study intervention are excluded from enrolment. The onset of study intervention-related allergic symptoms occurs shortly after study intervention administration. In order to treat participants with a serious allergic reaction to study intervention, all participants will need to remain under observation (i.e., visibly followed, no specific procedure) at the study site for at least 60 minutes after study intervention administration.
Potential immune-mediated diseases	pIMDs are a theoretical concern with adjuvanted vaccines [Tavares, 2013].	During the informed consent process, participants will be informed of this theoretical risk and asked to report any AEs that they consider serious/significant and/or for which they received medical attention at any point during the study. A pIMD is an AE of special interest and occurrence of pIMDs will be captured and described. All pIMDs will be collected up to 6 months after administration of the last dose of study intervention.
Study Procedures		
Pain and bruising	Pain or bruising at the site where blood is drawn.	Blood samples will be obtained by a trained professional and medical assistance will be available.
Syncope	Syncope (fainting) can occur following or even before any vaccination as a psychogenic response to the needle injection.	All participants will remain under observation at the study site for at least 60 minutes after study intervention administration.

AE: adverse event; CCI **pIMD:** potential immune-mediated disease.

2.3.2. Benefit assessment

Participants may gain information and medical advice about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations and blood testing [hematology and biochemistry data]).

2.3.3. Overall benefit/risk assessment

[redacted] is currently in a very early stage of clinical development and no efficacy has been demonstrated in humans yet. Considering the measures taken to minimize the risk to participants taking part in this study, the potential risks identified in association with the [redacted] are justified by the potential benefits linked to the development of the study intervention.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Study objectives, endpoints and estimands

Objectives	Endpoints and estimands
Primary	
To evaluate the reactogenicity and safety of the HSVTI.	• Percentage of participants reporting each solicited administration site event (redness, pain, and swelling) within 7 days (Day 1-Day 7) post-each dose. • Percentage of participants reporting each solicited systemic event (fever, fatigue, headache, myalgia, arthralgia) within 7 days (Day 1-Day 7) post-each dose. • Percentage of participants reporting unsolicited AEs within 28 days (Day 1-Day 28) post-each dose. • Percentage of participants reporting MAEs from Dose 1 (Day 1) up to 28 days post-Dose 2 (Day 57). • Percentage of participants reporting SAEs from Dose 1 (Day 1) up to 28 days post-Dose 2 (Day 57). • Percentage of participants reporting newly diagnosed pIMDs from Dose 1 (Day 1) up to 28 days post-Dose 2 (Day 57). • Percentage of participants reporting exacerbation of pre-existing pIMDs from Dose 1 (Day 1) up to 28 days post-Dose 2 (Day 57). • Percentage of participants reporting any hematological and biochemical laboratory abnormalities at pre-study intervention administration (Day 1), post-Dose 1 (Day 8 and Day 29), and post-Dose 2 (Day 36 and Day 57).
Secondary	
To evaluate the humoral immune response induced by the HSVTI.	• CCI [redacted] antibody GMC and seropositivity rate (assessed by ELISA) at pre-study intervention administration (Day 1), 28 days post-Dose 1 (Day 29), and 28 days post-Dose 2 (Day 57).
To evaluate the cellular immune response induced by the HSVTI.	• Geometric mean of CCI [redacted] CD4+/CD8+ T-cells frequency expressing at least 2 activation markers (IFN-γ, TNF-α, IL-2, IL-13, IL-17, 4-1BB and/or CD40L) and including at least one cytokine (assessed by CFC) at pre-study intervention administration (Day 1), 28 days post-Dose 1 (Day 29) and 28 days post-Dose 2 (Day 57).
To evaluate the safety of the HSVTI up to the end of follow-up period.	• Percentage of participants reporting MAEs from Dose 1 (Day 1) up to study end (Day 209). • Percentage of participants reporting SAEs from Dose 1 (Day 1) up to study end (Day 209). • Percentage of participants reporting newly diagnosed pIMDs from Dose 1 (Day 1) up to study end (Day 209). • Percentage of participants reporting pre-existing pIMDs from Dose 1 (Day 1) up to study end (Day 209).

Objectives	Endpoints and estimands
CCI [redacted]	

AE: adverse event; **CD4+/CD8+ :** cluster of differentiation 4/8; **CD40L:** cluster of differentiation 40 ligand; **CFC:** cell flow cytometry; **ELISA**: enzyme-linked immunosorbent assay; CCI [redacted] **GMC**: geometric mean concentration; CCI [redacted] **HSVTI:** HSV-targeted immunotherapy**; IFN-γ** : interferon-gamma; **IL (IL-2, IL-13, IL-17) :** interleukin; **MAE**: medically attended event; **pIMD**: potential immune-mediated disease; **SAE**: serious adverse event; **TNF-α:** tumour necrosis factor-alpha.

Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

4. STUDY DESIGN

4.1. Overall design

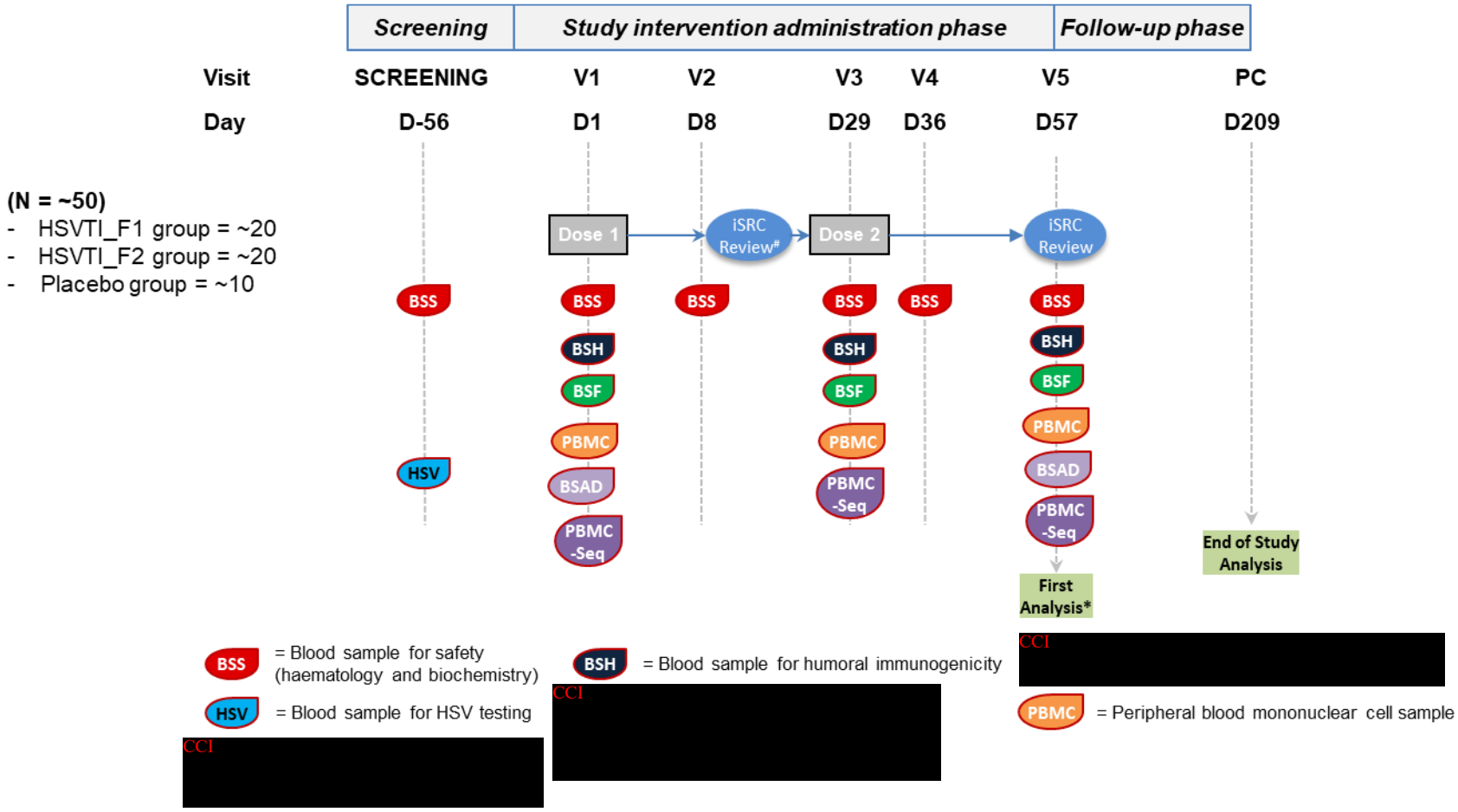
This is a Phase 1, randomized, placebo-controlled, observer-blind, single-country study with 3 parallel groups (refer to Figure 1):

- **HSVTI_F1group**: approximately 20 HSV-2 seronegative participants aged 18 to 40 years will receive 2 doses of HSVTI CCI [redacted].
- **HSVTI_F2 group**: approximately 20 HSV-2 seronegative participants aged 18 to 40 years will receive 2 doses of HSVTI CCI [redacted].
- **Placebo group**: approximately 10 HSV-2 seronegative participants aged 18 to 40 years will receive 2 doses of placebo as control.

The study will be overseen by an iSRC (refer to Section 8.2.3).

Day 57 will be considered as the Primary Completion Date.

Figure 1 Study design overview



D: day; **HSVTI**: HSV-targeted immunotherapy **iSRC**: internal safety review committee; **N**: number of participants; **PC**: phone call; **V**: visit; **PBMC:** peripheral blood mononuclear cell
The iSRC evaluation will take place approximately once a month until all participants complete the Day 57 visit to review all accumulated safety data. *Ad hoc* iSRC evaluations can be triggered in case any safety concern is observed.
* A first analysis will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 57 are available

Table 4 Study groups, intervention and blinding

Study groups	Number of participants	Age (Min-Max)	Study interventions	Blinding	
				Visit 1 → Visit 5 (Observer-blind)	Phone call (Observer-blind)
HSVTI_F1 group	~20	18 - 40 years	HSVTI	X	X
HSVTI_F2 group	~20	18 - 40 years	HSVTI	X	X
Placebo group	~10	18 - 40 years	Placebo (saline)	X	X

4.2. Scientific rationale for study design

This study will provide reactogenicity, safety and immunogenicity data in HSV-2 seronegative ethnic Japanese participants for 2 formulations of CCI [redacted]

Randomization is used to reduce selection bias and the placebo group is included as a control for reactogenicity, safety and immunogenicity assessments since there are currently no other existing HSV interventions that could be used as control. The study will be observer-blind as the presentation of the study intervention and the placebo is different.

4.3. Justification for dose

The 2 HSVTI formulations used in the present study were selected based on the safety and immunogenicity data obtained in study TH HSV REC-003 (215336) PART I on HSV-2 seronegative men and women aged 18 to 40 years.

4.4. End of Study definition

A participant is considered to have completed the study if the participant is available for the last scheduled contact (Day 209) as described in the protocol.

EoS is defined as LSLV (Day 209) or Date of the last testing released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

All participants must satisfy ALL the following criteria at study entry:

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the participant prior to performance of any study-specific procedure.
- Healthy participants as established by medical history and physical examination, at the discretion of the investigator, before entering into the study.
- Man or woman aged 18 to 40 years, included, at the time of screening.
- Japanese ethnic origin (defined as having been born in Japan with 4 ethnic Japanese grandparents and able to speak Japanese).
- Women of non-childbearing potential may be enrolled in the study. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche and menopause.
- Women of childbearing potential may be enrolled in the study, if the participant:
  - Has practiced highly effective contraception for 1 month prior to study intervention administration, and
  - Has a negative pregnancy test result at the Screening visit and on the day of each study intervention administration, and
  - Has agreed to continue highly effective contraception until Day 118, approximately 3 months post-Dose 2.

  Refer to Section 10.4.1.1 for definitions of woman of childbearing potential and Section 10.4.2 for highly effective contraception.

  Blood sample for simultaneous FSH and estradiol levels may be collected and tested locally at the discretion of the investigator to confirm non-reproductive potential according to local laboratory reference range.
- Seronegative for HSV-2 as determined by Western blot performed at the Screening visit.

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic, endocrine, or renal functional abnormality, as determined by physical examination or laboratory screening tests.
  - Clinically significant abnormalities may include but are not limited to: evidence of cardiac damage, heart failure categorized as class II or greater according to the New York Heart Association functional classification, heart valve disease, pulmonary uncontrolled persistent asthma despite treatment, uncontrolled

diabetes, or disease or disorder that may put the participant at risk or influence study results.

– Participants with a controlled underlying chronic co-morbidity may be enrolled, provided there have been no changes to their medication within 3 months prior to the Screening visit.

- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study or that would interfere with the immunogenicity assessments planned in this study.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention.
- Any confirmed or suspected immunosuppressive or immunodeficient condition or documented or suspected HIV infection, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- Recurrent history of or uncontrolled neurological disorders or seizures.
- At the screening visit: hematological parameters (hemoglobin level, white blood cell, platelet) and/or biochemical parameters (ALT, AST, creatinine, blood urea nitrogen) outside the normal laboratory ranges, unless the laboratory abnormalities are considered not clinically significant by the investigator.
- Body mass index $\leq$18 kg/m^2 or $\geq$35 kg/m^2.
- History of any form of ocular HSV infection, HSV-related erythema multiforme, or HSV-related neurological complications (including meningitis, encephalitis, radiculopathy, myelitis).

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention during the period beginning as of the Screening visit, or their planned use during the study period.
- Planned administration or administration of a vaccine* in the period starting 15 days* before each dose and ending 15 days* after each dose of study intervention administration**.

  * In case of adjuvanted and live-attenuated vaccines, this time window is to be increased to 30 days before and after each dose.

  ** In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced if, necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Administration or planned administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).

- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study intervention or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants. Inhaled, intra-articular and topical steroids are allowed.
- Prior receipt of a vaccine containing HSV antigens.

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug or invasive medical device).

5.2.4. Other exclusions

- Pregnant or lactating woman.
- Woman planning to become pregnant or planning to discontinue contraceptive precautions before Day 118 (approximately 3 months post-Dose 2).

5.3. Lifestyle considerations

Not applicable.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not randomized to a study intervention. Limited data for screening failures (at least informed consent date, demographic data, eligibility criteria check, reason for screening failure, and SAEs related to study participation or to a concurrent GSK medication/vaccine) will be collected and reported in the eCRF.

5.5. Criteria for temporarily delaying enrolment/study intervention administration

Study intervention administration (at Visit 1 [Day 1] and Visit 3 [Day 29]) may be postponed within the permitted time interval (see Table 2) until transient conditions cited below are resolved:

- Participants with hematological/biochemical values out of normal range* which are expected to be temporary may be enrolled/may receive the study intervention at a later date within the allowed time interval.

  *Unless the laboratory abnormalities are considered not clinically significant by the investigator.

- Acute disease and/or fever. Refer to the Table 1 (schedule of activities) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.

If the study intervention cannot be administered because of the special circumstance(s) (e.g., temporary hold of the study intervention administration as described in Section 8.2.3) and cannot not be resolved within the permitted time interval (see Section 1.3), the time interval between Dose 1 and Dose 2 can be extended up to 90 days.

Regarding participants with symptoms suggestive of Coronavirus disease 2019 (COVID-19) or with a confirmed severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection (as per WHO case definition [WHO, 2022]), and for whom a SARS-CoV-2 polymerase chain reaction test has not been confirmed as negative, the return of the participant to the site will follow the specific guidance from local public health and other competent authorities.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 5 Study interventions administered

Study intervention name:	HSVTI_F1		HSVTI_F2		Placebo (saline)
Study intervention formulation:	CCI [redacted]				NaCl (0.9%); Water for injections
Dose form (presentation):	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)	Solution for injection (syringe)
Type:	Investigational				Control
Product category:	Biologic				Combination Product
Route of administration:	Intramuscular				
Administration site:					
• Location	Deltoid				
• Directionality	Not applicable				
• Laterality**	Non-dominant arm				
Number of doses to be administered:	2		2		2
Volume to be administered***	Whole content		Whole content		At least 0.5 mL[#]
Packaging and labeling:	Refer to the Study Procedures Manual for further details				
Manufacturer:	GSK		GSK		GSK

CCI [redacted]

* The HSVTI formulations used in the present study were selected based on the safety and immunogenicity data obtained in study TH HSV REC-003 (215336) PART I on HSV-2 seronegative men and women aged 18 to 40 years.

** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.

*** Refer to the Study Procedures Manual for the volume after dilution.

[#] The volume of the saline pre-filled syringe may be between 0.6 and 0.8 mL. The full volume is to be injected.

Study participants must be observed closely for at least 60 minutes after the administration of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

All participants will be instructed to contact the study staff immediately should they manifest any signs or symptoms they perceive as severe or serious.

6.2. Preparation, handling, storage, and accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the SPM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study. The study center will be allocated a range of participant identification numbers.

6.3.2. Randomization to study intervention

The randomization of supplies within blocks will be performed at GSK, using MATerial EXcellence (MATEX), a program developed for use in SAS (Cary, North Carolina, US) by GSK. Entire blocks will be shipped to the study sites/warehouse.

6.3.3. Intervention allocation to the participant

Participants will be allocated individually numbered doses of the study intervention.

Approximately 50 participants are targeted to be enrolled (20 in HSVTI_F1 group, 20 in HSVTI_F2 group and 10 in Placebo group).

The randomization algorithm will use a minimization procedure accounting for HSV-1 status (positive vs. negative) and sex (women vs. men). All minimization factors will have equal weighting.

Allocation of the participant to a study group at the investigator site will be performed using a randomization system on internet. Refer to the SPM for additional information about the study intervention number allocation.

After obtaining the signed and dated ICF from the participant and having checked and confirmed their eligibility, the study staff in charge of the study intervention administration will access the randomization system on internet.

Once a participant is confirmed as a screen success, the randomization system will determine the study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated randomization system on internet.

The number of each study intervention administered must be recorded in the eCRF on the study intervention administration screen.

When randomization system on internet is not available, please refer to the randomization system on internet user guide or SPM for specific instructions.

6.3.4. Blinding and unblinding

Data will be collected in an observer-blind manner. The participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded, while other study personnel may be aware of the treatment assignment. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e., safety).

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

6.3.4.1. Emergency unblinding

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information is essential for the clinical management or welfare of the participant.

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via a randomization system on internet. The investigator may contact a GSK Helpdesk (refer to Table 6) if help is needed to access participant's study intervention information (i.e., if the investigator is unable to access SBIR).

A physician other than the investigator (e.g., an emergency room physician) or participant or family member may also request emergency access to the participant's study intervention information either via the investigator (preferred option) or investigator's back-up or via the GSK Helpdesk (back-up option). The participant card provides contact information for the investigator(s), their back-up and GSK Helpdesk.

Table 6 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Japan: 00 531 320 109 Back-up: 00 800 4344 1111 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.3.4.2. Unblinding prior to regulatory reporting of SAEs

GSK Global Safety staff may unblind the intervention assignment for any participant with a SUSAR. GSK Global Safety is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.11.1). For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy. GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting.

6.4. Study intervention compliance

When the study intervention is administered at the study site, participants will receive it directly from the unblinded study staff, under medical supervision. The date of administration of each study intervention dose will be recorded in the source documents.

6.5. Dose modification

Not applicable.

6.6. Continued access to study intervention after the end of the study

Not applicable.

6.7. Treatment of overdose

Not applicable.

6.8. Concomitant therapy

At each study visit/contact, the investigator(s) or their delegate(s) should question the participant about all medications/products taken, and vaccinations received by the participant.

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

- All concomitant medications, including vaccines/products, administered until Day 57.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines (refer to Sections 5.2.2 and 9.2.1 for further details).
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMDs including vaccines/products, as defined in Sections 8.3.1 and 10.3.9. These must also be recorded in the Expedited Adverse Event report.
- All concomitant medications associated with MAEs, including vaccines/products, administered after the first dose of study intervention (Day 1) until study end (Day 209).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. A participant who discontinued the study intervention may continue other study procedures (e.g., safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- AE requiring expedited reporting to GSK
- Unsolicited non-serious AE
- Solicited AE
- Not willing to receive study intervention
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.9.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be related to study intervention or non-study concomitant vaccine/product.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of study intervention. Refer to Section 10.3.6.1 for the definition of pIMDs.
- Abnormal hematological and biochemical parameters, unless the laboratory abnormalities are considered temporary or not clinically significant by the investigator.
- Occurrence of an AE assessed as related to the study intervention following the previous dose administration, which may place the participant at unreasonable or significant risk of injury or illness following repeat exposure to study intervention, based on the investigator's judgment.
- Anaphylaxis or other hypersensitivity reactions following the administration of study intervention.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Pregnant or lactating.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for them since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who was not available for the concluding contact planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- AEs requiring expedited reporting to GSK (refer to Section 10.3.11.1 for details)
- Unsolicited non-serious AEs
- Solicited AE
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because the participant has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.9.2).

7.3. Lost to follow-up

Participants will be considered 'lost to follow-up' if they fail to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the schedule of activities (Section 1.3).

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles), and obtained before the participant signed the ICF, may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the schedule of activities [Section 1.3]).

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

In exceptional situations (e.g., pandemic), consider following points:

- Safety follow-up can be performed by phone calls as a way of communicating with the participant to monitor the participant's progress.
- Diary cards can be sent by conventional mail.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with the participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

Table 7 Biological samples

Sample Type	Quantity	Unit	Timepoint	Sub-cohort Name
Blood sample HSV testing	Approximately 3.5	mL	Screening*	All screened participants
Blood sample for hematology analysis	Approximately 2.0	mL	Screening*	All screened participants
			Days 1, 8, 29, 36 and 57	All participants
Blood sample for biochemical analysis	Approximately 3.5	mL	Screening*	All screened participants
			Days 1, 8, 29, 36 and 57	All participants
Blood sample for antibody determination (humoral immunogenicity) analysis	Approximately 8.5	mL	Days 1, 29 and 57	All participants
Blood sample (PBMC) for CMI response analysis	Approximately 30.0	mL	Days 1, 29 and 57	All participants
CCI [redacted]	Approximately 17.0	mL	Days 1, 29 and 57	All participants
	Approximately 10.0	mL	Days 1 and 57	All participants
	Approximately 30.0	mL	Days 1, 29 and 57	All participants who will consent for it

CCI [redacted] **HSV:** herpes simplex virus; CCI [redacted] **CMI**: cell-mediated immunity; **PBMC:** peripheral blood mononuclear cell
*If deemed necessary by the investigator, re-testing can be performed within the allowed interval.

An overall blood volume of ~ 313 mL will be collected during the entire study period from all participants.

8.1.2. Laboratory assays

Table 8 Laboratory assays

Assay Type	System	Component	Method	Laboratory
Screening	Serum	Anti-HSV antibodies	Western Blot	University of Washington Molecular Virology laboratory
Humoral immunity (antibody determination)	Serum	CCI [redacted] antibodies	ELISA	GSK* or in a laboratory designated by GSK
Cell-mediated immunity	PBMC	CCI [redacted] (CD4+/CD8+) T-cells	CFC	

ELISA: enzyme-linked immunosorbent assay; CCI [redacted] **HSV:** herpes simplex virus; **PBMC:** peripheral blood mononuclear cell; **CD4+/CD8+:** cluster of differentiation 4/8; **CFC:** cell flow cytometry
* GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

CCI [redacted]

Note that tertiary objectives and endpoints/estimands are optional and might be assessed only if needed; therefore, not all related testings might be performed and reported.

CCI [redacted]

Additional exploratory testing on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK's laboratory or a laboratory designated by GSK. These assay(s) may not be represented in the objectives/endpoints/estimands of the Protocol and may be described in ancillary study Protocol(s), as needed.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	> 50	Anti-HSV antibodies
Humoral Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 57)	All participants	~ 50	CCI [redacted] antibodies
Cell-mediated Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 57)	All participants	~ 50	CCI [redacted] (CD4+/CD8+) T-cells

CCI [redacted]; **HSV:** herpes simplex virus; **CD4+/CD8+**: cluster of differentiation 4/8

8.1.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the HSVTI.

8.2. Safety assessments

The investigator(s) and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention and/or study.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Record demographic data such as year of birth, sex at birth, HSV-1 status, race, and ethnicity in the participant's eCRF during the Screening visit.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2.1.2. Measure and record height and weight

Height and weight will be collected during the Screening visit in order to calculate the participant's body mass index (as part of the eligibility criteria). Data will be recorded in the eCRF.

8.2.1.3. Medical and vaccination history

Obtain the participant's medical and vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the Screening visit in the eCRF.

*The following vaccination history must be checked and recorded, if applicable:

- Any previous administration of an investigational HSV vaccine at any time.
- Any vaccines to be administered between the Screening visit and Visit 1 (Day 1).

8.2.1.4. Perform physical examination

- A physical examination will be performed for each participant at the Screening visit and before each study intervention administration (Visit 1 [Day 1] and Visit 3 [Day 29]). The following information will be recorded in the eCRF: oral body temperature, resting vital signs (before blood collection for laboratory test),

including systolic/diastolic blood pressure, and heart rate after at least 10 minutes of rest.

- A targeted physical examination at each subsequent visit will be performed only if the participant indicates during questioning that he/she might have some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Collected data do not need to be recorded in the eCRF, unless required (see Section 8.3).
- If the investigator determines that the participant's health on the day of study intervention administration (Visit 1 [Day 1] and Visit 3 [Day 29]) temporarily precludes dosing, the visit will be rescheduled within the allowed interval (see Table 2). Refer to Section 5.5 for the list of criteria for temporary delay of study intervention administration.
- Treatment of any abnormality observed during this examination must be performed according to local medical practice outside this study or by referral to an appropriate healthcare provider.

8.2.1.5. Perform pregnancy test

Women of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

- Only women with negative pregnancy test result at the Screening visit will be included in the study.
- The study intervention may only be administered if the pregnancy test result is negative at Visit 1 (Day 1) and Visit 3 (Day 29).

For women of non-childbearing potential, the specific reason for not performing a pregnancy test (pre-menarche, bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy, post-menopause or other) needs to be documented in the participant's source document.

Refer to Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.2. Clinical safety laboratory tests

Refer to Section 10.2.2 for the list of clinical laboratory safety assessments required by the protocol. These assessments must be conducted according to the clinical laboratory manual and the schedule of activities (Section 1.3). The analyses of these samples will be performed locally.

8.2.3. Study holding rules and safety monitoring

This study will be overseen by an iSRC operating under a charter and by a SRT (in a blinded manner). The iSRC is a group of GSK experts (clinicians, safety representatives and statisticians), independent from the HSV-targeted immunotherapy project team, with

a proper medical and scientific expertise to guarantee the safety and wellbeing of the participants.

The iSRC evaluation will take place approximately once a month until all participants complete Day 57 visit to review all accumulated safety data. In addition to the planned iSRC evaluations, ad hoc iSRC evaluations can be triggered if any potential safety issue is observed.

During an iSRC evaluation, the iSRC will determine whether any of the predefined holding rules (refer to Table 10) are met or whether there is any other safety signal, based on all available unblinded safety data.

8.2.3.1. Study Holding Rules

Holding rules to be applied during the Study Intervention Administration Phase are presented in Table 10. Meeting any of these holding rules will trigger a hold of study intervention irrespective of number of participants enrolled and/or timing of the event.

- Holding rules 1a-1d will be monitored by the investigators on a continuous basis throughout the study. Meeting any of these holding rules will trigger a hold of study intervention administration, irrespective of number of participants enrolled and/or timing of the event.

  If an investigator detects one of the holding rules mentioned above, the study intervention administration will be immediately put on hold. GSK will be immediately informed and the data will be entered in the eCRF. It is GSK's responsibility to put the study intervention administration on hold at all sites.

- Holding rules will be assessed by the iSRC during safety evaluations on unblinded data. Meeting any of these holding rules will trigger a hold of study intervention administration.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs (those that are not meeting the definition of holding rule 1b), missed visits due to study intervention related AEs, Grade 1 and Grade 2 solicited and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from 7 to 28 days after study intervention administration (refer to Section 10.3.10.1 for assessment of intensity). However, to the extent of their availability, these data will also be reviewed by the SRT and iSRC to allow an overall assessment of the benefit/risk ratio of study intervention administration.

Table 10 Study Holding Rules

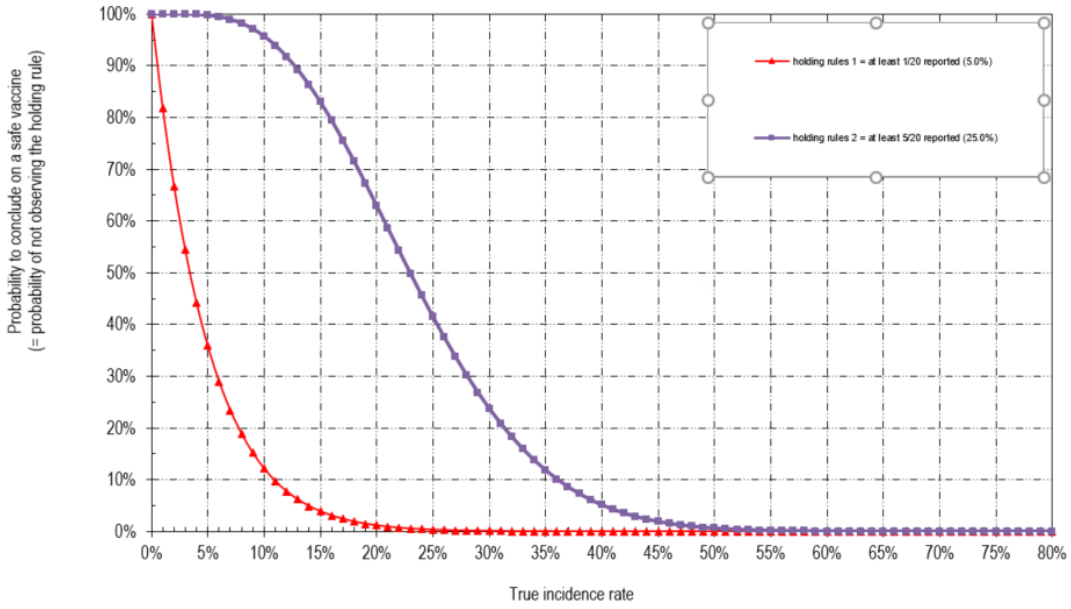
Holding Rule	Event	Number of Participants
1a	Death or any life-threatening **SAE**, regardless of causality	≥ 1
1b	Any **non-life-threatening SAE** that can be reasonably attributed to the study intervention administration	≥ 1
1c	Any **withdrawal** from the study (by investigator's or participant's request) and/or study intervention administration, following a Grade 3 AE	≥ 1
1d	Any solicited administration site or solicited systemic AE leading to **hospitalization**, or **necrosis** at the injection site, with an event onset within the 7-day (Days 1-7) post-study intervention administration period	≥ 1
2a	**Any Grade 3 solicited administration site AE** (lasting 48 hours or more) in an investigational group, with an event onset within the 7-day (Days 1-7) post-study intervention administration period	≥ 25% (and ≥ 2 participants in each HSVTI group)
2b	Any **Grade 3 solicited systemic AE** (lasting 48 hours or more) in an investigational group, with an event onset within the 7-day (Days 1-7) post-study intervention administration period	≥ 25% (and ≥ 2 participants in each HSVTI group)
2c	Any **Grade 3 unsolicited AE** in an investigational group, that can be reasonably attributed to the study intervention administration, with an event onset within the 28-days (Days 1-28) post-study intervention administration period OR Any Grade 3 abnormality* in pre-specified hematological or biochemical **laboratory parameters** in an investigational group, between Day 1 and Day 29 post-study intervention administration period	≥ 25% (and ≥ 2 participants in each HSVTI group)

AE: adverse event; **SAE:** serious adverse event
*Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see Table 18).

Figure 2 illustrates the probability to reach the study holding rules following study intervention administration:

- For holding rules 1, using a cut-off of 1/20, there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 8% and there is more than 36% chance that the holding rule is not met for a study intervention with a true incidence rate below 5%.
- For holding rules 2, using a cut-off of 5/20, there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 32% and there is more than 63% chance that the holding rule is not met for a study intervention with a true incidence rate below 20%.

Figure 2 Risk Assessment Curves for Study Holding Rules



If a holding rule is met, the investigator must suspend administration of the study intervention and inform GSK immediately (e.g. holding rules 1a-d). Refer to Table 13 for contact information. GSK will inform the investigator if holding rules 2a-c are met.

The following communication sequence must be followed:

- The concerned study staff must put study interventions administration on hold.
- The concerned study staff must immediately inform their local GSK contact defined in Section 8.3.3.1).
- LML will inform the CSL, who will then inform the iSRC chair and the SRT lead.
- All informed study staff will confirm to their local contact that action has been taken to provide appropriate documentation to GSK.
- GSK will further evaluate the case by the iSRC and GSK's GSB and will take the decision to restart the study intervention administration, modify or stop the study. All study staff will be informed about that final decision by their local GSK contact.

In case the study is put on hold while a participant is in the screening process, and the timing to conduct the first study intervention administration at Visit 1 (Day 1) would exceed the interval defined in Table 2, all screening procedures as detailed in the SoA (Table 1) must be performed again. Data from this re-screening, if performed, must be encoded in the eCRF.

8.2.3.2. Outcome of Safety Evaluation

- If no safety concern is observed, the favorable outcome of safety evaluations will be documented and provided in a written way to the investigators.

- If a safety concern is observed during the safety evaluations or if any of the holding rules is met (Table 10):
  - The study CSL (or his/her delegate) will be accountable for notifying the investigator to temporarily put all study intervention administration on hold immediately, but all other procedures relating to safety and immunogenicity can continue as planned for participants received at least one dose of study intervention.
  - Following an internal review, GSK will decide to suspend, modify or continue the conduct of the study. This decision will be communicated to the investigator/ IEC/IRB and PMDA as applicable by national regulation.

Refer to Section 10.1.5 for details regarding the iSRC and SRT.

8.3. Adverse Events, Serious Adverse Events and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 11 Timeframes for collecting and reporting of safety information

Event	Screening*	Visit 1		Visit 2		Visit 3		Visit 4	Visit 5	Phone call
		Day 1	Day 7	Day 8	Day 28	Day 29	Day 35	Day 36	Day 57	Day 209
	Up to **56** days before Visit 1	**Dose 1**	7 days post-Dose 1		28 days post-Dose 1	**Dose 2**	7 days post-Dose 2		28 days post-Dose 2	**Study conclusion**
Administration site and systemic solicited events										
Unsolicited AEs										
MAEs pIMDs										
SAEs (all, fatal, related) AEs/SAEs leading to withdrawal from the study										
SAEs related to study participation or concurrent GSK medication/vaccine										
Pregnancies and outcome										

AE: adverse event; **MAE:** medically attended event; **pIMD:** potential immune-mediated disease; **SAE:** serious adverse event
*i.e., consent obtained

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.11. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and if the investigator considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 13.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/pIMD/pregnancies are detailed in Section 10.3.9.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.10.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pIMD/pregnancy.

8.3.2.1. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that the review occurred, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values reported during the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator. Refer to Section 10.3.7 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified, and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD/pregnancy, it must be reported to GSK using the required

documentation and within the timeframes mentioned in Table 12. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.10.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Please refer to Section 10.3.11 for further details regarding the reporting of SAEs/pIMDs/pregnancies.

Table 12 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ⌗	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report
pIMDs	24 hours** ⌗	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

*** Timeframe allowed after receipt or awareness of the information by the investigator/site staff.**
****Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.**
⌗ For each SAE/pIMD, the investigator(s) must document in the medical notes that they have reviewed the SAE/pIMD and have provided an assessment of causality.

8.3.3.1. Contact information for reporting SAEs, pIMDs, pregnancies and study holding rules

Table 13 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pIMDs, pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** If a holding rule is met, the investigator must immediately inform the LML.
Back-up study contact for reporting SAEs, pIMDs, pregnancies Available 24/24 hours and 7/7 days: **GSK Global Safety** Email address: ogm28723@gsk.com	**Back-up study contact for escalation of holding rules** Refer to the local study contact information document

8.3.4. Treatment of expedited adverse events (SAE/pIMD)

Any medication administered for the treatment of an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to Section 10.3.11.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back-up.

8.3.6. Safety follow-up call

At 6 months post-Dose 2 telephone contacts, participants will be queried in accordance with a template script provided separately by GSK. Participants will be queried about concomitant medications, any intercurrent medical conditions, and the occurrence of pIMDs, SAEs, concurrent vaccination, SAEs related to study participation or to a concurrent GSK medication/vaccine, and AEs or SAEs leading to withdrawal. Information collected will be documented in the source document and will be recorded in the eCRF.

8.4. Pharmacokinetics

Not applicable.

8.5. Genetics

In this study, genetics may be evaluated after review by the ethical review committee in accordance with the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects.

A 30 mL blood sample (PBMC) for DNA isolation will be collected at Visits 1, 3 and 5 (Days 1, 29 and 57) from participants who have consented to participate in the genetic research of the study.

Participants who do not wish to participate in the genetic research may still participate in the study.

See Section 10.5 for information regarding genetic research.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

No formal statistical hypotheses are to be tested. All analyses will be descriptive.

9.2. Analysis sets

Table 14 Analysis sets

Analysis set	Description
Screened set	All participants who were screened for eligibility
Enrolled set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening procedure)
Exposed Set (ES)	All participants who will receive at least 1 dose of the study intervention.
Per Protocol for immunogenicity set (PPS_Immuno)	All eligible participants who will receive all doses as per protocol, will have immunogenicity results post-dose, will comply with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.
Per Protocol for CMI set (PPS_CMI)	All eligible participants who will receive all doses as per protocol, will have CMI results post-dose, will comply with dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.

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9.3. Statistical analyses

The SAP will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses.

The analyses will be descriptive with the aim to characterize the safety/reactogenicity, and immunogenicity in each group.

Any deviation(s) or change(s) from the original statistical plan outlined in this Protocol will be described and justified in the final CSR.

9.3.1. Participants Disposition

The number of enrolled and administered (at least one dose, full dose course) participants, included in each group and in total, will be described.

9.3.2. Demography and Baseline Characteristics Analyses

Demographic characteristics (age at first study intervention administration in years, sex at birth, HSV-1 status, race, and ethnicity) will be summarized overall and by study intervention group using descriptive statistics:

- Frequency tables will be generated for categorical variables.
- Mean, SD, median, minimum and maximum will be provided for continuous data such as age, height, weight, and body mass index.

Withdrawal status will be summarized by group using descriptive statistics:

- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.
- The number of participants enrolled into the study as well as the number of participants excluded from the PPS will be tabulated.

9.3.3. Primary Endpoints/Estimands Analyses

The analysis of the primary reactogenicity and safety objective will be performed on the ES.

Statistical Analysis Methods
The percentage of participants reporting at least one solicited AE, at least one solicited administration site AE, and at least one solicited systemic AE during the 7-day follow-up period (i.e., Day 1-Day 7 post-each study intervention administration) will be tabulated for each group after each dose and overall. The percentage of participants reporting each individual solicited administration site AE (any grade and Grade 3) and solicited systemic AE (any grade and Grade 3) during the 7-day follow-up period (i.e., Day 1-Day 7 post-each study intervention administration) will be tabulated for each group after each dose and overall. For solicited AEs, percentages will be computed based on the total number of solicited symptoms screens completed. For each group and for each hematology and biochemistry parameter: • The percentage of participants having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by timepoint. • The summary of grading post-study intervention administration will be tabulated vs. baseline. Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"; see Section 10.2.2). The laboratory parameters not included on FDA Toxicity Grading Scale will not be graded. The percentage of participants with any unsolicited AEs during the 28-day follow-up period (i.e., Day 1-Day 28 post-each study intervention administration) with its exact 95% CI will be tabulated by group and by MedDRA PTs. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate PT. For unsolicited AEs, percentages will be computed based on the total number of exposed participants. Participants not reporting an AE will be considered as not having experienced any AE. The percentage of participants with any AEs (solicited and unsolicited) resulting in a medically attended visit from Dose 1 up to 28 days post last dose administered (Day 57, or Day 29 if only one dose administered) will also be tabulated by MedDRA SOC and PT by group, after each dose and overall with exact 95% CI. The percentage of participants with at least one report of SAE, with at least one report of causally related SAE, with at least one report of fatal SAE, and with at least one report of causally related fatal SAE classified by the MedDRA SOC and PTs reported from Dose 1 up to 28 days post last dose administered (Day 57, or Day 29 if only one dose administered) will be tabulated by group with exact 95% CI. The percentage of participants with at least one newly diagnosed pIMD and at least one exacerbation of a pre-existing pIMD classified by the MedDRA SOC and PTs and reported from Dose 1 up to 28 days post last dose administered (Day 57, or Day 29 if only one dose administered) will be tabulated by group with exact 95% CI. The percentage of participants using concomitant medication (any medication, any antipyretic, and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., Day 1-Day 7 post-each study intervention administration) and during the 28-day follow-up period (i.e., Day 1-Day 28 post-each study intervention administration) will be summarized by group after each dose and overall.

9.3.4. Secondary Endpoints/Estimands Analyses

The analysis of the secondary humoral immunogenicity objectives will be performed on the PPS for analysis of immunogenicity (PPS_immuno). The analysis of the secondary CMI objectives will be performed on the PPS for analysis of CMI (PPS_CMI). If more than 10% of participants are eliminated from any of the PPS in any treatment group, a sensitivity analysis will be carried out using the ES. The analysis of the secondary safety objective will be performed on the ES.

Statistical Analysis Methods
The percentage of participants with any AEs (solicited and unsolicited) resulting in a medically attended visit from Dose 1 up to study end (Day 209) will also be tabulated by MedDRA SOC and PT by group, after each dose and overall with exact 95% CI. The percentage of participants with at least one report of SAE, with at least one report of causally related SAE, with at least one report of fatal SAE, and with at least one report of causally related fatal SAE classified by the MedDRA SOC and PTs reported from Dose 1 up to study end (Day 209) will be tabulated by group with exact 95% CI. The percentage of participants with at least one newly diagnosed pIMD and at least one exacerbation of a pre-existing pIMD classified by the MedDRA SOC and PTs and reported from Dose 1 up to study end (Day 209) will be tabulated by group with exact 95% CI. For each group, at each timepoint that blood samples are collected for immune responses and for each assay (unless otherwise specified): • Seropositivity rates and their 95% CI will be tabulated. • GMCs/GMTs and their 95% CI will be tabulated and represented graphically. CCI [redacted] • Mean geometric fold increases and their 95% CI will be tabulated and represented graphically. CCI [redacted] • Percentage of participants that had a study intervention response defined as a 4-fold increase in concentration and their CI will be tabulated by group. CCI [redacted]. • Antibody titer/concentration will be displayed using reverse cumulative curves. • The kinetics of titers will be plotted as a function of time for participants. • The frequency of specific CD4+/CD8+ T-cells will be summarised (mean, SD, minimum, Q1, median, Q3, and maximum) by group, at each timepoint during which blood samples are collected for CMI (descriptive statistics).

9.3.5. Tertiary Endpoints/Estimands Analyses

Tertiary endpoint analyses will be described in the statistical analysis plan.

9.4. Sequence of analyses

- A **primary analysis** will be performed on all data available and when data for at least primary and secondary endpoints up to Day 57 are available.

  At this point, the statistician will be unblinded (i.e., will have access to the individual participant treatment assignment). The remaining study personnel will stay blinded (i.e., will not have access to the individual participant treatment assignment). It is possible however, due to the limited sample size, that unblinding occurs for a few participants having a specific AE or SAE (e.g., an AE/SAE occurring only in a single participant). Therefore, anyone having access to this analysis could become unblinded regarding those specific cases. This would be acceptable given the early/descriptive nature of the study and the limited number of expected unblinding. Investigators and participants will remain blinded up to study end (Day 209). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.
- The **end of study analysis** will be performed when all data for primary and secondary endpoints up to study conclusion are available (Day 209). Individual listings will only be provided at this stage.
- If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The names and addresses of all third parties involved in this study are provided in a separate document accompanying this study protocol.

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant prior to participation in the study.

The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

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

Participants who are rescreened are required to sign a new ICF, only if there are changes to the original ICF. If there are no changes to the original ICF, participants should confirm that they still agree to be part of the study. This information should be captured in the participant source document.

In case of unexpected pregnancy, participant must be informed that personal information such as date of birth or sex of the baby will be collected as part of safety follow-up.

Consent for the baby may be obtained from the participants and/or their partner as per local regulations.

10.1.4. Data protection

Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

The participants must be informed that:

- Their personal study-related data will be used by the sponsor in accordance with local data protection law.
- Their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

10.1.5. Committees structure

This Protocol will be reviewed and approved by an IEC/IRB before initiation (refer to Section 10.1.1 for further details).

Safety oversight will be carried out by an iSRC that will be set-up for the safety monitoring throughout the study intervention administration phase and by an existing project SRT (refer to Section 8.2.3 for further details):

- The iSRC is a group of GSK experts (including physicians), external to the ongoing study/project and with lack of conflicts of interest in the outcome of the study, who assess the reactogenicity and safety data in an unblinded (on a participant-level or study intervention administration group-level) fashion. Based on its review, the iSRC gives recommendations to the primary contact (study CSL) regarding study modification, continuation or termination. Should any issues or potential safety concerns be identified, the iSRC Chair escalates issues to the GSB Co-Chairs (Chief Medical Officer and Head of Global Safety).
- The SRT of the HSVTI project includes as core members GSK's Central Safety product specialists (including a physician), the CPL, Epidemiologist, Global Regulatory Lead, Global Medical Affairs Lead, and Biostatistician of the project, as well as study CSL and study Statistician as ad hoc members. The SRT is responsible for ongoing safety monitoring of the entire project and meets on a regular basis. The SRT will inform the iSRC and GSB about any potential safety concern relevant to the study (should there be any identified in a blinded manner).

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (refer to the Glossary of terms for the definitions of essential and source documents). The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g. source documents, eCRF), the copy should fulfill the requirements for certified copies (refer to the Glossary of terms for the definition of certified copy).

All participant data related to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (refer to the Glossary of terms for the definition of source documents) that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (refer to the Glossary of terms for the definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g. via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

QTLs will be predefined in the Quality Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These predefined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

First act of recruitment

The start of study is defined as FSFV at a country level.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator will:

- Review collected data to ensure accuracy and completeness.
- Complete Screening Conclusion for screen failures in the eCRF.
- Complete the Study Conclusion screen in the eCRF.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

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

10.1.10. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the LSLV for interventional studies and follows the guidance from the ICMJE.

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Laboratory Assays Description

Descriptions of available assays are provided below. Descriptions could be subject to change, due to assay(s) being under development.

HSV serology by Western blot

CCI proteins from detergent lysates of HSV infected cells are separated by electrophoresis then transferred to nitrocellulose paper. The strips of paper or 'blots' containing either separated, fixed proteins from CCI are then incubated with the participant's serum. Antibodies, which bind to the viral proteins, are then detected by an enzyme-mediated color change. The pattern of staining on the 2 blots (CCI) is dictated by the number and identity of the HSV proteins to which the participant's immune system has responded. Thus, a predominance of staining on either the CCI antigen-containing blot allows serotyping of the sera. In 80% of cases, this is all that is required. If the serotype is uncertain, the serum is adsorbed against both CCI proteins, and re-run on fresh blots to obtain clearer profiles (essentially removing type common antibody) [Ashley, 1988].

CCI testing by ELISA

The CCI IgG ELISA is under development and the procedure could change. The assay will be based on an indirect solid phase ELISA allowing the detection and quantification of total IgG antibodies directed against the CCI heterodimer in human serum samples.

The principle of this assay will be as follows: the mutated heterodimer CCI antigen will be adsorbed onto a 96-well polystyrene microplate. After a washing and a blocking step, dilutions of serum samples, controls and standard(s) will be added to the coated microplate. After incubation, the microplate will be washed to remove unbound primary antibodies. Bound IgG will be detected by the addition of a secondary anti-IgG human antibody conjugated to HRP. Bound antibodies will be quantified by the addition of the HRP substrate solution, whereby a colored product develops proportionally to the amount of CCI IgG antibodies present in the serum sample. The corresponding antibody concentration, corrected for the dilution factor, will be expressed in EU/mL, units arbitrarily chosen as no existing reference standard is available.

Intracellular cytokine staining

Intracellular cytokine staining has been used to assess CMI responses as previously described [Díez-Domingo, 2010; Moris, 2011].

Briefly, thawed PBMC are stimulated *in vitro* with either CCI) or with culture medium only in the presence of anti-CD28 and anti-CD49d antibodies. After 2 hours of incubation at 37°C, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation. Cells are subsequently harvested, stained for surface markers (CD4+ and CD8+) and then fixed.

Fixed cells are then permeabilised and stained with fluorescently labelled antibodies specific for the following immune markers:

- CD3: phenotyping T-cells,
- CD40L (CD154), 4-1BB: expressed on activated CD4 (or CD8) T-cells [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006],
- Interleukin (IL)-2: key for the development, survival and function of T-cells [Boyman, 2012],
- Tumour necrosis factor-alpha (TNF-α): antiviral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014],
- Interferon-gamma (IFN-γ): antiviral factor, associated with the Th1 profile (and CD8) T-cells [Schoenborn, 2007],
- IL-13: associated with the Th2 profile [Bao, 2015],
- IL-17: associated with the Th17 profile [Korn, 2009].

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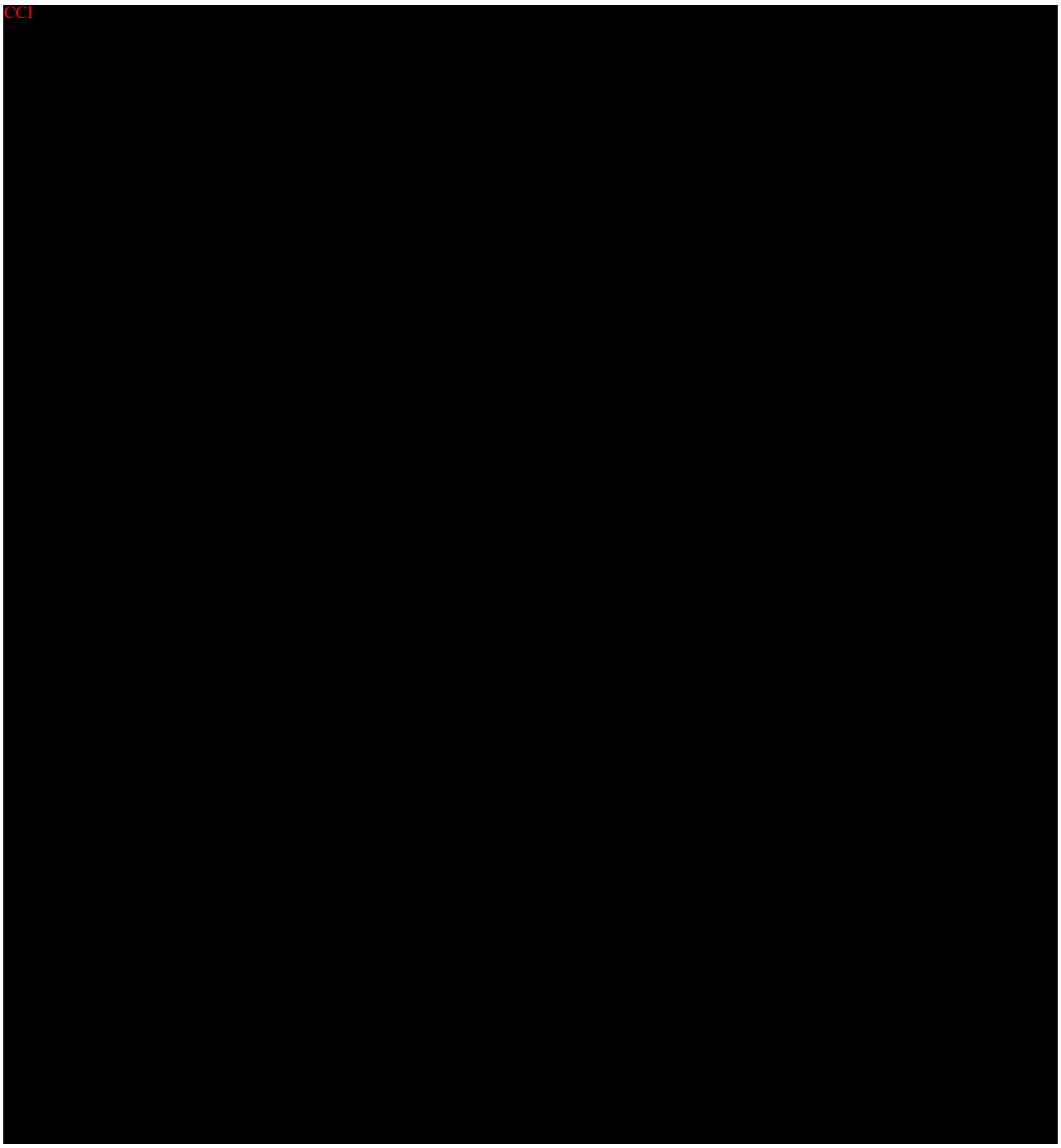

10.2.2. Protocol required safety laboratory assessments

The tests detailed in Table 17 will be performed by a laboratory designated by the sponsor.

Table 17 Hematology and Biochemistry Read-Outs

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	≥ 50	Hemoglobin
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 4 (Day 36) Visit 5 (Day 57)	All participants	~50	WBC differential Platelets ALT AST Creatinine Blood urea nitrogen

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **WBC:** white blood cells

Table 18 Toxicity Grading Scales for Hematology and Biochemistry Parameters Applicable for this Study

Component	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hematology (Whole Blood)				
Hemoglobin (g/dL) - female	11.0 - 12.0	9.5 - 10.9	8.0 - 9.4	< 8.0
Hemoglobin (g/dL) - male	12.5 - 13.5	10.5 - 12.4	8.5 - 10.4	< 8.5
Hemoglobin (g/dL) - female change from baseline value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (g/dL) - male change from baseline value	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
Platelets decrease (cell/mm^3)	125 000 - 140 000	100 000 - 124 000	25 000 - 99 000	< 25 000
Biochemistry (Serum)				
ALT (increase by factor)	1.1 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10.0 x ULN
AST (increase by factor)	1.1 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10.0 x ULN
Creatinine (mg/dL)	1.5 - 1.7	1.8 - 2.0	2.1 - 2.5	> 2.5 or requires dialysis
Blood urea nitrogen (mg/gL)	23 - 26	27 – 31	> 31	Requires dialysis

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **ULN:** upper limit of the normal range; **WBC:** white blood cells

The laboratory values provided in the table are taken from the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007. These laboratory values serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an adverse event (AE)

An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition

- **Significant or unexpected worsening or exacerbation of the condition/indication under study.**
- **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.**
- **New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.**
- **Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.**
- **Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.**
- **Signs or symptoms temporally associated with administration of the study intervention.**
- **Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).**
- **Pre- or post-intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).**
- **Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.**
- **AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.**

10.3.1.2. Events NOT Meeting the AE Definition

- **Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).**
- **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.**

- **Pre-existing conditions or signs and/or symptoms present in a participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF.**
- **Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.**
- **Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.**

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:	
a.	**Results in death**
b.	**Is life-threatening** **Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.**
c.	**Requires hospitalization or prolongation of existing hospitalization** **Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.**
d.	**Results in disability/incapacity** **Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.**
e.	**Is a congenital anomaly/birth defect in the offspring of a study participant.**
f.	**Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).**
g.	**Other situations**

Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 19 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site

b. Solicited systemic events

The following systemic events will be solicited:

Table 20 Solicited systemic events

Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)

Note: Participants will be instructed to measure and record the oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited AEs

An unsolicited AEs is an adverse event that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by a participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e. symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. SAEs related to Study Participation

Any SAEs related to study participation (e.g. SAEs due to study mandated procedures, invasive tests or change in existing therapy) should be reported as per Section 8.3.3.

10.3.6. Adverse events of special interest

10.3.6.1. Potential immune-mediated diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 21 (refer to Section 10.3.9.1 for reporting details).

The investigator(s) must exercise their medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. *In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following study intervention administration) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following study intervention administration) in the eCRF.*

Table 21 List of potential immune-mediated diseases (pIMDs)

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”

Medical Concept	Additional Notes
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis") • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease

Medical Concept	Additional Notes
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)

Medical Concept	Additional Notes
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g. Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)

Medical Concept	Additional Notes
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to:

Medical Concept	Additional Notes
	• Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

When there is enough evidence to make any of the above diagnoses, the AE must be reported as pIMD. Symptoms, signs or conditions which might (or might not) lead to one of the above diagnoses, should be recorded and reported as AEs but not as pIMD until the final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely.

10.3.7. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

The investigator(s) must exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.8. Events or outcomes not qualifying as AEs or SAEs

10.3.8.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to Section 10.3.2 for definition of SAE.

10.3.9. Recording and follow-up of AEs, SAEs, pIMDs and pregnancies

The participants will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE instead of individual signs/symptoms.

A Paper Diary (pDiary) will be used in this study to capture solicited and unsolicited administration site or systemic events. The participant should be trained on how and when to complete the pDiary. At each study intervention administration visit, pDiary will be provided to the participant. The participant will be instructed to measure and record the oral body temperature and any solicited administration site or systemic events or any

unsolicited AEs occurring after study intervention administration. The participant will be instructed to return the completed diary card to the Investigator at the next study visit.

Anyone who measures administration site or systemic events and who will record the event in the pDiary should be trained on using the pDiary. This training must be documented in the participant's source record.

If any individual other than the participant is making entries in the pDiary, their identity must be documented in the participant's source record.

Any unreturned pDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.9.1. Time period for collecting and recording AEs, SAEs, pIMDs and pregnancies

All AEs that occur during 7 days following administration of each dose of study intervention (Day 1 to Day 7) must be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

All unsolicited AEs that occur during 28 days following administration of each dose of study intervention (i.e., on the day of study intervention administration and 27 subsequent days) must be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

The time period for collecting and recording SAEs (all, fatal and related) will begin at the first receipt of study intervention (Day 1) and will end at study end (Day 209). See Section 10.3.11 for instructions on reporting of SAEs. However, any SAEs assessed as related to study participation (e.g., Protocol-mandated procedures, invasive tests or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to take part in the study (i.e., at the Screening visit).

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention (Day 1) until study end (Day 209).

The time period for collecting and recording MAEs will begin at the first receipt of study intervention (Day 1) and will end at study end (Day 209).

The time period for collecting and recording pIMDs will begin at the first receipt of study intervention (Day 1) and will end at study end (Day 209). See Section 10.3.11 for instructions on reporting of pIMDs.

The time period for collecting and recording pregnancies will begin at the first receipt of study intervention (Day 1) and will end at study end (Day 209). See Section 10.3.11 for instructions on reporting of pregnancies.

10.3.9.2. Follow-up of AEs, SAEs, pIMDs, pregnancies or any other events of interest

After the initial AE/SAE/pIMD/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs (as defined in the Section 10.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until event is resolved, stabilized, otherwise explained, or until the participant is lost to follow-up.

10.3.9.2.1. Follow-up during the study

All AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 28 days after the last study intervention administration.

All SAEs and (serious or non-serious) pIMDs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last study visit of the participant.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.9.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/pIMD using an electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE/pIMD as fully as possible.

10.3.9.2.3. Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.11.

10.3.9.3. Updating of SAE, pIMD and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, pIMD or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 12).

10.3.10. Assessment of intensity and causality

10.3.10.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 22 Intensity scales for solicited events

Event	Intensity grade	Parameter
Pain at administration site	**0**	**None**
	1	**Mild: Any pain neither interfering with nor preventing normal everyday activities.**
	2	**Moderate: Painful when limb is moved and interferes with everyday activities.**
	3	**Severe: Significant pain at rest. Prevents normal everyday activities.**
Redness at administration site	0	< 25 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	> 100 mm
Swelling at administration site	0	< 25 mm
	1	25 - 50 mm
	2	51 - 100 mm
	3	> 100 mm
Temperature*	0	< 38.0°C (< 100.4°F)
	1	38.0°C (100.4°F) - 38.4°C (101.1°F)
	2	38.5°C (101.2°F) - 38.9°C (102.0°F)
	3	> 38.9°C (> 102.0°F)
Headache	**0**	**None**
	1	**Mild: Headache that is easily tolerated**
	2	**Moderate: Headache that interferes with normal activity**
	3	**Severe: Headache that prevents normal activity**
Fatigue (tiredness)	**0**	**None**
	1	**Mild: Fatigue that is easily tolerated**
	2	**Moderate: Fatigue that interferes with normal activity**
	3	**Severe: Fatigue that prevents normal activity**
Myalgia (muscle pain)	**0**	**None**
	1	**Mild: Myalgia present but does not interfere with activity**
	2	**Moderate: Myalgia that interferes with normal activity**
	3	**Severe: Myalgia that prevents normal activity**

Event	Intensity grade	Parameter
Arthralgia (joint pain)	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

* Refer to the Table 1 (schedule of activities) for the definition of fever and the preferred location for temperature measurement.

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. *The intensity should be assigned to one of the following categories (see* Table 23*). Where applicable*, the assessment will be based on the investigator's clinical judgment.

Table 23 Intensity Scales for Unsolicited AEs

Event	*Grade 1 (mild)*	*Grade 2 (moderate)*	*Grade 3 (severe)*
Tachycardia (beats per minute)	*101 – 115*	*116 – 130*	*> 130*
Bradycardia (beats per minute)	*50 – 54*	*45 – 49*	*< 45*
Hypertension (systolic) (mm Hg)	*141 – 150*	*151 – 155*	*> 155*
Hypertension (diastolic) (mm Hg)	*91 – 95*	*96 – 100*	*> 100*
Hypotension (systolic) (mm Hg)	*85 – 89*	*80 – 84*	*< 80*
Respiratory rate (breaths per minute)	*17 – 20*	*21 – 25*	*> 25*
Nausea/vomiting	*No interference with activity or 1 – 2 episode(s)/24 hours*	*Some interference with activity or > 2 episodes/24 hours*	*Prevents daily activity, requires outpatient intravenous hydration*
Diarrhoea	*2 – 3 loose stools or < 400 g/24 hours*	*4 – 5 stools or 400 - 800 g/24 hours*	*≥6 watery stools or > 800 g/24 hours or requires outpatient intravenous hydration*
Illness or clinical adverse event	*No interference with activity*	*Some interference with activity not requiring medical intervention*	*Prevents daily activity and requires medical intervention*

The values/definitions provided in the table are taken from the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the predefined outcomes as described in the Section 10.3.2.

10.3.10.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB while making their assessment.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?

YES	**:**	**There is a reasonable possibility that the study intervention contributed to the AE.**
NO	**:**	**There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There are other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.**

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedures not required by the protocol.
- An error in study intervention administration.
- Other causes (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator(s) may change their opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.10.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's diary. Medical attention received for SAEs/pIMDs will have to be reported using the normal AE reporting process in the eCRF.

10.3.10.4. Assessment of outcomes

The investigator will assess the outcome of all serious and non-serious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.11. Reporting of SAEs, pIMDs, pregnancies and other events

10.3.11.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 12 for the details on timeframes for reporting of SAEs/pIMDs/pregnancies.

Refer to Section 10.3.11.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.11.2. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK Global Safety department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Current bilateral tubal ligation or occlusion

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

- **Postmenopausal female**

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 24).

Table 24 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to Sections 8.3.1, 8.3.2, 10.3.9.1, 10.3.9.2 and 10.3.9.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any woman who becomes pregnant during the study must not receive additional dose(s) of the study intervention but may continue other study procedures at the discretion of the investigator.

10.5. Appendix 5: Genetics

Genetic determinants that impact immune response may result in variable immune response to the study intervention(s). Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

DNA samples will be used for research related to HSVTI. They may also be used to develop tests/assays (including diagnostic tests) related to HSVTI.

DNA samples will be analyzed if it is hypothesized that this may help further understanding of the clinical data.

10.6. Appendix 6: Definition of medical device AE, adverse device effect, serious adverse device effect and unanticipated SADE

Not applicable.

10.7. Appendix 7: Country-specific requirements

10.7.1. Regulatory and ethical considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and Pharmaceuticals and Medical Devices Act.

The statement "I agree to assume responsibility for the proper conduct of the study at this site." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

GSK Japan will submit the CTN to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

10.7.2. Study administrative structure

Administrative Information and List of Medical Institutions and Investigators are included in Exhibit 1 and Exhibit 2, respectively.

10.7.3. Unapproved medical device

Details, if any, will be added in Exhibit 3.

10.8. Appendix 8: Abbreviations and glossary of terms

10.8.1. List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
CCI [redacted]	
AST	Aspartate aminotransferase
CCI [redacted]	
CD4+/CD8+	Cluster of differentiation 4/8
CD40L	Cluster of differentiation 40 ligand
CFC	Cell flow cytometry
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
CPL	Clinical Project Lead
CSL	Clinical Sciences Lead
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
eCRF	electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study

ES	Exposed Set
CCI [redacted]	
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
CCI [redacted]	
GMC/GMT	Geometric Mean Concentration/ Geometric Mean Titer
GSB	Global Safety Board
GSK	GlaxoSmithKline Biologicals SA
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
CCI [redacted]	
HRP	Horseradish peroxidase
HRT	Hormonal replacement therapy
HSV	Herpes Simplex Virus
HSVTI	HSV-targeted immunotherapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IgA/G/M	Immunoglobulin A/G/M
IL (IL-2, IL-13, IL-17)	Interleukin

IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
LML	Local Medical lead
LSLV	Last Subject Last Visit
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities
MHC I/II	Major Histocompatibility Complex I/II
CCI [redacted]	
PBMC	Peripheral blood mononuclear cell
pIMD	Potential immune-mediated disease
PPS	Per Protocol Set
PT	Preferred term
CCI [redacted]	
QTL	Quality Tolerance Limit
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SBIR	Source data Base for Internet Randomization
SD	Standard Deviation
SOC	System Organ Class
SPM	Study Procedures Manual
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction

TNF-α	Tumour necrosis factor-alpha

10.8.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device	EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.
Investigational product:	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified

	individual or party to perform those study-related duties and functions
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the, "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of

	participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Sub-cohort:	A group of participants for whom specific study procedures are planned as compared to other participants

	or a group of participants who share a common characteristic (e.g. ages, vaccination schedule, etc.) at the time of enrolment.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Virtual visit:	This term refers to study visits conducted using multimedia or technological platforms.

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