CLINICAL STUDY PROTOCOL

SPONSOR:
GLAXOSMITHKLINE BIOLOGICALS SA (GSK)
RUE DE L'INSTITUT, 89
1330 RIXENSART, BELGIUM

Primary study intervention and number	GlaxoSmithKline Biologicals SA's (GSK) investigational Herpes Simplex Virus (HSV)-targeted immunotherapy (GSK3943104A)
Other study intervention	Placebo (sodium chloride)
eTrack study number and abbreviated title	215336 (TH HSV REC-003)
EudraCT number	2021-003586-35
EU CT number	2024-510571-37-00
Date of Protocol	Final: 22 September 2021
Date of Protocol Amendment	Amendment 1 Final: 7 January 2022 Amendment 2 Final: 9 August 2022 Amendment 3 Final: 20 October 2022 Amendment 4 Final: 20 June 2023 Amendment 5 Final: 28 August 2023 Amendment 6 Final: 05 October 2023 Amendment 7 Final: 18 Sep 2024
Title	A Phase I/II, observer-blind, randomised, placebo-controlled, multi-country study to evaluate reactogenicity, safety, immune response, and efficacy of an HSV-targeted immunotherapy in healthy participants aged 18-40 years or in participants aged 18-60 years with recurrent genital herpes
Brief title	A study on the reactogenicity, safety, immune response, and efficacy of a targeted immunotherapy against HSV in healthy participants aged 18-40 years or in participants aged 18-60 years with recurrent genital herpes

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

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Protocol Amendment 7 Sponsor Signatory Approval

eTrack study number and abbreviated title	215336 (TH HSV REC-003)
EudraCT number	2021-003586-35
EU CT number	2024-510571-37-00
Date of Protocol Amendment	Amendment 7 Final: 18 Sep 2024
Title	A Phase I/II, observer-blind, randomised, placebo-controlled, multi-country study to evaluate reactogenicity, safety, immune response, and efficacy of an HSV-targeted immunotherapy in healthy participants aged 18-40 years or in participants aged 18-60 years with recurrent genital herpes
Sponsor signatory	Lan Lin, Clinical Project Lead, Herpes Simplex Virus project Vaccines Research & Development Centre (RDC) Belgium
Signature	_____
Date of signature	_____

Note: Not applicable if an alternative signature process (e.g., electronic signature or email approval) is used to get the Sponsor approval.

Protocol Amendment 7 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, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- 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 on site 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 his/her 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 one 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.

eTrack study number and abbreviated title	215336 (TH HSV REC-003)
EudraCT number	2021-003586-35
EU CT number	2024-510571-37-00
Date of Protocol Amendment	Amendment 7 Final: 18 Sep 2024
Title	A Phase I/II, observer-blind, randomised, placebo-controlled, multi-country study to evaluate reactogenicity, safety, immune response, and efficacy of an HSV-targeted immunotherapy in healthy participants aged 18-40 years or in participants aged 18-60 years with recurrent genital herpes
Investigator name	_____
Signature	_____
Date of signature	_____
Leiter der klinischen Prüfung name, function and title	_____
Signature	_____
Date of signature	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart, Belgium

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 Serious Adverse Events (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 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 7 (18 Sep 2024):

Overall rationale for the current Amendment:

The results of the primary analysis of TH HSV REC-003 (215336) study (PART II) failed to show superiority over placebo for clinical efficacy. This Protocol is being amended for the following reasons:

- Because the anticipated benefit of the HSVTI was not demonstrated, the study duration is shortened from 24 months to 12 months post-Dose 2 to ensure the required safety follow-up of participants.
- The requirement of withholding chronic suppressive therapy (CST) during the entire study period is removed to allow participants to resume or to start CST according to the local clinical guidelines.
- All study procedures except those related to safety monitoring may continue up to 6 months post Dose-2 on a voluntary basis.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and Title	Description of Change	Brief Rationale
Cover page	Addition of EU CT number.	To comply with the new EU CTR regulations.
Section 8.3.3. Regulatory Reporting Requirements for SAEs, […]	Addition of a wording related to SUSAR reporting.	
Section 10.1.4. Data Protection	Text added to cover that GSK staff and complementary workers are required to report data breaches and take appropriate remediation steps, in compliance with applicable laws.	
Section 1.3. Schedule of Activities Section 4.1. Overall Design Section 8.1. Efficacy and/or Immunogenicity Assessments Section 8.3.1. Time Period and Frequency for Collecting AE, […]	The procedures of the follow-up phase (as of 6 months post-dosing and beyond) were revised. Additionally, as of Protocol Amendment 7 implementation, the procedures related to reporting of RGH events, twice daily anogenital swabbing and blood sampling are on a voluntary basis.	Because the anticipated benefit of the HSVTI was not demonstrated, the study duration is shortened from 24 months to 12 months post-Dose 2 to ensure the required safety follow-up of participants.
Section 3. Objectives, Endpoints, and Estimands	Objectives and endpoints were aligned with the updates in study design.	
Section 4.1. Overall Design	The trigger for the Primary Completion Date was selected as the primary clinical efficacy analysis occurred before Day 394.	

Section # and Title	Description of Change	Brief Rationale
Section 6.8. Concomitant Therapy	Reporting periods for the different concomitant therapies were shortened.	
Section 2.3. Benefit/Risk Assessment	This section was revised as no efficacy was observed following the primary analysis.	Because the anticipated benefit of the HSVTI was not demonstrated, the benefit/risk ratio was revised according to new data from the primary analysis.
Section 4.4. End of Study Definition	The EoS definition was changed from “date of the last testing released of the samples related to primary and secondary endpoints” to “Last Subject Last Visit (LSLV)”.	The definition was updated to reflect the changes in study design.
Section 6.8. Concomitant Therapy	Suppressive antiviral medications and tenofovir are allowed as of Protocol Amendment 7 implementation.	Because the anticipated benefit of the HSVTI was not demonstrated, withhold of chronic suppressive therapy and tenofovir (e.g., in case of pre-exposure prophylaxis to prevent HIV infection) is no longer required.
Section 9. Statistical Considerations	Where applicable, statistical sections were updated to align with the revised study design (e.g., to modify the condition of triggering interim analysis #3; to remove the analysis of at 18 and 24 months post-Dose 2).	Because the anticipated benefit of the HSVTI was not demonstrated, the analysis plan was updated according to the planned changes in this protocol amendment (including shortening study period).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

Prior attempts to develop a prophylactic or therapeutic vaccine for herpes simplex virus (HSV) were unsuccessful. Several previous vaccine candidates focused on eliciting immunoglobulin G (IgG) and neutralising antibody responses to glycoprotein D (gD), the most abundant and immunodominant surface antigen. HSV gD was the first well-characterised HSV entry molecule, which explains why many vaccine trials performed to date have included gD subunit antigen. The goal was to induce neutralising antibodies that block infection. The ability of HSV to persist and recur in otherwise healthy individuals is likely due to its capacity to evade the host's antiviral responses.

CCI [redacted]

The purpose of this study is to evaluate the safety, reactogenicity, immunogenicity, and efficacy of GlaxoSmithKline Biologicals SA's (GSK) HSV-targeted immunotherapy (HSVTI) (gE-gI with Adjuvant System 01 [AS01]).

Objectives and endpoints, and estimands:

Refer to Section 3, Table 9.

1.2. Schema

Refer to Section 4.1, Figure 1 (PART I), Figure 2 (PART II; shedding sub-cohort), and Figure 3 (PART II; non-shedding sub-cohort).

1.3. Schedule of Activities

This section presents the schedule of activities for the different PARTs and sub-cohorts planned in this study:

- PART I (Section 1.3.1; Table 1).
- PART II (Section 1.3.2):
  - Activities to be performed by study staff (Section 1.3.2.1):
    - Procedures for the shedding sub-cohort (Table 2).
    - Procedures for the non-shedding sub-cohort (Table 3).
    - Procedures during the Unscheduled visit (Table 4).
  - Activities to be performed by the participant (Section 1.3.2.2):
    - Shedding sub-cohort (Table 5).
    - Non-shedding sub-cohort (Table 6).

General notes related to the tables:

● 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.

The double-line borders indicate analyses which will be performed on all data obtained up to those timepoints (refer to Section 9.4).

Only for PART II: Visit 6 (Day 71), Visit 7 (Day 181), Visit 8 (Day 209), Visit 9 (Day 299), and Visit 10 (Day 394) can be replaced by a virtual contact when applicable and at the investigator's discretion. Visit 10 can be conducted remotely only provided that the ICF addendum has been discussed and signed during a previous on-site visit, at the investigator's discretion (see Section 8).

1.3.1. Schedule of Activities for PART I

Table 1 Schedule of Activities for PART I (Healthy Adults, Aged 18 to 40 Years)

Type of Contact	Screening	Study intervention administration Phase							Follow-up Phase	
	Screening[1]	Visit 1	Phone Contact 1[(2)]	Visit 2	Visit 3	Phone Contact 2[(2)]	Visit 4	Visit 5	Visit 6	Visit 7
Timepoints	Day -56	Day 1	Day 1 + 24h	Day 8	Day 29	Day 29 + 24h	Day 36	Day 64	Day 209	Day 394
Obtain informed consent (see Section 10.1.3)	●									
Check inclusion/exclusion criteria (see Sections 5.1 and 5.2)	●	○								
Collect demographic data (see Section 8.2.1.1)	●									
Measure and record height and weight (see Section 8.2.1.2)	●									
Record medical and vaccination history (see Section 8.2.1.3)	●									
Perform physical examination (see Section 8.2.1.8)	●	●		○	●		○	○	○	○
Perform pregnancy test (see Section 8.2.1.9)	●	●[4]			●[4]					
Record pre-study intervention administration body temperature[3]		●			●					
Study group and treatment number allocation (see Sections 6.3.2 and 6.3.3)		○								
Treatment number allocation for subsequent dose (see Section 6.3.3)					○					
Check contraindications to subsequent study intervention administration (see Section 7.1.1)					●					
Study intervention administration (see Section 6.1)		●			●					
Recording of administered treatment number		●			●					
Blood sampling for HSV testing (~3.5 mL) (see Section 8.1.1)	●									
Blood sampling for HIV testing (~8.5 mL) (see Section 8.1.1)	●									
Blood sampling for haematology analysis (~2.0 mL) (see Section 8.1.1)	●	●[4]		●	●[4]		●	●		
Blood sampling for biochemical analysis (~3.5 mL) (see Section 8.1.1)	●	●[4]		●	●[4]		●	●		
Blood sampling for antibody determination (humoral immunogenicity) analysis (~8.5 mL) (see Section 8.1.1)		●[4]			●[4]			●	●	●
Blood sampling (PBMCs) for CMI response analysis (~30.0 mL) (see Section 8.1.1)		●[4]			●[4]			●	●	●
Blood sampling (PBMCs) for CCI [redacted] analysis (~20.0 mL) (see Section 8.1.1)		●[4]						●		
Blood sampling for antibodies induced by the HSVTI that block CCI [redacted] (~17.0 mL) (see Section 8.1.1)		●[4]			●[4]			●	●	●
Distribution of 'Participant card' (see Section 8.3.5)	○									

Type of Contact	Screening	Study intervention administration Phase							Follow-up Phase	
	Screening[1]	Visit 1	Phone Contact 1[(2)]	Visit 2	Visit 3	Phone Contact 2[(2)]	Visit 4	Visit 5	Visit 6	Visit 7
Timepoints	**Day -56**	**Day 1**	**Day 1 + 24h**	**Day 8**	**Day 29**	**Day 29 + 24h**	**Day 36**	**Day 64**	**Day 209**	**Day 394**
Check participant's device compatibility with the app for collecting study information (see Section 8.2.1.10.1)	○	○		○	○		○			
Download the eDiary app or distribution of electronic device (see Section 8.2.1.10.2)		○								
Train participant on the use of eDiary (see Section 8.2.1.10.2)		○								
Return of eDiary (see Section 8.2.1.11)								○		
Record any concomitant medications/vaccinations (see Section 6.8)		●	●	●	●	●	●	●		
Record any concomitant medications/vaccinations associated with MAEs (see Section 6.8)		●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions (see Section 9.2.1)	●	●	●	●	●	●	●	●	●	●
Recording of solicited AEs (Days 1 to 7 post-each study intervention administration) in eDiary (see Section 10.3.8)		Δ	Δ	Δ	Δ	Δ	Δ			
Review of eDiary data via the web portal (see Section 10.3.8)			○	○	○	○	○	○		
Recording of unsolicited AEs (Days 1 to 28 post-each study intervention administration) (see Section 10.3.8)		●	●	●	●	●	●	●		
Recording of MAEs (see Section 10.3.8)		●	●	●	●	●	●	●	●	●
Recording of pIMDs (see Section 10.3.8)		●	●	●	●	●	●	●	●	●
Recording of SAEs (all, fatal and related) (see Section 10.3.8)		●	●	●	●	●	●	●	●	●
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)		●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●	●	●	●	●	●	●	●	●	●
Recording of pregnancies (see Section 10.3.8)		●	●	●	●	●	●	●	●	●
Study conclusion (see Section 4.4)										●

Refer to Section 10.7.1 for the list of abbreviations.

Δ is used to indicate a study procedure recorded in the eDiary.

[1] If deemed necessary by the investigator, re-sampling can be performed within the allowed interval. Only data from the re-sampling testing, if done, will be taken into consideration.

[2] Phone contacts only applicable for the sentinel participants from Step 1 of PART I (see Section 8.2.2.2). These contacts are to be made 24 hours after each study intervention administration (at Day 1 and Day 29).

[3] 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/100.4°F, regardless of the location of measurement).

[4] Blood sampling and pregnancy tests to be performed before each study intervention administration.

1.3.2. Schedule of Activities for PART II

1.3.2.1. Activities to be Performed by Study Staff

Table 2 Shedding Sub-cohort: Activities to be Performed by Study Staff

Note that the Screening visit and the Baseline Day -28 Visit can be combined if the participant was not on antiviral treatment at the time of the Screening visit to allow the participant to start the baseline swabbing period immediately after the Screening visit. If the participant was on antiviral treatment at the time of the Screening visit, a 7-day wash-out period should be respected. If these visits are combined, all procedures to be performed at the Baseline Day -28 Visit should be done during the Screening visit. Procedures that are common between these 2 visits do not have to be repeated if the visits are combined.

Type of Contact	Screening			Study Intervention Administration Phase						Follow-up Phase			
	Scr[1]	Baseline		V1	V2	V3	V4	V5	V6	V7	V8	V9[15]	V10
Timepoints	**D -90**	**D -28**	**D -14**	**D1**	**D8**	**D29**	**D36**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Obtain informed consent (see Section 10.1.3)[11]	●												
Check inclusion/exclusion criteria (see Sections 5.1 and 5.2)	●	○	○	○[2]									
Collect demographic data (see Section 8.2.1.1)	●												
Measure and record height and weight (see Section 8.2.1.2)	●												
Record history of genital herpes (see Section 8.2.1.4)	●												
Record medical and vaccination history (see Section 8.2.1.3)	●	●	●	●									
Perform physical examination (see Section 8.2.1.8)	●	○	○	●	○	●	○	○	○[6]	○[6]	○[6]	○[6]	○[6]
Perform pregnancy test (see Section 8.2.1.9)	●			●[4]		●[4]							
Plan participant in the randomisation system (SBIR)	○												
Distribution of 'Participant card' (see Section 8.3.5)	○												
Record pre-study intervention administration body temperature[3]				●		●							
Study group and treatment number allocation (see Sections 6.3.2 and 6.3.3)				○									
Treatment number allocation for subsequent dose (see Section 6.3.3)						○							
Check contraindications to subsequent study intervention administration (see Section 7.1.1)						●							
Study intervention administration and recording of administered treatment number (see Section 6.1)				●		●							
If no documentation of laboratory-confirmed HSV-2 genital herpes: Blood sampling for HSV type-specific serology testing (~3.5 mL) (see Section 8.1.1)	●												
Blood sampling for HSV testing by Western Blot (~3.5 mL) (see Section 8.1.1)[8]				●									

Type of Contact	Screening			Study Intervention Administration Phase						Follow-up Phase			
	Scr[1]	Baseline		V1	V2	V3	V4	V5	V6	V7	V8	V9[15]	V10
Timepoints	**D -90**	**D -28**	**D -14**	**D1**	**D8**	**D29**	**D36**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Blood sampling for HIV testing (~8.5 mL) (see Section 8.1.1)	●												
Blood sampling for haematology analysis (~2.0 mL) (see Section 8.1.1)	●			●[4]	●	●[4]	●	●					
Blood sampling for biochemical analysis (~3.5 mL) (see Section 8.1.1)	●			●[4]	●	●[4]	●	●					
Blood sampling for antibody determination (humoral immunogenicity) analysis (~8.5 mL) (see Section 8.1.1)				●[4]		●[4]		●			●[12]		
Blood sampling (PBMCs) for CMI response analysis (~30.0 mL) (see Section 8.1.1)				●[4]		●[4]		●			●[12]		
Blood sampling (PBMCs) for CCI [redacted] analysis (~45.0 mL) (see Section 8.1.1)[7]				●[4]		●[4]		●					
Blood sampling for exploratory humoral response testing (~34.0 mL) (see Section 8.1.1)				●[4]		●[4]		●			●[12]		
Check participant's device compatibility with the app for collecting study information (see Section 8.2.1.10.1)	○	○	○	○	○	○	○	○	○	○			
Download the eDiary app or distribution of electronic device (see Section 8.2.1.10.2)		○											
Train participant on the use of eDiary and provide a refresher training if needed (see Section 8.2.1.10.2)		○	○	○	○	○	○	○	○	○			
Lesion swab collection procedure explained to the participant (see Section 8.2.1.7)		○											
Anogenital swab collection procedure explained to the participant (see Section 8.2.1.7)		○					○			○[9]			
Distribution of materials for lesion swabbing (see Section 8.2.1.7)		○											
Distribution of materials for anogenital swabbing (see Section 8.2.1.7)		○	○				○	○		○[9]			
Demo anogenital swab collected by the study staff (see Section 8.2.1.7)		○					○[5]			○[5, 9]			
First anogenital swab collected by the participant on site (see Section 8.2.1.7)		●								●[6, 9]			
Return of the collected anogenital swabs (see Section 8.1.1.2)			●	●				●	●		●[9]		
Record the date since when participant has stopped reporting RGH episodes, when applicable										●[10]	●[10]	●[10]	●[10]
Check if the participant has enough materials for the anogenital and lesion swabbing, as needed			○	○	○	○	○	○	○	○[9]			
Return of eDiary device or deletion of the app (see Section 8.2.1.11)										○[13]	○[13]	○[13]	○[13]
Record concomitant medications/vaccinations (see Section 6.8)				●	●	●	●	●	●	●	●	●	●
Record use of any antivirals (see Section 6.8)		●	●	●	●	●	●	●	●	●	●	●	●

Type of Contact	Screening			Study Intervention Administration Phase						Follow-up Phase			
	Scr[1]	Baseline		V1	V2	V3	V4	V5	V6	V7	V8	V9[15]	V10
Timepoints	D -90	D -28	D -14	D1	D8	D29	D36	D57	D71	D181	D209	D299	D394
Record any intercurrent medical conditions (see Section 9.2.1)	●	●	●	●	●	●	●	●	●	●	●	●	●
Review of eDiary data via the web portal, as applicable (see Section 10.3.8)		○	○	○	○	○	○	○	○	○	○	○	○
Recording of unsolicited AEs (Days 1 to 28 post-each study intervention administration) (see Section 10.3.8)				●	●	●	●	●					
Recording of MAEs (see Section 10.3.8)				●	●	●	●	●	●	●	●	●	●
Recording of SAEs (all) (see Section 10.3.8)				●	●	●	●	●	●	●	●	●	●
Recording of pIMDs (see Section 10.3.8)				●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●	●	●	●	●	●	●	●	●	●	●	●	●
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)				●	●	●	●	●	●	●	●	●	●
Recording of pregnancies (see Section 10.3.8)				●	●	●	●	●	●	●	●	●	●
Study conclusion (see Section 4.4)													●[14]

Refer to Section 10.7.1 for the list of abbreviations.

[1] If deemed necessary by the investigator, re-sampling can be performed within the allowed interval. Only data from the re-sampling testing, if done, will be taken into consideration.

[2] Refer to Section 5.1 for the additional criterion to be checked at Day 1.

[3] 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/100.4°F, regardless of the location of measurement).

[4] Blood sampling and pregnancy testing to be performed before each study intervention administration.

[5] At the beginning of each swabbing period post-study intervention administration, if the participant comes to the site, an anogenital swab could be collected by the study staff (demo swab), if the investigator thinks the participant should be retrained (for the second swabbing period, this can be done at Day 36 instead of Day 43).

[6] Not applicable if the visit is conducted virtually.

[7] Optional blood sampling. A separate ICF will be signed by participants who agree to give their blood sample for this optional blood sampling.

[8] A blood sample will be taken at Visit 1 for HSV-2 Western Blot analysis at University Washington (UWWB) from all enrolled participants except for those who were already tested by UWWB during the Screening visit.

[9] Participants may voluntarily participate in the third swabbing period.

[10] As of Protocol Amendment 7 implementation, investigators should record in eCRF the date since when a participant has stopped the reporting of RGH episodes.

[11] The investigator or study staff will contact each participant to discuss the ICF addendum associated with Protocol Amendment 7 as soon as effective. The date of contact should be record in the source document and in the eCRF. The date of ICF addendum signature is to be encoded in the eCRF. This signature must be obtained during the next on-site visit following the approval of the ICF addendum.

[12] On a voluntary basis as of Protocol Amendment 7 implementation.

[13] eDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.

[14] If a participant will have already completed their Visit 10 (Day 394) by the time Protocol Amendment 7 is effective, they will be contacted and instructed by the study staff to come back to the site to sign the ICF addendum related to this amendment.

[15] At Day 299, a phone contact is applicable for sites where Protocol Amendment 7 is not yet implemented; a site visit or virtual contact is applicable for sites where Protocol Amendment 7 is implemented.

Table 3 Non-Shedding Sub-cohort: Activities to be Performed by Study Staff

Type of Contact	Screening	Study Intervention Administration Phase						Follow-up Phase			
	Scr[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9[(11)]	V10
Timepoints	**D -90**	**D1**	**D8**	**D29**	**D36**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Obtain informed consent (see Section 10.1.3)[7]	●										
Check inclusion/exclusion criteria (see Sections 5.1 and 5.2)	●	○									
Collect demographic data (see Section 8.2.1.1)	●										
Measure and record height and weight (see Section 8.2.1.2)	●										
Record history of genital herpes (see Section 8.2.1.3)	●										
Record medical and vaccination history (see Section 8.2.1.3)	●	●									
Perform physical examination (see Section 8.2.1.8)	●	●	○	●	○	○	○[4]	○[4]	○[4]	○[4]	○[4]
Perform pregnancy test (see Section 8.2.1.9)	●	●[3]		●[3]							
Plan participant in the randomisation system (SBIR)	○										
Distribution of 'Participant card' (see Section 8.3.5)	○										
Record pre-study intervention administration body temperature[2]		●		●							
Study group and treatment number allocation (see Sections 6.3.2 and 6.3.3)		○									
Treatment number allocation for subsequent dose (see Section 6.3.3)				○							
Check contraindications to subsequent study intervention administration (see Section 7.1.1)				●							
Study intervention administration and recording of administered treatment number (see Section 6.1)		●		●							
If no documentation of laboratory-confirmed HSV-2 genital herpes: Blood sampling for HSV type-specific serology testing (~3.5 mL) (see Section 8.1.1)	●										
Blood sampling for HSV testing by Western Blot (~3.5 mL) (see Section 8.1.1)[5]		●									
Blood sampling for HIV testing (~8.5 mL) (see Section 8.1.1)	●										
Blood sampling for haematology analysis (~2.0 mL) (see Section 8.1.1)	●	●[3]	●	●[3]	●	●					
Blood sampling for biochemical analysis (~3.5 mL) (see Section 8.1.1)	●	●[3]	●	●[3]	●	●					
Blood sampling for antibody determination (humoral immunogenicity) analysis (~8.5 mL) (see Section 8.1.1)		●[3]		●[3]		●			●[8]		
Blood sampling for exploratory humoral response testing (~34.0 mL) (see Section 8.1.1)		●[3]		●[3]		●			●[8]		
Check participant's device compatibility with the app for collecting study information (see Section 8.2.1.10.1)	○	○	○	○	○	○	○	○			
Download the eDiary app or distribution of electronic device (see Section 8.2.1.10.2)		○									

Type of Contact	Screening	Study Intervention Administration Phase						Follow-up Phase			
	Scr[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9[11]	V10
Timepoints	**D -90**	**D1**	**D8**	**D29**	**D36**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Train participant on the use of eDiary and provide a refresher training if needed (see Section 8.2.1.10.2)		○	○	○	○	○	○	○			
Lesion swab collection procedure explained to the participant (see Section 8.2.1.7)		○									
Anogenital swab collection procedure explained to the participant (see Section 8.2.1.7)		○									
Distribution of materials for lesion swabbing (see Section 8.2.1.7)		○									
Demo anogenital swab collected by the study staff (see Section 8.2.1.7)		○									
First anogenital swab collected by the participant on site (see Section 8.2.1.7)		○									
Record the date since when participant has stopped reporting RGH episodes, when applicable								●[6]	●[6]	●[6]	●[6]
Check if the participant has enough materials for the anogenital and lesion swabbing, as needed			○	○	○	○	○	○			
Return of eDiary device or deletion of the app (see Section 8.2.1.11)								○[9]	○[9]	○[9]	○[9]
Record concomitant medications/vaccinations (see Section 6.8)		●	●	●	●	●	●	●	●	●	●
Record use of any antivirals (see Section 6.8)		●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions (see Section 9.2.1)	●	●	●	●	●	●	●	●	●	●	●
Review of eDiary data via the web portal, as applicable (see Section 10.3.8)		○	○	○	○	○	○	○	○	○	○
Recording of unsolicited AEs (Days 1 to 28 post-each study intervention administration) (see Section 10.3.8)		●	●	●	●	●					
Recording of MAEs (see Section 10.3.8)		●	●	●	●	●	●	●	●	●	●
Recording of SAEs (all) (see Section 10.3.8)		●	●	●	●	●	●	●	●	●	●
Recording of pIMDs (see Section 10.3.8)		●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●	●	●	●	●	●	●	●	●	●	●
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)		●	●	●	●	●	●	●	●	●	●
Recording of pregnancies (see Section 10.3.8)		●	●	●	●	●	●	●	●	●	●
Study conclusion (see Section 4.4)											●[10]

Refer to Section 10.7.1 for the list of abbreviations.

[1] If deemed necessary by the investigator, re-sampling can be performed within the allowed interval. Only data from the re-sampling testing, if done, will be taken into consideration.

[2] 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/100.4°F, regardless of the location of measurement).

[3] Blood sampling and pregnancy testing to be performed before each study intervention administration.

[4] Not applicable if the visit is conducted virtually.

[5] A blood sample will be taken at Visit 1 for HSV-2 UWWB from all enrolled participants except for those who were already tested by UWWB during the Screening visit.

[6] As of Protocol Amendment 7 implementation, investigators should record in eCRF the date since when a participant has stopped the reporting of RGH episodes.
[7] The investigator or study staff will contact each participant to discuss the ICF addendum associated with Protocol Amendment 7 as soon as effective. The date of contact should be record in the source document and in the eCRF. The date of ICF addendum signature is to be encoded in the eCRF. This signature must be obtained during the next on-site visit following the approval of the ICF addendum.
[8] On a voluntary basis as of Protocol Amendment 7 implementation.
[9] eDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.
[10] If a participant will have already completed their Visit 10 (Day 394) by the time Protocol Amendment 7 is effective, they will be contacted and instructed by the study staff to come back to the site to sign the ICF addendum related to this amendment.
[11] At Day 299, a phone contact is applicable for sites where Protocol Amendment 7 is not yet implemented; a site visit or virtual contact is applicable for sites where Protocol Amendment 7 is implemented.

Table 4 Activities to be Performed by Study Staff During the Unscheduled Visit (Planned in Case of Genital Herpes Recurrence) until end of RGH event reporting period

Type of Contact Timepoints	Unscheduled Visit for Genital Herpes Recurrence (see Section 8.1.5)
Perform physical examination (see Section 8.2.1.8)	○
Provide a refresher training on the anogenital and/or lesion swabbing procedures, if needed	○
Check participant's device compatibility with the app for collecting study information and provide a refresher training on the use of eDiary, if needed (see Section 8.2.1.10.1)	○
Lesion swab collected by study staff in case of genital herpes recurrence (see Section 8.1.5)	●
Assessment of the suspected RGH episode + recording of the diagnosis and management (see Section 8.1.5.1)	●
Check if the participant has enough materials for the anogenital and lesion swabbing, as needed	○
Record concomitant medications/vaccinations (see Section 6.8)	●
Record use of any antivirals (see Section 6.8)	●
Record any intercurrent medical conditions (see Section 9.2.1)	●
Review of eDiary data via the web portal (see Section 10.3.8)	○
Recording of MAEs (see Section 10.3.8)	●
Recording of pIMDs (see Section 10.3.8)	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●
Recording of SAEs (all, fatal and related) (see Section 10.3.8)	●
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)	●
Recording of pregnancies (see Section 10.3.8)	●

Refer to Section 10.7.1 for the list of abbreviations.

Note: If the timing to plan for an 'Unscheduled visit' falls within the time window of a planned study visit (see Table 8), evaluations and assessments must not be duplicated. All evaluations foreseen for the study visit will be performed and in addition, the lesion and anogenital swabbing and documentation will be performed as described in Section 8.1.5.

1.3.2.2. Activities to be Performed by the Participant

Table 5 Shedding Sub-cohort: Activities to be Performed by the Participant

Note that the Screening visit and the Baseline Day -28 Visit can be combined if the participant was not on antiviral treatment at the time of the Screening visit to allow the participant to start the baseline swabbing period immediately after the Screening visit. If the participant was on antiviral treatment at the time of the Screening visit, a 7-day wash-out period should be respected. If these visits are combined, all procedures to be performed at the Baseline Day -28 Visit should be done during the Screening visit. Procedures that are common between these 2 visits do not have to be repeated if the visits are combined.

Type of Contact	Screening			Study Intervention Administration Phase							Follow-up Phase			
	Scr	Baseline		V1	V2	V3	V4	-	V5	V6	V7	V8	V9	V10
Timepoints	**D -90**	**D -28**	**D -14**	**D1**	**D8**	**D29**	**D36**	**D43**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Twice daily anogenital swabbing by the participant (for **28 consecutive days**) (see Section 8.1.1.2)		From D-28** to D-1						From D43 to D70			From D181** to D208#			
Recording of the use of antivirals in eDiary (yes/no)		Each time genital herpes symptoms/lesions are reported by the participant***												
Recording of genital herpes recurrence information (symptoms/lesions) in eDiary (see Section 8.1.5)		Each time genital herpes symptoms/lesions are reported by the participant***												
Completion of HSC in eDiary (see Section 8.1.5.2)		Once daily, each time genital herpes symptoms are reported by the participant***												
Collection of lesion and anogenital swabs (see Section 8.1.5)*		Once per new recurrence, when the participant reports the appearance of genital herpes lesions***												
Return of the anogenital swabs collected during the swabbing periods			X	X					X	X		X#		X§
Recording of solicited AEs (Days 1 to 7 post-each dosing) in eDiary (see Section 10.3.8)				From D1 to D7		From D29 to D35								
Recording of the presence of unsolicited AEs (Days 1 to 28 post-each dosing) in eDiary (see Section 10.3.8)				From D1 to D28		From D29 to D56								
Return of eDiary (see Section 8.2.1.11)			X	X	X	X	X		X	X	X	XΔ	XΔ	XΔ

Refer to Section 10.7.1 for the list of abbreviations.
*If genital herpes lesions appear during a 28-day swabbing period, only the lesion swab is to be collected in addition to the planned twice daily anogenital swabbing
**On Day -28, an anogenital swab will be collected by the study staff during the site visit (demo swab). Participants will also be asked to collect an anogenital swab on site afterwards.
***As of Protocol Amendment 7 implementation, reporting of suspected RGH episodes and related procedures will be on a voluntary basis until Day 209 Visit.
ΔeDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.
#As of Protocol Amendment 7 implementation, participants may voluntarily participate in the third swabbing period.
§ Not required as of Protocol Amendment 7 implementation.

Table 6 Non-Shedding Sub-cohort: Activities to be Performed by the Participant

Type of Contact	Screening	Study Intervention Administration Phase							Follow-up Phase			
	Scr	V1	V2	V3	V4	-	V5	V6	V7	V8	V9	V10
Timepoints	**D -90**	**D1**	**D8**	**D29**	**D36**	**D43**	**D57**	**D71**	**D181**	**D209**	**D299**	**D394**
Recording of the use of antivirals in eDiary (yes/no)		Each time genital herpes symptoms/lesions are reported by the participant*										
Recording of genital herpes recurrence information (symptoms/lesions) in eDiary (see Section 8.1.5)		Each time genital herpes symptoms/lesions are reported by the participant*										
Completion of HSC in eDiary (see Section 8.1.5.2)		Once daily, each time genital herpes symptoms are reported by the participant*										
Collection of lesion and anogenital swabs (see Section 8.1.5)*		Once per new recurrence, when the participant reports the appearance of genital herpes lesions*										
Recording of solicited AEs (Days 1 to 7 post-each dosing) in eDiary (see Section 10.3.8)		From D1 to D7		From D29 to D35								
Recording of the presence of unsolicited AEs (Days 1 to 28 post-each dosing) in eDiary (see Section 10.3.8)		From D1 to D28		From D29 to D56								
Return of eDiary (see Section 8.2.1.11)			X	X	X		X	X	X	X**	X**	X**

Refer to Section 10.7.1 for the list of abbreviations.
*As of Protocol Amendment 7 implementation, reporting of suspected RGH episodes and related procedures will be on a voluntary basis until Day 209 Visit.
**eDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.

Site staff have to check that the participant brings back their collected lesion swab(s) during the Unscheduled visit. Additionally, for participants in the shedding sub-cohort, they will be instructed to also bring back the anogenital swabs they would have collected during a swabbing period.

Note: If the data related to the study objectives/endpoints to be collected by the participants cannot be encoded in their eDiary (e.g., unresolved technical issues), they can be reported directly to the site staff and submitted via the eCRF.

1.3.3. Intervals Between Study Visits

Table 7 Intervals Between Study Visits for PART I (Healthy Adults, Aged 18 to 40 Years)

Interval	Reference Visit	Planned Visit Interval	Allowed Interval Range
Screening (Day -56) → Visit 1 (Day 1)	Screening visit	Up to 56 days*	
Visit 1 (Day 1) → Phone Contact 1 (Day 1 + 24 hours)**	Study intervention Dose 1	24 hours	20 – 28 hours
Visit 1 (Day 1) → Visit 2 (Day 8)		7 days	7 – 9 days
Visit 1 (Day 1) → Visit 3 (Day 29)		28 days	28 – 33 days***
Visit 3 (Day 29) → Phone Contact 2 (Day 29 + 24 hours)**	Study intervention Dose 2	24 hours	20 – 28 hours
Visit 3 (Day 29) → Visit 4 (Day 36)		7 days	7 – 9 days
Visit 3 (Day 29) → Visit 5 (Day 64)		35 days	28 – 42 days***
Visit 3 (Day 29) → Visit 6 (Day 209)		180 days	173 – 187 days***
Visit 3 (Day 29) → Visit 7 (Day 394)		365 days	358 – 372 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 HIV and HSV testing results, and haematology/biochemical results.
**Phone contacts only applicable for the sentinel participants from Step 1 of PART I (see Section 8.2.2.2).
***Visits out of the allowed interval can lead to elimination from the Per-Protocol set for analysis of immunogenicity.

Table 8 Intervals Between Study Visits for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Interval	Planned Visit Interval	Allowed Interval Range
ΔScreening (Day -90) → Baseline Day -28 Visit	Up to 62 days*	
ΔBaseline Day -28 Visit → Baseline Day -14 Visit	14 days	11 – 17 days
Screening (Day -90) → Visit 1 (Day 1)	Up to 90 days	
Visit 1 (Day 1) → Visit 2 (Day 8)	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)	7 days	7 – 9 days
Visit 3 (Day 29) → Visit 5 (Day 57)	28 days	28 – 33 days***
Visit 3 (Day 29) → Visit 6 (Day 71)	42 days	42 – 47 days
ΔDay 43 → Visit 6 (Day 71)	28 days**	28** – 33 days
Visit 3 (Day 29) → Visit 7 (Day 181)	152 days	145 – 159 days
Visit 3 (Day 29) → Visit 8 (Day 209)	180 days	165 – 195 days***
Visit 7 (Day 181) → Visit 8 (Day 209)	28 days**	28** – 33 days***
Visit 3 (Day 29) → Visit 9 (Day 299)	270 days	256 – 284 days
Visit 3 (Day 29) → Visit 10 (Day 394)	365 days	337 – 393 days

ΔOnly for participants in the shedding sub-cohort

*Note that the Screening visit and the Baseline Day -28 Visit can be combined if the participant was not on antiviral treatment at the time of the Screening visit to allow the participant to start the baseline swabbing period immediately after the Screening visit. If the participant was on antiviral treatment at the time of the Screening visit, a 7-day wash-out period should be respected.

**Participants in the shedding sub-cohort will be instructed to collect swabs only for 28 days, in order to have up to 56 consecutive swabs (2 swabs per day; i.e., one in the morning and one in the evening).

***Visits out of the allowed interval can lead to elimination from the Per-Protocol set for analysis of immunogenicity. Note that if the study intervention cannot be administered because of special circumstance(s), the time interval between the Screening visit and Dose 1 can be extended for 90 additional days and the time interval between Dose 1 and Dose 2 can be extended to 90 days (see Section 5.5).

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]. 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, travelling 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]. 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 clinical manifestations of HSV infection are similar between HSV-1 and HSV-2. 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 industrialised 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].

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]. In industrialised countries, the prevalence of HSV-2 (i.e., prevalence of antibodies to HSV-2 from tested sera) varies from 10% to 25% in the general 15 to 49-year-old population [Looker, 2008]. 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 United States (US), 16% of adults (and 12% among those aged 14 to 49 years) are HSV-2 seropositive [CDC, 2010], but only approximately 20% of HSV-2 infected people have recognised genital herpes [CDC, 2010; Looker, 2015; Wald, 2000]. In the US, Bernstein *et al*. estimated an incidence of primary HSV-2 genital herpes (newly infected with symptoms) of 0.4 per 100 person-years in young women aged 18 to 30 years that were HSV seronegative [Bernstein, 2013].

HSV-2 shedding remains at high levels for many years following infection. In Phipps study, shedding was observed up to 34% of days among patients in the first year after their primary genital herpes episode and even 10 years after the first episode, shedding can be detected at 17% of days [Phipps, 2011].

The observed median number of genital herpes recurrences was 5 per year in patients with newly acquired HSV-2 infection in the first year of follow-up, with a decrease of 2 recurrences between years 1 and 5 of follow-up [Benedetti, 1999].

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 human immunodeficiency virus type 1 (HIV-1) [Freeman, 2006]), there is still a high medical need for an improved treatment.

These infections are lifelong, incurable, stigmatising and no existing interventions can effectively prevent them at population level [Gottlieb, 2019]; therefore, the need for a novel therapeutic approach has become apparent.

2.2. Study Rationale

Prior attempts to develop a prophylactic or therapeutic vaccine for HSV were unsuccessful. Several previous vaccine candidates focused on eliciting IgG and neutralising antibody responses to gD, the most abundant and immunodominant surface antigen. HSV gD was the first well-characterised HSV entry molecule, which explains why many vaccine trials performed to date have included gD subunit antigen. The goal was to induce neutralising antibodies that block infection. The ability of HSV to persist and recur in otherwise healthy individuals is likely due to its capacity to evade the host's antiviral responses.

CCI [redacted]

The purpose of this study is to evaluate the safety, reactogenicity, immunogenicity, and efficacy of GSK's HSVTI (gE-gI with AS01).

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical studies of the HSVTI.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks, and expected adverse events (AEs) of the HSVTI 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
Study Intervention (HSVTI)		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any study intervention administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of study intervention administrations, depending on the study intervention 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 administration, 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 study interventions [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 12 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.	A topical analgesic may be applied to the site where blood will be taken. 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 study intervention administration 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.

Important / Potential / Identified / Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Procedures (*continued*)		
Nerve injury	There is a possibility that in the process of collecting blood a nerve may be injured.	Blood samples will be obtained by a trained professional and medical assistance will be available.
Local inflammatory reaction	Intramuscular study intervention administration commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling.	All participants will remain under observation at the study site for at least 60 minutes after study intervention administration.
Risks from blood sampling (e.g., discomfort, dizziness)	Blood sampling-associated risk of discomfort, syncope, dizziness, and infection at the injection site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available.
Only for PART II: Discomfort associated with anogenital swabbing	Rubbing swabs over the mucosal surfaces can cause momentary discomfort, especially if lesions are present.	Participants will be properly trained by an investigator or delegate, will watch tutorial videos, and will receive instructions and a handout ('Participant leaflet') detailing the anogenital swabbing procedure.

pIMD = potential immune-mediated disease; **AE** = adverse event

No new safety risks have been characterized for the HSVTI up to the proof-of-concept analysis conducted in August 2024.

2.3.2. Benefit Assessment

For both PART I and PART II: 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 [haematology and biochemistry data]).

Only for PART II: The primary analysis results failed to demonstrate the superiority of HSVTI over placebo in prolonging the time to first PCR-confirmed genital herpes event up to ~2 months of follow-up starting 14 days post-Dose 2. Therefore, the anticipated benefit was not demonstrated. Participants may gain information and medical advice on genital herpes management through the continuous monitoring of their genital herpes events and clinical evaluation in the study. In addition, for participants included in the shedding sub-cohort, they may gain information at the end of the study about their shedding through the twice daily anogenital swabbing performed during the study.

2.3.3. Overall Benefit/Risk Assessment

The HSVTI is currently in Phase 2 of clinical development. All participants have completed the HSVTI or placebo administration in this study.

Considering the lack of anticipated clinical efficacy but no observed additional safety risks up to the ~2-months of follow-up starting 14 days post-Dose 2, it is no longer justified for further follow-up until 2 years post-Dose 2 and withholding the chronic suppressive therapy. Participants may continue the monitoring of genital herpes events, viral shedding (for shedding sub-cohort only) and immune responses up to 6 months post-Dose 2 on a voluntary basis. To observe the long-term safety risk associated with HSVTI administration, participants will be monitored for 12 months post-last dose.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 9 Study Objectives, Endpoints, and Estimands

Objectives	Endpoints and Estimands
Primary	
Safety	
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 12 months after last study intervention administration (Day 394). • Percentage of participants reporting any SAEs from Dose 1 (Day 1) up to 12 months after last study intervention administration (Day 394). • Percentage of participants reporting any pIMDs (classified as newly diagnosed or exacerbation of pre-existing events) from Dose 1 (Day 1) up to 12 months after last study intervention administration (Day 394). • Only for PART I: Percentage of participants reporting any haematological and biochemical laboratory abnormalities post-Dose 1 (Day 8 and Day 29), post-Dose 2 (Day 36 and Day 64). • Only for PART II: Percentage of participants reporting any haematological and biochemical laboratory abnormalities post-Dose 1 (Day 8 and Day 29), post-Dose 2 (Day 36 and Day 57).
Efficacy	
Only for PART II: To demonstrate the efficacy of the HSVTI in reducing the risk of having confirmed HSV-2 RGH episodes. Refer to Section 4.2.2 for the definition of confirmed HSV-2 RGH episode.	• Time-to-first confirmed HSV-2 RGH episode.

Objectives	Endpoints and Estimands
Secondary	
Efficacy	
Only for PART II: To compare the HSVTI to placebo in terms of incidence rate of RGH episodes. Refer to Section 4.2.2 for the definition of RGH episode. Refer to Section 8.1.5 for the definition of end of RGH event reporting period.	• Number of confirmed HSV-2 RGH episodes divided by the number of days of follow-up assessed until end of RGH event reporting period.
Only for PART II: To compare the HSVTI to placebo in terms of percentage of RGH-free participants at 6 months after the last dose of study intervention.	• Percentage of participants free from confirmed HSV-2 RGH episode at 6 months after the last dose of study intervention.
Only for PART II: To compare the HSVTI to placebo in terms of severity of RGH episode-associated symptoms during each RGH episode. Refer to Section 8.1.5 for the definition of end of RGH event reporting period.	• HSC total score during each confirmed HSV-2 RGH episode assessed until end of RGH event reporting period.
Only for PART II: To compare the HSVTI to placebo in terms of duration of RGH episode-associated symptoms, as assessed by the participant. Refer to Section 8.1.5 for the definition of end of RGH event reporting period.	• Number of days with RGH-associated symptoms during each confirmed HSV-2 RGH episode assessed until end of RGH event reporting period.
Only for PART II: To evaluate the lesion rate after administration of the last dose of the HSVTI. Refer to Section 4.2.2 for the definitions of lesion rate reduction. Refer to Section 8.1.5 for the definition of end of RGH event reporting period.	• Number of days with confirmed HSV-2 genital herpes lesions divided by the number of days of follow-up assessed until end of RGH event reporting period.
Only for PART II (shedding sub-cohort): To evaluate the effect of the HSVTI, about 6 weeks after the last dose of the HSVTI on shedding rate. Refer to Section 9.3.4.1 for the definitions of shedding rate reduction.	• HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to about 6 weeks post-Dose 2 (Day 71).
Only for PART II (shedding sub-cohort): To evaluate the HSV shedding.	• Number and duration of HSV-2 DNA shedding episodes during the 28-day periods starting at baseline (Day -28), Day 43, Day 181 (overall, asymptomatic and symptomatic).
Immunogenicity	
To evaluate the humoral immune response induced by the HSVTI.	• Only for PART I: Anti-gE-gI antibody GMC and seropositivity rate (assessed by ELISA) at pre-study intervention administration (Day 1), post-Dose 1 (Day 29), post-Dose 2 (Day 64), 6 months post-Dose 2 (Day 209) and 12 months post-Dose 2 (Day 394). • Only for PART II: Anti-gE-gI antibody GMC and seropositivity rate (assessed by ELISA) at pre-study intervention administration (Day 1), post-Dose 1 (Day 29), and 1 month post Dose- 2 (Day 57).
To evaluate the cellular immune response induced by the HSVTI.	• Only for PART I: Geometric mean of gE-gI-specific CD4+/CD8+ Tcells frequency expressing at least 2 activation markers (IFN-γ, TNF-α, IL-2, IL-13, IL17, 4-1BB and/or CD40L) and including at least one cytokine (assessed by CFC) at pre-study intervention administration (Day 1), postDose 1 (Day 29), postDose 2 (Day 64), 6 months postDose 2 (Day 209) and 12 months post-Dose 2 (Day 394).

Objectives	Endpoints and Estimands
	• Only for PART II: Geometric mean of gE-gI-specific 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), post-Dose 1 (Day 29), and 1 month post-Dose 2 (Day 57).
Tertiary *(Note that tertiary objectives, endpoints, and estimands are optional and might be assessed only if needed; therefore, not all testings might be performed and reported)*	
CCI [redacted]	

Objectives	Endpoints and Estimands
CCI [redacted]	

AE = adverse event; **MAE** = medically attended event; **SAE** = serious adverse event; **pIMD** = potential immune-mediated disease; **HSV(-2)** = herpes simplex virus (type 2); **RGH** = recurrent genital herpes; **gE-gI** =glycoprotein E-glycoprotein I; **GMC** = geometric mean concentration; **ELISA** = enzyme-linked immunosorbent assay; **CD4+/CD8+** = cluster of differentiation 4/8; **IFN-γ** = interferon-gamma; **TNF-α** = tumour necrosis factor-alpha; **IL (IL-2, IL-13, IL-17)** = interleukin; **CD40L** = cluster of differentiation 40 ligand; **CFC** = cell flow cytometry; **HSC** = Herpes Symptoms Checklist; **DNA** = deoxyribonucleic acid; CCI [redacted]

Details related to attributes of estimands covering intercurrent events, population and treatment definition are provided in Sections 9.2 and 9.2.2.

4. STUDY DESIGN

4.1. Overall Design

This is a first-time-in-human, Phase I/II, randomised, placebo-controlled, observer-blind, self-contained, multi-country, multi-centre study.

The study will be conducted in 2 parts: PART I (conducted only in Belgium), will be a 2-step design to assess the reactogenicity, safety, and immunogenicity of up to 9 formulations of the HSVTI (refer to Figure 1); PART II (to be conducted in several countries, including the US), will be a 1-step parallel design to assess the reactogenicity, safety, immunogenicity, and efficacy of the selected formulations of the HSVTI (refer to Figure 2):

- In **PART I**, ~245 healthy participants aged 18 to 40 years will receive the HSVTI or placebo (according to a 0, 1-month schedule) in 2 steps:
  - During **Step 1**, a first wave of ~45 participants (~5 per group) will be enrolled and receive a first dose of either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI (40 µg or 80 µg or 160 µg) (at Day 1) in a staggered manner. Administration of the second dose in Step 1 (at Day 29) will depend on the favourable outcome of the internal safety review committee (iSRC) evaluation (refer to Section 8.2.2). In addition, administration of the first dose in Step 2 (as detailed below) will depend on the favourable outcome of the iSRC evaluation.
  - During **Step 2**, ~200 healthy participants (~20 per group) will be enrolled and receive a first dose of either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI (40 µg, 80 µg or 160 µg) or placebo (at Day 1) in a parallel manner (10 groups). Administration of the second dose in Step 2 (at Day 29) will depend on the favourable outcome of the iSRC evaluation (refer to Section 8.2.2).

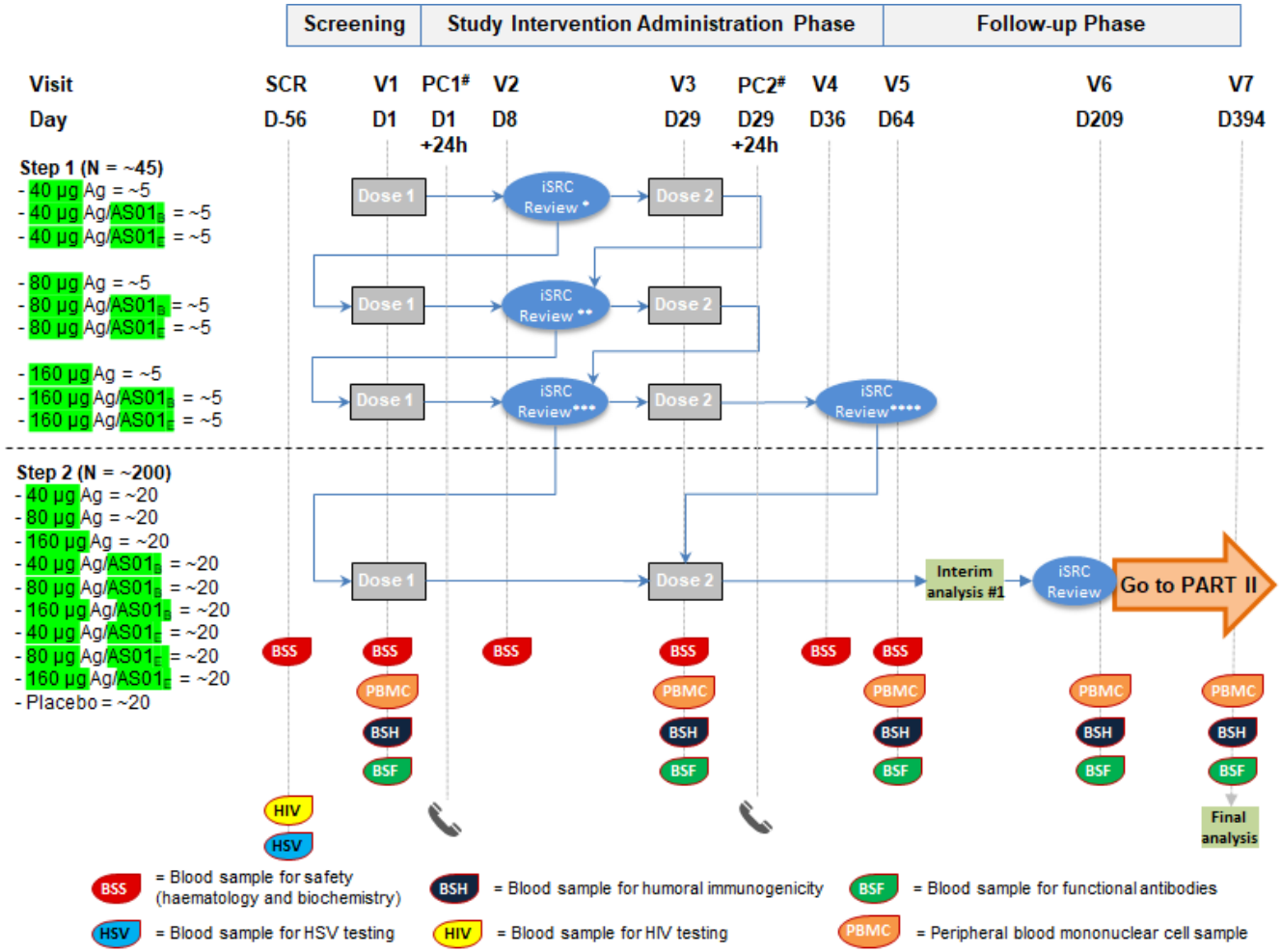
  At the time of the PART I Interim Analysis to be performed when all participants will have attended their Visit 5 (Day 64), an iSRC evaluation on all available safety and reactogenicity data (including safety laboratory data) will be performed before moving to PART II (refer to Section 9.4.1).

  The safety, reactogenicity, and immunogenicity data from these 2 steps will allow selection of 2 HSVTI formulations for evaluation in the target population in PART II (refer to Section 9.5.4).
- In **PART II**, ~270 participants aged 18 to 60 years with HSV genital herpes will receive 2 doses of the HSVTI formulations (selected during PART I) or placebo according to a 0, 1-month schedule (at Days 1 and 29). Several iSRC meetings (refer to Section 8.2.2) and an internal Data Review Committee (iDRC) meeting (refer to Section 9.4) are foreseen during this part of the study.

Data collection will be done via standardised eCRF and electronic diary (eDiary).

Day 394 of PART II will be considered as the Primary Completion Date.

Figure 1 Study Design Overview of PART I (Healthy Adults, Aged 18 to 40 Years)



SCR = screening; **V** = visit; **D** = day; **PC** = phone contact; **N** = number of participants; **Ag** = antigen; **AS01B** = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); **AS01E** = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); **iSRC** = internal safety review committee

#Phone contacts only applicable for the sentinel participants from Step 1 of PART I (see Section 8.2.2.2). These contacts are to be made 24 hours after each study intervention administration (at Day 1 and Day 29).

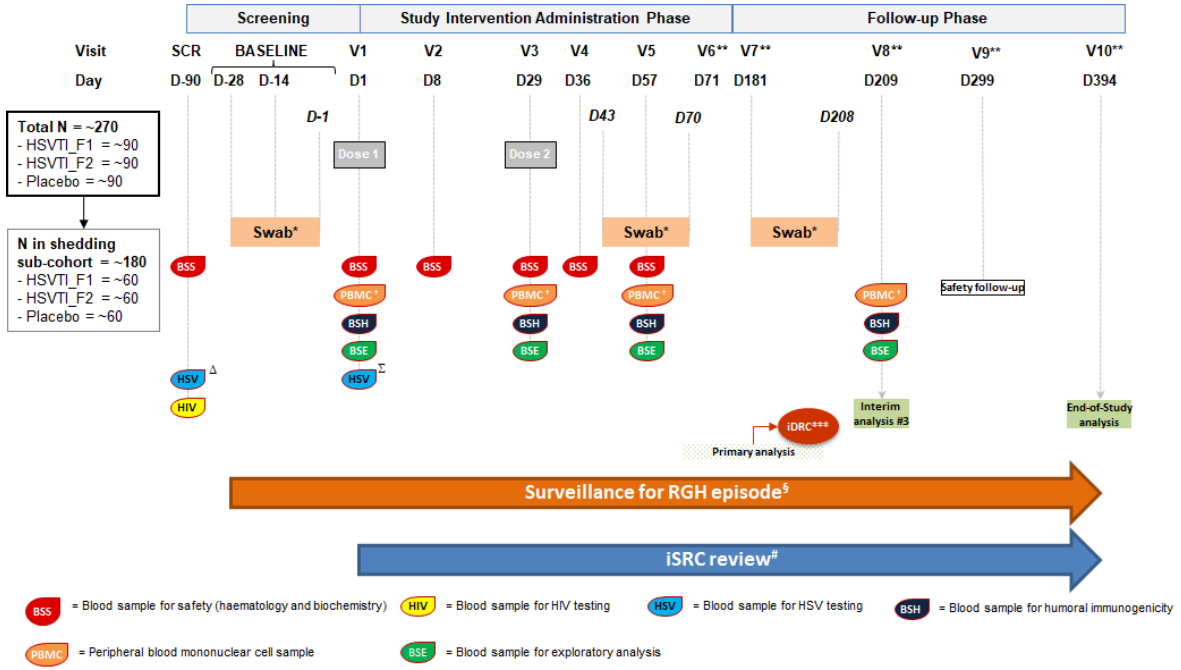
*An iSRC will occur as soon as all 15 participants (who received the 40 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$) will have been followed-up for 7 days post-Dose 1. If the outcome of the iSRC evaluation is favourable, those participants will receive their second dose and participants who will receive the 80 µg formulation nonadjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be enrolled and administered with the first dose.

**An iSRC will occur as soon as all 15 participants (who received the 80 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$) will have been followed-up for 7 days post-Dose 1. In addition, all available safety data of participants who received the 40 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first study intervention dose will receive their second study intervention dose and participants who will receive the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be enrolled and administered with the first study intervention dose.

***An iSRC will occur as soon as all 15 participants (who received the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$) will have been followed-up for 7 days post-Dose 1. In addition, all available safety data of participants who received the 40 µg and 80 µg formulations non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first study intervention dose will receive their second study intervention dose and participants of Step 2 will be enrolled and administered with the first study intervention dose.

****An iSRC will occur as soon as all 15 participants (who received the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$) will have been followed-up for 7 days post-Dose 2. In addition, all available safety data of participants enrolled and dosed in Step 1 and in Step 2 (with the first study intervention dose) will be reviewed. If the iSRC evaluation outcome is favourable, participants enrolled in Step 2 will be administered their second study intervention dose. No Dose 2 will be administered in Step 2 until all data from Step 1 (including post-Dose 2) are reviewed.

Figure 2 Study Design Overview of PART II for Participants in the Shedding Sub-cohort



SCR = screening; **V** = visit; **D** = day; **N** = number of participants; **iSRC** = internal Safety Review Committee; **iDRC** = internal Data Review Committee

Note that the Screening visit and the Baseline Day -28 Visit can be combined if the participant was not on antiviral treatment at the time of the Screening visit to allow the participant to start the baseline swabbing period immediately after the Screening visit. If the participant was on antiviral treatment at the time of the Screening visit, a 7-day wash-out period should be respected.

#To learn more about iSRC meetings planned during the study, refer to Section 8.2.2.1.

*Twice daily (i.e., one in the morning and one in the evening) anogenital swabbing by a sub-cohort of participants (for 28 consecutive days) (shedding sub-cohort). Note that on Day -28, the first anogenital swab will be collected at the site.

**These visits might be replaced by a virtual contact.

***CCI [redacted] (see Section 9.4.3).

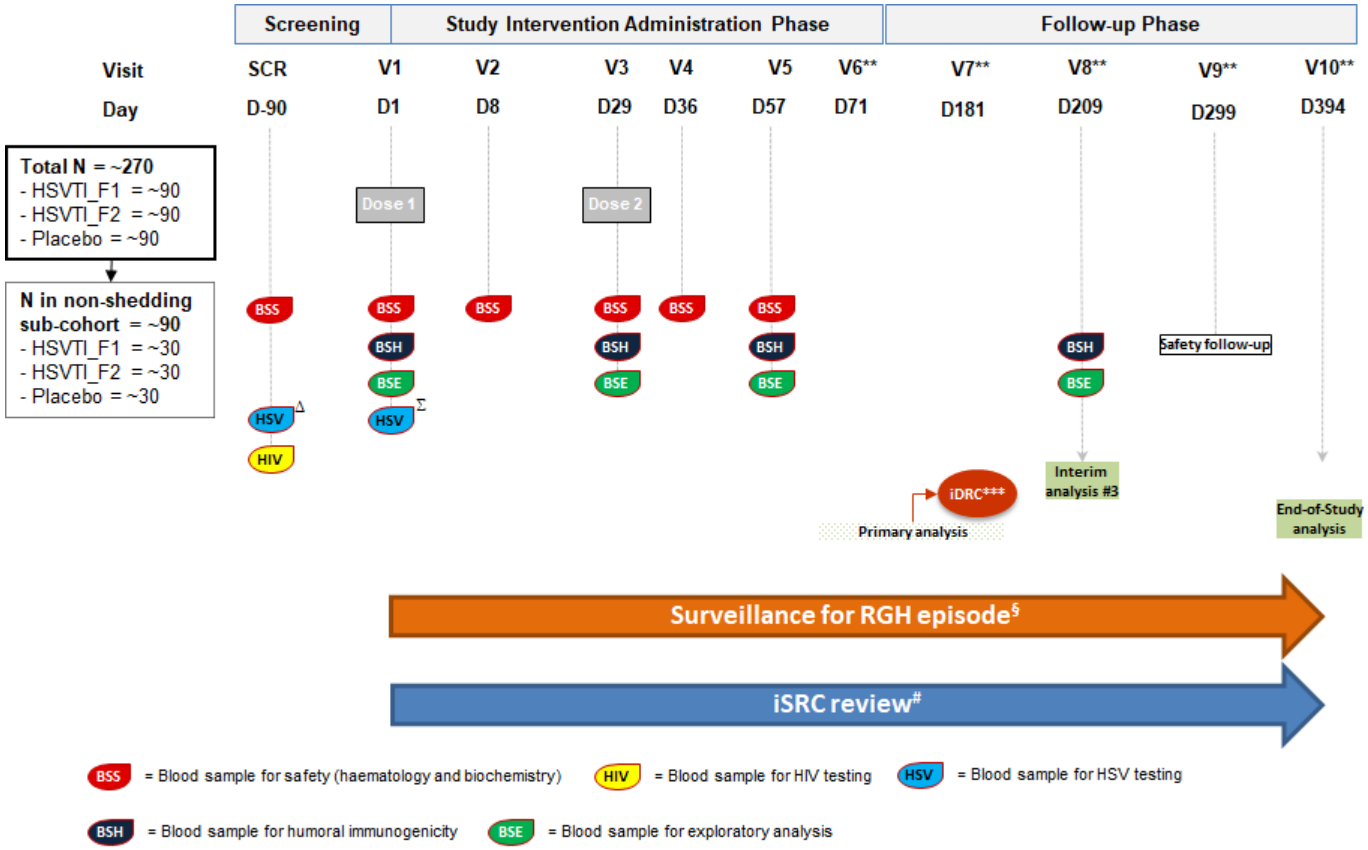
† In a sub-cohort of participants (shedding sub-cohort). Additional PBMC samples for exploratory analyses are to be taken at specified timepoints (refer to Table 17).

Δ If no documentation of laboratory-confirmed HSV-2 genital herpes.

Σ For all enrolled participants except for those who were already tested by UWWB during the Screening visit.

§ Refer to Section 8.1.5 for the definition of end of RGH event reporting period following Protocol Amendment 7 approval by relevant IECs/IRBs and Regulatory Authorities.

Figure 3 Study Design Overview of PART II for Participants Not in the Shedding Sub-cohort



SCR = screening; **V** = visit; **D** = day; **N** = number of participants; **iSRC** = internal safety review committee
#To learn more about iSRC meetings planned during the study, refer to Section 8.2.2.1.
**These visits might be replaced by a virtual contact.
***CCI [redacted] (see Section 9.4.3).
Δ If no documentation of laboratory-confirmed HSV-2 genital herpes.
Σ For all enrolled participants except for those who were already tested by UWWB during the Screening visit.
§ Refer to Section 8.1.5 for the definition of end of RGH event reporting period following Protocol Amendment 7 approval by relevant IECs/IRBs and Regulatory Authorities.

Table 10 Study Groups, Intervention, and Blinding

Study Groups	Number of Participants	Age (Min-Max)	Study Interventions	Blinding Visit 1 → Visit 7 (Observer-blind)
PART I (Step 1 and Step 2)				
40 µg Ag	~5 + ~20	18 – 40 years	40 µg Ag	X
80 µg Ag	~5 + ~20	18 – 40 years	80 µg Ag	X
160 µg Ag	~5 + ~20	18 – 40 years	160 µg Ag	X
40 µg Ag/AS01$_B$	~5 + ~20	18 – 40 years	40 µg Ag/AS01$_B$	X
80 µg Ag/AS01$_B$	~5 + ~20	18 – 40 years	80 µg Ag/AS01$_B$	X
160 µg Ag/AS01$_B$	~5 + ~20	18 – 40 years	160 µg Ag/AS01$_B$	X
40 µg Ag/AS01$_E$	~5 + ~20	18 – 40 years	40 µg Ag/AS01$_E$	X
80 µg Ag/AS01$_E$	~5 + ~20	18 – 40 years	80 µg Ag/AS01$_E$	X
160 µg Ag/AS01$_E$	~5 + ~20	18 – 40 years	160 µg Ag/AS01$_E$	X
Placebo (saline)	~20	18 – 40 years	Placebo (saline)	X
PART II				
Study Groups	**Number of Participants**	**Age** (Min-Max)	**Study Interventions**	**Blinding Visit 1 → Visit 10** (Observer-blind)
HSVTI_F1	~90	18 – 60 years	80 µg Ag/AS01$_B$	X
HSVTI_F2	~90	18 – 60 years	80 µg Ag/AS01$_E$	X
Placebo (saline)	~90	18 – 60 years	Placebo (saline)	X

Ag = antigen; **AS01$_B$** = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); **AS01$_E$** = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)

4.2. Scientific Rationale for Study Design

This study will provide reactogenicity, safety, immunogenicity, and efficacy data for the HSVTI before moving to the larger Phase III efficacy study.

PART I will be a 2-step staggered design to assess the reactogenicity, safety, and immunogenicity of up to 9 formulations of the HSVTI (refer to Figure 1) to select the formulations that will be used in PART II. As this is a first-time-in-human study, healthy participants aged 18 to 40 years will be enrolled. For more information, refer to Section 8.2.2. Two formulations have been selected for further evaluation in PART II (refer to Section 9.5.4).

In Step 1 of PART I (refer to Figure 1), a stepwise dose-escalation design is used to assess the safety and reactogenicity of the non-adjuvanted and AS01$_B$- or AS01$_E$-adjuvanted formulations of HSVTI. To ensure safety of the participants, the enrolment and dosing will be staggered to allow a stepwise dose-escalation in a limited number of participants before study intervention administration of a larger number of participants in Step 2 (refer to Sections 8.2.2.1 and 8.2.2.2).

Step 2 of PART I is using a factorial design to characterise the safety and immunogenicity of the HSVTI (refer to Figure 1). At the end of this step, safety, reactogenicity, and immunogenicity data will allow selection of 2 HSVTI formulations for evaluation in the target population in PART II (patients with HSV genital herpes aged 18 to 60 years). Immunogenicity data have been selected as endpoints for the HSVTI formulations selection as proposed by the 'World Health Organization' [WHO, 2017].

Two formulations from PART I, which have been demonstrated with the best profile with regards to tolerability/safety and immune response, have been selected to proceed to PART II, to further assess the long-term reactogenicity, safety, clinical and virologic efficacy (as measured by HSV shedding in a sub-cohort), and immunogenicity of the HSVTI in participants at risk of genital herpes recurrence (refer to Section 4.3.2).

Randomisation is used to reduce bias of selection and the placebo group is included as a control in an observer-blinded manner to allow the discrimination of the HSVTI treatment effect for reactogenicity, safety, immunogenicity, and efficacy assessments while avoiding placebo effect. In the context of lack of efficacy, the study duration is shortened from 24 months to 12 months post-Dose 2 to allow the observation of safety risk beyond 1 month post-Dose 2. The blinding is remained till end of 12 months post-Dose 2 to minimise the potential confounding factors for safety signals and risk identification.

4.2.1. Participant Input Into Design

An epidemiological study (EPI-HSV-006 BOD TH) has been completed to assess genital herpes recurrence rates and to assess patient-reported outcomes and quality of life endpoints. In anticipation of this study, 2 surveys were conducted in 262 HSV-2 positive patients aged ≥18 years:

- To understand more about patients' experience of living with genital herpes,
- To assess patients' willingness to engage in study needs, and,
- To explore patients' likelihood to comply with study procedures and follow-up.

The outcome of these surveys was taken into consideration when designing the present study.

4.2.2. Case Definitions

Case definitions applicable to the PART II of the study are presented in Table 11.

Table 11 Case Definitions for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Suspected RGH episode (can be referred to as "recurrences" throughout the document)	Re-appearance of active lesions (swelling, blisters, sores, or crusts) in the anogenital area associated with prodromal symptoms or erythema, if any. A RGH episode starts from the day on which the participant first reports signs of lesions and/or prodromal symptoms or erythema (if any) and ends on the day on which no active lesion is reported. A day with missing data in between 2 days of active lesion (swelling, blisters, sores, or crusts) is considered part of the same RGH episode. A reported episode during which only prodromal symptoms or erythema is reported will not be counted as an RGH episode. Note: A new RGH episode starts with the appearance of self-reported HSV lesions following at least 2 days without lesions.
Confirmed HSV-2 RGH episode	A suspected RGH episode will be classified as confirmed HSV-2 RGH episode if at least one of the lesional or anogenital swabs taken during the concerned episode is positive for HSV-2 as measured by PCR.
Lesion rate	Number of days on which lesions (swelling, blisters, sores, or crusts) are reported by the participant in the anogenital area during confirmed RGH episodes divided by the number of days of follow-up.
HSV shedding rate	Number of HSV-positive swabs divided by the number of swabs collected during the predefined 28-day period.

HSV(-2) = herpes simplex virus (type 2); **RGH** = recurrent genital herpes; **WB** = Western Blot; **PCR** = polymerase chain reaction

Further definitions and details will be provided in the Statistical Analysis Plan (SAP).

4.3. Justification for Dose

4.3.1. Formulations Used in PART I

4.3.1.1. Antigen Dose Selection

The gE-gI doses to be investigated in the present study are based on what has been done for *Shingrix*, GSK's varicella zoster virus vaccine, which contains a similar antigen (i.e., gE). Antigen doses of 25 µg, 50 µg, and 100 µg that were evaluated in the *Shingrix* programme are equimolar to the gE-gI doses of 40 µg, 80 µg, and 160 µg that will be tested in this study.

4.3.1.2. Adjuvant Selection

The adjuvants that will be tested ($AS01_B$ and $AS01_E$) are used in *Shingrix* and in *Mosquirix*, respectively. Data available to date demonstrate that $AS01_B$/$AS01_E$-adjuvanted vaccines induce high and robust humoral responses, as well as a strong CD4+ T-cell response, while showing an acceptable safety profile. Up to October 2020:

- $AS01_B$ has been extensively evaluated in more than 32 000 participants during several Phase I to Phase III vaccine studies. From those participants, $AS01_B$ has been administered in more than 1500 adults aged 18 to 49 years and in ~14 000 adults aged 50 to 69 years.
- $AS01_E$ has been evaluated in more than 16 000 children in several Phase I to Phase III vaccine studies of the malaria programme. In addition, it has been administered in more than 2600 adults aged 18 to 49 years and in ~500 adults aged 50 to 69 years.

In addition to the clinical studies, post-marketing safety data have become available since the launch of *Shingrix* in 2017 and its broad use in several countries. Spontaneous reports received since launch of *Shingrix* are generally consistent with what has been observed in clinical studies and the information provided in the Reference Safety Information for *Shingrix*. The benefit-risk profile of *Shingrix* continues to be favourable.

Pre-clinical studies conducted so far did not raise any safety concerns.

4.3.2. Formulations Used in PART II

CCI



CCI

[redacted]

4.4. End of Study Definition

A participant of PART I is considered to have completed the study if he/she returns for the last visit (Visit 7 [Day 394]) as described in the Protocol. A participant of PART II is considered to have completed the study if he/she returns for the last visit (Visit 10 [Day 394]) as described in the Protocol.

The End of Study (EoS) is defined as the date of the Last Subject Last Visit (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 jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

Note that the eligibility criteria defined below were those applied at the time of enrolment and were not updated in Protocol Amendment(s) developed after enrolment completion.

5.1. Inclusion Criteria

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

1. Participants, who, in the opinion of the investigator, can and will comply with the requirements of the Protocol (e.g., completion of the eDiary, return for follow-up visits).
2. Written informed consent obtained from the participant prior to performance of any study-specific procedure.
3. Women of non-childbearing potential can be enrolled in the study. Refer to Section 10.4.1.1.1 for definitions of women not considered as women of childbearing potential, menarche and menopause.
4. Women of childbearing potential can be enrolled in the study, if the participant:
   - Has practiced highly effective contraception for one 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,
   - For PART I: Has agreed to continue highly effective contraception until the end of the study.
   - For PART II: Has agreed to continue highly effective contraception until 3 months after last study intervention administration.

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

   Blood sample for simultaneous follicle-stimulating hormone (FSH) and oestradiol levels may be collected and tested locally at the discretion of the investigator to confirm non-reproductive potential according to local laboratory reference range.
5. Seronegative for HIV, as determined by laboratory screening tests. Participants documented to be seropositive to HIV will not be eligible for study participation.
6. Only for PART I: Healthy participants as established by medical history and physical examination, at the discretion of the investigator, before entering into the study.
7. Only for PART I: Man or woman aged 18 to 40 years, included, at the time of the first study intervention administration.

8. Only for PART I: Seronegative for HSV-2 as determined by Western blot performed at the Screening visit.
9. Only for PART II: Participants with recurrent genital herpes and with no significant health problems as established by medical history and physical examination, at the discretion of the investigator, before entering the study.
   - Diagnosis of genital herpes for at least 1 year before the Screening visit.
   - History of self-reported or documented recurrent lesional genital herpes frequency of at least 3 and no more than 9 recurrences in the 12 months preceding the Screening visit, or, if still on suppressive therapy within 3 months before the Screening visit, prior to initiation of suppressive therapy.
10. Only for PART II: Man or woman aged 18 to 60 years, included, at the time of the first study intervention administration.
11. Only for PART II: Seropositive for HSV-2 as determined by serological testing performed at the Screening visit, or having documented laboratory-confirmed HSV-2 genital herpes (i.e., HSV-2 DNA positive by a molecular technique such as polymerase chain reaction [PCR], or HSV-2 seropositive by a type-specific serology assay such as Western Blot or other immunoassay).
12. Only for PART II (shedding sub-cohort): Participants agreeing to collect 2 swabs per day from anogenital area for the full duration of the 5 swabbing periods planned in the study.
13. Only for PART II (shedding sub-cohort) after baseline completion: Participants having collected at least 45 out of 56 anogenital swabs during the baseline period. This criterion can only be checked at Visit 1 (Day 1).

5.2. Exclusion Criteria

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

5.2.1. Medical Conditions

14. 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 categorised 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 patient at risk or influence study results.
   - Participants a controlled underlying chronic co-morbidity may be enrolled, provided there have been no significant changes to their medication within 3 months prior to the Screening visit, as judged by the investigator.

15. 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 efficacy or immunogenicity assessments planned in this study.
16. History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention.
17. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
18. Hypersensitivity to latex.
19. Recurrent history or uncontrolled neurological disorders or seizures.
20. Haematological (haemoglobin level, white blood cell, platelet) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) parameters outside the normal laboratory ranges at the Screening visit, unless the laboratory abnormalities are considered not clinically significant by the investigator.
21. Body mass index < 18 kg/m^2 or > 35 kg/m^2.
22. Past or current Guillain-Barré syndrome.
23. 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

24. Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study intervention during the period beginning as of the Screening visit, or planned use during the study period.
25. Planned administration/administration of a vaccine* not foreseen by the Protocol 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 an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organised by public health authorities outside the routine immunisation programme, 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.
26. Administration or planned administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
27. 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.

28. 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, or equivalent. Inhaled, intra-articular and topical steroids are allowed.
29. Prior receipt of another vaccine containing HSV antigens.
30. Only for PART II: Planned use of suppressive anti-HSV therapy from the Screening visit until the end of the study.
31. Only for PART II: Planned use of tenofovir therapy (e.g., in case of pre-exposure prophylaxis to prevent HIV infection), or other medication known to affect HSV shedding or genital lesions from the Screening visit until the end of the study.
32. Only for PART II: Planned use of topical antiviral medication in the anogenital region from the Screening visit until the end of the study.
33. Only for PART II: Planned use of any episodic antiviral medications during the swabbing periods (including the baseline period) (*only for the shedding sub-cohort*).

NOTE:

In case of genital herpes recurrence, up to 5 days of oral antiviral treatment are permitted (in accordance with a medical prescription), except during the swabbing periods *(only for the shedding sub-cohort)* (*see bullet just above*)**.**

5.2.3. Prior/Concurrent Clinical Study Experience

34. 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). Refer to the Glossary of Terms for the definition of invasive medical device.

5.2.4. Other Exclusions

35. Pregnant or lactating women.
36. Woman planning to become pregnant or planning to discontinue contraceptive precautions in the period starting from the Screening visit up to 3 months post-last dose of study intervention.

5.3. Lifestyle Considerations

Refer to Section 8.2.1.1 for details on demographic data to be recorded in the eCRF.

5.4. Screening Failures

A screening failure is an individual who consents to participate in this study but is not randomised to a study intervention. Limited data for screening failures (at least informed consent date, demographic data, eligibility criteria check, reason for screening failure, and any serious adverse events [SAEs] that occurred at the visit) will be collected and reported in the eCRF.

Only for PART II *(shedding sub-cohort)*: During the baseline period, in case a participant does not collect the sufficient number of anogenital swabs (i.e., 45 out of 56) or meets one or more exclusion criteria, he/she will be considered as a screening failure. Such participant will be asked to come back to the site at the end of this baseline swabbing period to return all collected swabs and unused materials (as well as the eDiary device, if provided) and have a conclusion visit with the study staff.

5.5. Criteria for Temporarily Delaying Enrolment/Study Intervention Administration

Enrolment/study intervention administration (at Visit 1 [Day 1] and Visit 3 [Day 29]) should be postponed within the permitted time interval (see Table 7 [PART I] and Table 8 [PART II]) until transient conditions cited below are resolved:

- Acute disease and/or fever* at the time of enrolment and/or study intervention administration.

  *The preferred location for measuring temperature will be the oral cavity. Fever is defined as temperature ≥ 38.0°C/100.4°F, regardless of the location of measurement.

- Participants with haematological/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, if impacted values are back within normal ranges following retesting (see Table 41 [PART I]/Table 42 [PART II] and Table 43).

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

If the study intervention cannot be administered within the permitted time interval because of special circumstance(s), the time interval between the Screening visit and Dose 1 can be extended for 90 additional days and the time interval between Dose 1 and Dose 2 can be extended to 90 days. Examples of special circumstances include:

- Pandemic.
- Temporary hold of the study intervention administration as described in Section 8.2.2.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1. Study Interventions Administered

Table 12 Study Interventions Administered During PART I (Healthy Adults, Aged 18 to 40 Years)

Study Intervention Name	40 µg Ag		80 µg Ag		160 µg Ag		40 µg Ag/AS01B		80 µg Ag/AS01B		160 µg Ag/AS01B	
Study intervention formulation	GSKVx0000 00030810 (40 µg); Excipients	Excipients; Water for injections *q.s.* 0.5 mL	GSKVx0000 00030810 (80 µg); Excipients	Excipients; Water for injections *q.s.* 0.5 mL	GSKVx0000 00030810 (160 µg); Excipients	Excipients; Water for injections *q.s.* 0.5 mL	GSKVx0000 00030810 (40 µg); Excipients	AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections *q.s.* 0.5 mL	GSKVx0000 00030810 (80 µg); Excipients	AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections *q.s.* 0.5 mL	GSKVx0000 00030810 (160 µg); Excipients	AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections *q.s.* 0.5 mL
Dose form (Presentation)	Powder for suspension for injection (vial)	Solution for suspension for injection (vial)	Powder for suspension for injection (vial)	Solution for suspension for injection (vial)	Powder for suspension for injection (vial)	Solution for suspension for injection (vial)	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)
Type	Study		Study		Study		Study		Study		Study	
Product category	Biologic product		Biologic product		Biologic product		Biologic product		Biologic product		Biologic product	
Route of administration	Intramuscular		Intramuscular		Intramuscular		Intramuscular		Intramuscular		Intramuscular	
Administration site:												
• Location	Deltoid		Deltoid		Deltoid		Deltoid		Deltoid		Deltoid	
• Directionality	Not applicable		Not applicable		Not applicable		Not applicable		Not applicable		Not applicable	
• Laterality*	Non-dominant arm		Non-dominant arm		Non-dominant arm		Non-dominant arm		Non-dominant arm		Non-dominant arm	

Study Intervention Name	40 µg Ag	80 µg Ag	160 µg Ag	40 µg Ag/AS01$_B$	80 µg Ag/AS01$_B$	160 µg Ag/AS01$_B$
Number of doses to be administered	2	2	2	2	2	2
Vol. to be administered#	0.5 mL	Whole content	Whole content	0.5 mL	Whole content	Whole content
Packaging, labelling and trademark:	Refer to the SPM for further details					
Manufacturer:	GSK	GSK	GSK	GSK	GSK	GSK

Table continues below.

Study Intervention Name	40 µg Ag/AS01$_E$		80 µg Ag/AS01$_E$		160 µg Ag/AS01$_E$		Placebo (Saline)
Study intervention formulation	GSKVx000000030810 (40 µg); Excipients	AS01$_E$: QS-21 (25 µg), MPL (25 µg), liposomes; Water for injections *q.s.* 0.5 mL	GSKVx000000030810 (80 µg); Excipients	AS01$_E$: QS-21 (25 µg), MPL (25 µg), liposomes; Water for injections *q.s.* 0.5 mL	GSKVx000000030810 (160 µg); Excipients	AS01$_E$: QS-21 (25 µg), MPL (25 µg), liposomes; Water for injections *q.s.* 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections *q.s.* 0.5 mL
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)	Powder for suspension for injection (vial)	Suspension for suspension for injection (vial)	Solution for injection (vial)
Type	Study		Study		Study		Control
Product category	Biologic product		Biologic product		Biologic product		Not applicable
Route of administration	Intramuscular		Intramuscular		Intramuscular		Intramuscular
Administration site:							
• Location	Deltoid		Deltoid		Deltoid		Deltoid
• Directionality	Not applicable		Not applicable		Not applicable		Not applicable
• Laterality*	Non-dominant arm		Non-dominant arm		Non-dominant arm		Non-dominant arm
Number of doses to be administered	2		2		2		2
Vol. to be administered#	0.5 mL		Whole content		Whole content		0.5 mL
Packaging, labelling and trademark	Refer to the SPM for further details						

Study Intervention Name	40 µg Ag/AS01$_E$	80 µg Ag/AS01$_E$	160 µg Ag/AS01$_E$	Placebo (Saline)
Manufacturer	GSK	GSK	GSK	GSK

Ag = antigen; **AS01$_B$** = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); **AS01$_E$** = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); **QS-21** = *Quillaja saponaria* Molina, fraction 21 (licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation); **MPL** = 3-O-desacyl-4'-monphosphoryl lipid A; ***q.s.*** = *quantum sufficit* ('as much as is sufficient'); **Vol**. = volume; **SPM** = Study Procedures Manual

*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 SPM for the volume after dilution.

Table 13 Study Interventions Administered During PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Study Intervention Name	80 µg Ag/AS01$_B$		80 µg Ag/AS01$_E$		Placebo (Saline)
Study intervention formulation	GSKVx000000030810 (80 µg); Excipients	AS01$_B$: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections q.s. 0.5 mL	GSKVx000000030810 (80 µg); Excipients	AS01$_E$: QS-21 (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	Sodium chloride (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	Study		Study		Control
Product category	Biologic product		Biologic product		Combination product
Route of administration	Intramuscular		Intramuscular		Intramuscular
Administration site:					
• **Location**	Deltoid		Deltoid		Deltoid
• **Directionality**	Not applicable		Not applicable		Not applicable
• **Laterality***	Non-dominant arm		Non-dominant arm		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, labelling and trademark	Refer to the SPM for further details				
Manufacturer	GSK		GSK		GSK

Ag = antigen; **AS01$_B$** = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); **AS01$_E$** = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); **QS-21** = Quillaja saponaria Molina, fraction 21 (licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation); **MPL** = 3-O-desacyl-4'-monphosphoryl lipid A; ***q.s.*** = *quantum sufficit* ('as much as is sufficient'); **SPM** = Study Procedures Manual

*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.

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

#Refer to the SPM for the volume after dilution, as applicable.

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.

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 authorised 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 Study Procedures Manual (SPM) for more details on storage and handling of the study interventions.

6.3. Measures to Minimise Bias: Randomisation 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. Each study site will be allocated a range of participant identification numbers.

6.3.2. Randomisation to Study Intervention

The randomisation of supplies within blocks will be performed at GSK, using MATerial Excellence (MATEX), a programme developed for use in Statistical Analysis System (*SAS*) (Cary, North Carolina, US) by GSK. Entire blocks will be shipped to the study sites/warehouse(s).

6.3.3. Intervention Allocation to the Participant

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

6.3.3.1. Study Group and Treatment Number Allocation

For PART I: The target will be to enrol ~245 eligible participants aged 18 to 40 years:

- In **Step 1**, ~45 healthy participants will receive either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI (40 µg or 80 µg or 160 µg) HSVTI, i.e., 9 groups in total (1:1:1 ratio for the 40 µg formulation, 1:1:1 ratio for the 80 µg formulation and 1:1:1 ratio for the 160 µg formulation).
- In **Step 2**, ~200 healthy participants will receive either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI (40 µg, 80 µg or 160 µg) HSVTI or placebo, i.e., 10 groups in total (1:1:1:1:1:1:1:1:1:1 ratio).

For PART II: The target will be to enrol ~270 eligible participants (patients with HSV genital herpes aged 18 to 60 years): ~90 in the HSVTI_F1 group, ~90 in the HSVTI_F2 group, and ~90 in the Placebo group (1:1:1 ratio). The enrolment will be monitored so that at least 30% of men and at least 30% of women will take part in PART II of this study.

Randomisation of PART I will be independent of PART II. Both randomisations will use a minimisation algorithm [Pocock, 1983]. For PART I, the randomisation algorithm will use a minimisation procedure accounting for study site and HSV-1 status (positive vs. negative). For PART II, the randomisation algorithm will use a minimisation procedure accounting for study site, inclusion in the shedding sub-cohort (yes vs. no), sex (females vs. males), and historical genital herpes frequency (< 6 episodes vs. ≥ 6 episodes) in the relevant 12-month time period defined at screening (see Section 5.1, inclusion criteria #9 for more details). All minimisation factors will have equal weighting.

Allocation of the participant to a study group at the investigator site will be performed using a randomisation system on Internet, i.e., source database for Internet randomisation (SBIR). Refer to the SPM for additional information about the study intervention number allocation.

After obtaining the signed and dated Informed Consent Form (ICF) from the participant and having checked and confirmed their eligibility, the study staff in charge of the study intervention administration will access SBIR which will determine the study group and will provide the study intervention number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

6.3.3.2. Treatment Number Allocation for Subsequent Dose(s)

The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (i.e., SBIR). For the second dose, the study staff in charge of the study intervention administration will access SBIR, provide the participant identification number, and the system will provide a treatment number consistent with the allocated study group. The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

6.3.4. Allocation of Participants to Sub-cohort

In PART I, the cell-mediated immunity (CMI) will be assessed on all participants (i.e., ~245). These participants will have a peripheral blood mononuclear cell (PBMC) sample collected at different timepoints (see Table 1) for CMI, CCI [redacted] analyses.

In PART II:

- Approximately 180 participants (i.e., ~60 from each group) will be allocated to a shedding sub-cohort. These participants will:
  - Be asked to collect anogenital swabs as described in Section 8.1.1.2.
  - Have a PBMC sample collected at different timepoints (see Table 2 and Table 3) for CMI and CCI [redacted] analyses (refer to Section 8.5).

Refer to the SPM for details regarding the allocation of participants to the shedding sub-cohort.

6.3.5. Blinding and Unblinding

Data will be collected in an observer-blind manner (refer to the Glossary of Terms). 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., reactogenicity, safety, efficacy). Refer to the SPM for more details.

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.

6.3.5.1. 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 an automated Internet-based system (i.e., SBIR). The investigator may contact a GSK Helpdesk (refer to Table 14) if he/she needs help 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/participant's care giver or family member may also request emergency access to the participant's study intervention information either via the investigator or investigator's back-up (preferred option) or via the GSK Helpdesk (back-up option). The 'Participant card' provides contact information for the investigator, his/her back-up and GSK Helpdesk.

Table 14 Contact Information for Emergency Unblinding

GSK Helpdesk (Available 24/24 hours and 7/7 days)
The Helpdesk is available by phone, fax and email
Australia: 0011 800 4344 1111
Belgium, Estonia, Germany, Spain: 00 800 4344 1111
Canada: 1 833 541 0263
United Kingdom: 0800 056 7221
United States (toll-free number): 1 844 446 3133
Back-up: +32 2 656 68 04 (all countries except US)
Fax: +32 2 401 25 75
Email: GSKClinicalSupportHD@gsk.com

6.3.5.2. Unblinding Prior to Regulatory Reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to one 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.

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 and time of administration of each study intervention dose in the study site will be recorded in the source documents.

6.5. Dose Modification

This section is not applicable.

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

During the study conclusion visit, the investigator will ask each participant if they are interested in participating in a booster study and/or long-term evaluation study. If a participant is not interested in joining the booster study and/or long-term evaluation study, the reason for refusal will be documented, when available, in the participant's eCRF.

6.7. Treatment of Overdose

This section is not applicable.

6.8. Concomitant Therapy

At each study visit/contact, the investigator or his/her delegate 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 (refer to Table 15):

- All concomitant medications, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1) until Day 64.

  Note that any vaccine administered between the Screening visit and Visit 1 has to be recorded (refer to Section 8.2.1.3).

- All concomitant medications *associated with medically attended events (MAEs)*, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1) until Day 394.

- All concomitant medications leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines, administered after the first dose of study intervention (Day 1) until Day 394 (refer to Sections 5.2.2 and 9.2.1 for further details).

- All concomitant medications which may explain/cause/be used to treat an SAE/potential immune-mediated disease (pIMD), including vaccines/products, administered after the first dose of study intervention (Day 1) until Day 394 (refer to Sections 8.3.1 and 10.3.8).

- Any antipyretic administered in the period starting 6 hours before study intervention administration and ending 12 hours after study intervention administration.

- Only for PART II: All anti-herpetic antivirals (including the treatment for oral herpes, genital herpes, etc.) and concomitant medications other than anti-herpetic antivirals managing the recurrent genital herpes, administered during the baseline period (only for the shedding sub-cohort) and from Visit 1 (Day 1) until the end of RGH event reporting period.

NOTES:

- **Suppressive antiviral medications and tenofovir (e.g., in case of pre-exposure prophylaxis to prevent HIV infection) are permitted at the discretion of the investigator after acknowledgment of the unsuccessful primary analysis outcomes.**
- **In case of genital herpes recurrences, the participant is allowed to take up to 5 days of oral antiviral treatment (in accordance with a medical prescription), except during the swabbing periods *(only for the shedding sub-cohort)*.**
- **Topical therapy of GH with antiviral drugs is not permitted. However, topical supportive treatment is allowed, which can be applied only after the lesional swab is taken.**
- Topical treatment of herpes labialis infection is allowed throughout the study.

Table 15 Timeframes for Collecting and Reporting of Concomitant Medication(s)/Product(s)/Vaccine(s)

Event	Baseline	Day 1	Day 29	Day 64	Day 394
	Day -28 to Day -1	Dose 1	Dose 2		Study conclusion
All concomitant medications/ vaccines*/products					
All concomitant medications/vaccines/products associated with MAEs					
All concomitant medications / vaccines / products leading to discontinuation of the study intervention or elimination from the analysis					
All concomitant medications / vaccines / products which may explain/cause/be used to treat an SAE/pIMD (any)					
Any antipyretic		**	**		
Only for PART II: All anti-herpetic antivirals and other medications managing the recurrent genital herpes					***

MAE = medically attended event; **pIMD** = potential immune-mediated disease; **SAE** = serious adverse event
*Note that any vaccine administered between the Screening visit and Visit 1 has to be recorded (refer to Section 8.2.1.3).
**Any antipyretic administered in the period starting 6 hours before study intervention administration and ending 12 hours after study intervention administration.
***Until end of RGH reporting period.

The Clinical Sciences Lead (CSL) 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 study intervention. A participant who discontinued study intervention may continue other study procedures (e.g., safety or immunogenicity), planned in the 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 be dosed,
- Other (specify).

7.1.1. Contraindications to Subsequent Study Intervention Administration

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

All exclusion criteria (see Section 5.2) must be re-checked at Visit 3 (Day 29) to ensure that the participant is still eligible. In addition, 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 (see Section 10.3.8.2). 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, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to receive the second dose of study intervention.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the participant to unacceptable risk in case of subsequent study intervention administration. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of study intervention. Refer to Section 10.3.5.1 for the definition of pIMDs.
- Abnormal haematological and biochemical parameters, unless the laboratory abnormalities are considered 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 judgement.
- Anaphylaxis following the administration of study intervention.
- Any condition that in the judgement of the investigator would make intramuscular injection unsafe.

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 from him/her since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who did not return for the concluding visit 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 10.3.10.1 for details),
- Unsolicited non-serious AEs/MAEs,
- Solicited AE,
- Withdrawal by participant, not due to an AE*,

  *If a participant is withdrawn from the study because he/she has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.
- Migrated/moved from the study area,
- Lost to follow-up,
- Sponsor study termination,
- Acknowledgement of failure in primary efficacy analysis,
- Other (specify).

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 10.3.8.2).

7.3. Lost to Follow-up

A participant will be considered 'lost to follow-up' if he/she fails 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 site staff 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 summarised in the SoA (Table 1 [PART I] and Table 2 to Table 4 [PART II]).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria, including, for PART II only *(shedding sub-cohort)*, having collected the minimum required number of anogenital swabs (at least 45 out of 56).

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.

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

Only for PART II: Participants can be offered virtual contacts for Visit 6 [Day 71], Visit 7 [Day 181], Visit 8 [Day 209], Visit 9 [Day 299], and Visit 10 [Day 394], when applicable, provided that the participant has reconsented on the ICF addendum during a previous on-site visit (see Section 10.1.3) (refer to Table 2 to Table 4 for the procedures to be performed at each visit). These virtual contacts must be performed by qualified study staff/healthcare professionals (HCPs). Contacts may be via telephone, video conference, telemedicine, or other means, depending on local best practice. If the study site is the participant's primary healthcare facility, contact with study staff may also be made in the context of a visit for routine or event-driven care.

In exceptional situations (e.g., pandemic), the following procedures can be performed remotely/virtually, provided approved tools and infrastructures are used, as per local requirements (refer to the Glossary of Terms for the definitions of telemedicine, remote and virtual contacts):

- Safety follow-up may be performed by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff/HCPs may also identify AEs and report them to the investigator for evaluation.
- Blood samples may be collected remotely* by qualified study staff/HCPs. Blood samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.

  **It is the investigator's responsibility to ensure that this alternate location meets the International Council for Harmonisation (ICH) GCP requirements, such as adequate facilities to perform study procedures/data collection, appropriate training of the staff and documented delegation of responsibilities in this location. This location should be covered by proper insurance for the conduct of study by investigator/study staff at a site other than the designated study site.*
- Only for PART II: Anogenital and/or lesion swabs samples could be picked up by a courier or other appropriate means, as needed.

8.1. Efficacy and/or 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 Independent Ethics Committee (IEC)/Institutional Review Board (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 participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological Samples

8.1.1.1. Blood Samples

Blood samples will be collected as described in Table 16 (PART I) and Table 17 (PART II).

Table 16 Biological Samples for PART I (Healthy Adults, Aged 18 to 40 Years)

Sample Type	Quantity	Unit	Timepoint	Sub-cohort Name
Blood sample HSV testing	Approximately 3.5	mL	Screening*	All screened participants
Blood sample for HIV testing	Approximately 8.5	mL	Screening*	All screened participants
Blood sample for haematology analysis	Approximately 2.0	mL	Screening*	All screened participants
			Days 1, 8, 29, 36 and 64	All participants
Blood sample for biochemical analysis	Approximately 3.5	mL	Screening*	All screened participants
			Days 1, 8, 29, 36 and 64	All participants
Blood sample for antibody determination (humoral immunogenicity) analysis	Approximately 8.5	mL	Days 1, 29, 64, 209 and 394	All participants
Blood sample (PBMCs) for CMI response analysis	Approximately 30.0	mL	Days 1, 29, 64, 209 and 394	All participants
Blood sample (PBMCs) for CCI [redacted] analysis	Approximately 20.0	mL	Days 1 and 64	All participants
Blood sample for CCI [redacted]	Approximately 17.0	mL	Days 1, 29, 64, 209 and 394	All participants

HSV = herpes simplex virus; **HIV** = human immunodeficiency virus; **PBMC** = peripheral blood mononuclear cell; **CMI** = cell-mediated immunity; CCI [redacted]

*If deemed necessary by the investigator, re-sampling can be performed within the allowed interval.

An overall blood volume of ~362.5 mL will be collected during the entire study period from all participants in PART I.

Table 17 Biological Samples for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Sample Type	Quantity	Unit	Timepoint	Sub-cohort Name
Blood sample HSV testing	Approximately 3.5	mL	Screening*	All screened participants without documentation of laboratory-confirmed HSV-2 genital herpes
Blood sample HSV testing by Western Blot	Approximately 3.5	mL	Visit 1	All participants with no UWWB performed at screening
Blood sample for HIV testing	Approximately 8.5	mL	Screening*	All screened participants
Blood sample for haematology 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, 57, 209#	All participants
Blood sample (PBMCs) for CMI response analysis	Approximately 30.0	mL	Days 1, 29, 57, 209#	Shedding sub-cohort**
Blood sample (PBMCs) for CCI [redacted] analysis***	Approximately 45.0	mL	Days 1, 29, 57,	Shedding sub-cohort**
Blood sample for exploratory humoral response analysis	Approximately 34.0	mL	Days 1, 29, 57, 209#	All participants

HSV = herpes simplex virus; **UWWB** = Western Blot from the University of Washington; **HIV** = human immunodeficiency virus; **PBMC** = peripheral blood mononuclear cell; **CMI** = cell-mediated immunity
*If deemed necessary by the investigator, re-sampling can be performed within the allowed interval.
**Refer to Section 6.3.4 for shedding sub-cohort description.
***Optional blood sampling. A separate ICF will be signed by participants who agree to give their blood sample for this optional blood sampling.
#On a voluntary basis as of Protocol Amendment 7 implementation.
Note that by Protocol Amendment 7 implementation, only a few participants might have already completed Visit 10 (Day 394). Those blood samples may not be tested.

An overall blood volume of up to 218.5* mL (or up to 473.5* mL if part of the shedding sub-cohort and agreed to the optional blood sampling) will be collected during the entire study period from all participants in PART II, including up to 158.5 mL (or ~383.5 mL if part of the shedding sub-cohort and agreed to the optional blood sampling) during any 8-week period.

**If a participant does not opt for the optional blood sampling at Day 209, these volumes will be decreased to 176 mL and 401 mL, respectively.*

8.1.1.2. Only for PART II: Anogenital Swabs (Shedding Sub-cohort)

Refer to Section 8.1.5 for details about the procedures to be performed when a RGH episode is suspected (for all participants).

Participants in the shedding sub-cohort will be instructed to self-collect anogenital swabs twice a day (i.e., one in the morning and one in the evening) for **28 consecutive days** (in order to have 56 swabs), during 3 time periods:

- Period 1 (baseline): Day -28 to Day -1;

  Note that at Baseline Day -28 Visit, the first anogenital swab will be collected by the study staff during the visit (demo swab). Participants will also be asked to collect an anogenital swab on site afterwards, to make sure they correctly understood the procedure and are able to perform the swabbing themselves. Only the anogenital swab collected by the participants will be kept for the analysis (refer to the SPM for additional information).

- Period 2: Day 43 to Day 70;

  This swabbing period will start remotely as it does not coincide with a study visit. The first anogenital swab of this period will be taken by the participant on Day 43. If the investigator thinks the participant needs to be retrained on the swabbing process, the retraining (with demo swab) can be performed at Visit 4 (Day 36).

- Period 3: Day 181 to Day 208 (on a voluntary basis);

  For swabbing period 3, if the investigator thinks the participant needs to be retrained on the swabbing process, a demo swab can be collected by the study staff. The first swab of the period will be collected by the participant either on site during the study visit (if not virtually conducted), or at home. Only the anogenital swabs collected by the participants will be used for the analysis (refer to the SPM for additional information).

- By Protocol Amendment 7 implementation, only a few participants might have already completed Period 4 (Days 366 to 393). Those samples may not be tested.

Before each swabbing period, participants in the shedding sub-cohort will receive material (e.g., swabs) for 28 days. For the second swabbing period, material will be distributed to participants during the previous visit (Visit 4 [Day 36]). If not done, or in case this visit is replaced by a virtual contact, materials can be shipped by the site staff to the participant's house, if permitted by local regulations. Additional material will also be provided to avoid any supply shortage or should there be any issues. The site staff should ensure at each study visit that the participant has enough materials (for anogenital and/or lesion swabbing) for the remaining of the study.

Participants will be instructed to keep their collected anogenital swabs at home, preferably in their fridge (note that room temperature up to 37°C/98.6°F is also acceptable), until the next appointment and to bring their swabs to the study site as follows:

- For period 1 (baseline): At Day -14 Visit and at Visit 1 (Day 1);

- For period 2: At Visit 5 (Day 57) and Visit 6 (Day 71)*;
- For period 3: At Visit 8 (Day 209).

*If Visit 6 is conducted virtually (see Section 8), collected swabs will be picked up by a courier, if allowed by local regulations.

8.1.2. Laboratory Assays

All laboratory testings will be performed at GSK's laboratory or in a laboratory designated by GSK as detailed in Table 18 (PART I) and Table 19 (PART II).

Table 18 Laboratory Assays for PART I (Healthy Adults, Aged 18 to 40 Years)

Assay Type	System	Component	Method	Laboratory*
Screening	Serum	Anti-HIV antibodies	CMIA	Q^2 Solutions Quest Diagnostics
		HSV antibodies	Western Blot	University of Washington Molecular Virology laboratory
Humoral immunity (antibody determination)	Serum	Anti-gE-gI	ELISA	GSK** or in a laboratory designated by GSK
Cell-mediated immunity	PBMCs	gE-gI-specific (CD4+/CD8+) T-cells	CFC	

HIV = human immunodeficiency virus; **CMIA** = chemiluminescent microparticle immunoassay; **HSV** = herpes simplex virus; **gE-gI** = glycoprotein E-glycoprotein I; **ELISA** = enzyme-linked immunosorbent assay; **PBMC** = peripheral blood mononuclear cell; **CD4+/CD8+** = cluster of differentiation 4/8; **CFC** = cell flow cytometry
*Refer to the list of clinical laboratories for details.
**GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.

Table 19 Laboratory Assays for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Assay Type	System	Component	Method	Laboratory*
Screening	Serum	Anti-HIV antibodies	CMIA	Q^2 Solutions Quest Diagnostics
		HSV antibodies	Western Blot or other serological assay	University of Washington Molecular Virology laboratory or in a laboratory designated by GSK
Serology	Serum	HSV antibodies	Western Blot	University of Washington Molecular Virology laboratory
Humoral immunity (antibody determination)	Serum	Anti-gE-gI	ELISA	GSK** or in a laboratory designated by GSK
Cell-mediated immunity	PBMCs	gE-gI-specific (CD4+/CD8+) T-cells	CFC	
Molecular biology	Anogenital swabbing	HSV DNA	qPCR	University of Washington Molecular Virology laboratory
	Lesion and anogenital swabs taken during a suspected RGH episode	HSV DNA		
		β-globin gene		

HIV = human immunodeficiency virus; **CMIA** = chemiluminescent microparticle immunoassay; **HSV** = herpes simplex virus; **gE-gI** = glycoprotein E-glycoprotein I; **ELISA** = enzyme-linked immunosorbent assay; **PBMC** = peripheral blood mononuclear cell; **CD4+/CD8+** = cluster of differentiation 4/8; **CFC** = cell flow cytometry; **DNA** = deoxyribonucleic acid; **qPCR** = quantitative polymerase chain reaction
*Refer to the list of clinical laboratories for details.
**GSK laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.

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 Protocol.

Further exploratory/tertiary research to characterise biomarkers of safety and immunogenicity testing will include:

CCI

[redacted]

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

Other assays may be developed and/or conducted on samples obtained in this study, with the aim to explore biomarkers of safety and immunogenicity. The research may include, but is not limited to:

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. Laboratory Read-outs

8.1.3.1. For PART I (Healthy Adults, Aged 18 to 40 Years)

Table 20 Read-outs for Screening Tests for PART I

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	> 245	Anti-HIV antibodies Anti-HSV antibodies

HIV = human immunodeficiency virus; **HSV** = herpes simplex virus

Table 21 Immunological Read-outs for PART I

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Humoral Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 209) Visit 7 (Day 394)	All participants	~245	Anti-gE-gI
Cell-mediated Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 209) Visit 7 (Day 394)	All participants	~245	gE-gI-specific (CD4+/CD8+) T-cells

gE-gI = glycoprotein E-glycoprotein I; **CMI** = cell-mediated immunity; **CD4+/CD8+** = cluster of differentiation 4/8

8.1.3.2. For PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Table 22 Read-outs for Screening Tests for PART II

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	> 270	Anti-HIV antibodies Anti-HSV antibodies

HIV = human immunodeficiency virus

Table 23 Immunological Read-outs for PART II

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Humoral Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 57) Visit 8 (Day 209)**	All participants	~270	Anti-gE-gI
Cell-mediated Immunity			
Visit 1 (Day 1) Visit 3 (Day 29) Visit 5 (Day 57) Visit 8 (Day 209)**	Shedding sub-cohort*	~180	gE-gI-specific (CD4+/CD8+) T-cells

gE-gI = glycoprotein E-glycoprotein I; **CMI** = cell-mediated immunity; **CD4+/CD8+** = cluster of differentiation 4/8
*Refer to Section 6.3.4 for sub-cohort description
**On a voluntary basis and might be tested for the tertiary objectives

Table 24 Read-outs for Molecular Biology Tests for PART II

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Baseline Day -28 to Baseline Day -1* Day 43 to Day 70* Day 181 to Day 208*,#	Shedding sub-cohort	~180	HSV DNA
In case of genital herpes recurrence is suspected anytime as of Baseline Day -28 (shedding participants)/Day 1 (non-shedding participants) until the end of RGH event reporting period**	All participants with suspected genital herpes recurrences	-	HSV DNA
			β-globin gene

HSV = herpes simplex virus; **DNA** = deoxyribonucleic acid
*Twice daily (i.e., one in the morning and one in the evening) anogenital swabbing
**Refer to Section 8.1.5.
#On a voluntary basis and might be tested for the tertiary objectives.

All collected swab (anogenital and lesion) samples from all enrolled participants will be tested by quantitative PCR (qPCR) to detect and measure HSV-2 and HSV-1 DNA.

Table 25 Read-outs for Serology Tests for PART II

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Visit 1 (Day 1)	All participants with no UWWB performed at screening	-	HSV antibodies

UWWB = Western Blot from the University of Washington

8.1.4. Immunological Correlates of Protection

No generally accepted immunological correlate of protection has been demonstrated so far for the gE-gI antigens.

8.1.5. For PART II Only: Procedures When a Genital Herpes Recurrence is Suspected

RGH event reporting period: As of baseline (from Baseline Day -28) (for the shedding sub-cohort)/as of Day 1 (for non-shedding sub-cohort) and until end of RGH event reporting period.

The end of RGH event reporting period is defined as:

- Day 209 (for participants who have not yet completed Visit 8 [Day 209] at the time the ICF addendum (associated with Protocol Amendment 7) is signed and consented voluntary to RGH event reporting till Day 209); or
- The date on which the participants decided to stop RGH reporting following the acknowledgement of the unsuccessful primary analysis outcomes before ICF addendum consent (associated with Protocol Amendment 7); or
- The day the investigator deactivates the eDiary for participants who have continued RGH event reporting beyond Day 209 at the time the ICF addendum (associated with Protocol Amendment 7) is signed.

Participants will be asked to report the presence of genital herpes symptoms and genital herpes lesions, using the eDiary (refer to the Glossary of Terms):

a. In case signs or symptoms potentially related to genital herpes are reported, the participant will be asked to complete daily the Herpes Symptoms Checklist (HSC) (see Section 8.1.5.2) and the use of antivirals.

b. On the onset day of genital herpes lesions (e.g., swelling, blisters, sores, crusts): participants will also be asked to collect a lesion swab and an anogenital swab (from the anogenital area) as soon as possible after the onset of the lesions (ideally the same day) before coming to the study site. For participants in the shedding sub-cohort, if the lesions appear during a swabbing period, they will collect only 1 lesion swab in addition to the planned morning and evening anogenital swabs (see Section 8.1.1.2). Once a participant reports the presence of genital herpes lesions in the eDiary, an 'Unscheduled visit' will be arranged by the site staff.

c. Within 72 hours of lesions onset: The participant will attend an 'Unscheduled visit' as soon as possible (preferably within 48 hours of lesions onset, but no later than 72 hours):

   – Participants will bring to the site the collected lesion and anogenital swabs taken on the lesions onset day at that 'Unscheduled visit'.

   – The investigator or designee will perform a clinical examination and record the assessment in the eCRF. If the lesions are assessed as "unlikely to be genital herpes", an alternative diagnosis (if any) can be recorded in the eCRF.

   – In addition, the investigator or designee will take a lesion swab.

- In addition, other procedures will be performed such as:
  - Recording of the management of the suspected RGH episode and any concomitant medications/vaccinations as per the predefined reporting period (see Section 6.8).
  - Recording of complications and intercurrent medical conditions specified in Section 9.2.1,

  Refer to Table 4 for all procedures to be performed during the Unscheduled visit.

d. When the participant encodes in their eDiary that there are no more lesions, the study staff will contact them to make sure all data related to the suspected RGH episode are reported in the eCRF: start and end dates of the lesions, management of the suspected RGH episode (including, but not limited to: the antiviral medication(s) and complication(s), if any).

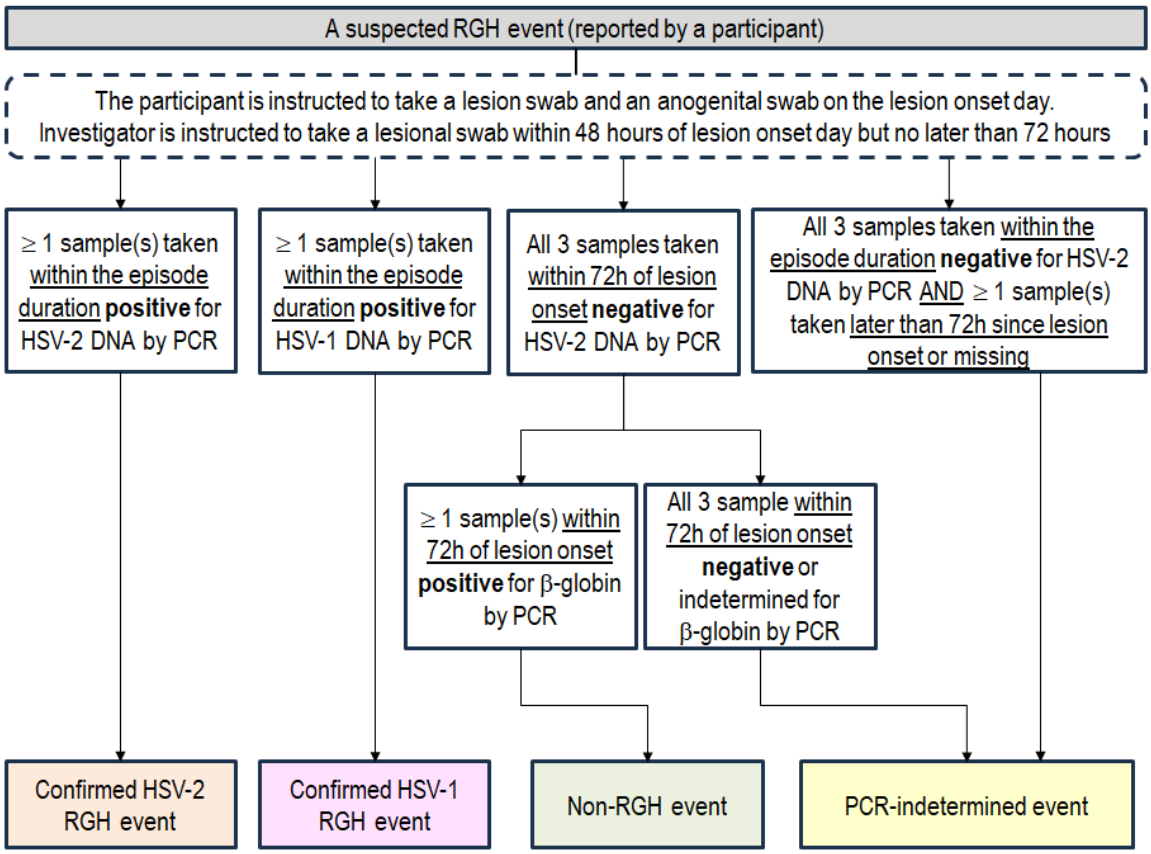
   During the entire duration of the suspected RGH episode, the investigator or designee should closely monitor the data in the eDiary. If the participant misses the data entry into the eDiary, the site staff should call the participant to collect those missing data and encode them into the eCRF as soon as possible.

Note: If the timing to plan for an 'Unscheduled visit' falls within the time window of a planned study visit (see Table 8), evaluations and assessments must not be duplicated. All evaluations foreseen for the study visit will be performed and in addition, the lesion and anogenital swabbing and documentation will be performed as described above.

8.1.5.1. Algorithm for Recurrent Genital Herpes Episode Determination

All lesion and anogenital swabs collected during a suspected RGH episode will be tested by qPCR to detect HSV-2 and β-globin DNA. Classification of RGH episodes will follow the algorithm presented in Figure 4.

Figure 4 Recurrent Genital Herpes Episode Determination Algorithm



RGH = recurrent genital herpes; **qPCR** = quantitative polymerase chain reaction

8.1.5.2. Herpes Symptoms Checklist

During genital herpes recurrences, participants will be asked to complete the HSC, a 13-item checklist of herpes symptoms, where respondents record the severity of symptoms on a 4-point scale. Total scores range from 0 to 39, in increasing severity [Doward, 2009; Meads, 2009]. At the onset of the genital herpes recurrence, this questionnaire is to be completed once daily, until no lesions or symptoms are present.

8.2. Safety Assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE (see Sections 10.3.1 and 10.3.2, respectively). 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-Study Intervention Administration Procedures

8.2.1.1. Collection of Demographic Data

Record demographic data such as year of birth, sex, 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 study participants, and to determine if the study 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 BMI (as part of the eligibility criteria). Data will be recorded in the eCRF.

8.2.1.3. Record 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. For PART II Only: Record History of Genital Herpes

The following information related to genital herpes (based on the participant's interview/medical records) is to be collected in the eCRF: (i) most accurate possible date of diagnosis, (iia) number of lesional genital herpes recurrences in the 12 months preceding the Screening visit or (iib) if still on suppressive antiviral therapy within 3 months preceding the Screening visit, the number of lesional genital herpes recurrences occurring during the 12 months preceding the start of suppressive therapy.

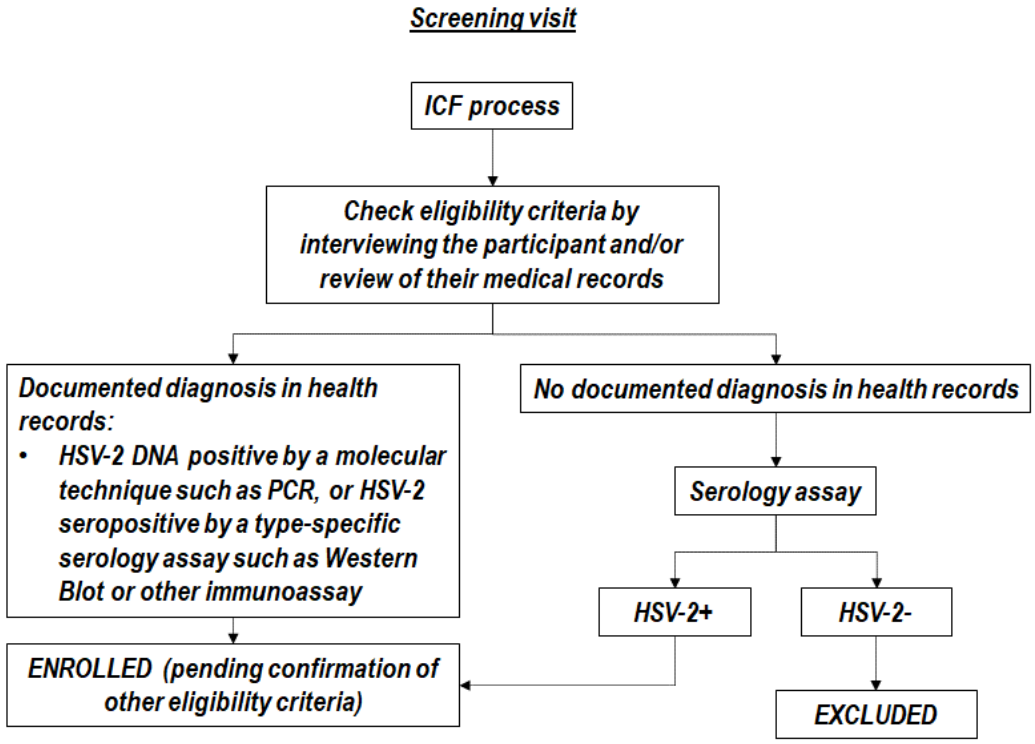
8.2.1.5. For PART II Only: HSV historical diagnostic test

For participants with documented laboratory-confirmed HSV-2 genital herpes at screening, the assay used to diagnose HSV-2 genital herpes should be collected in the eCRF.

8.2.1.6. For PART II Only: HSV screening test

For participants without documented laboratory-confirmed HSV-2 genital herpes, a blood sample will be taken at the Screening visit for HSV serology test.

Figure 5 HSV Testing Screening Process



ICF = informed consent form; **PCR** = polymerase chain reaction

8.2.1.7. For PART II Only: Participant Education

During Day -28 (shedding sub-cohort)/Day 1 (non-shedding sub-cohort), the investigator or delegate will educate the participant on genital herpes lesion recognition, lesion and anogenital swabbing procedures, and will show them how to take an anogenital swab, after which the participant will take a sample (practice self-swab). The investigator or delegate will also advise on the management of the suspected RGH episode.

Participants will also receive a handout ('Participant leaflet') detailing the anogenital and lesion swabbing procedures, labelling, storage and delivery to the site. Videos explaining both swabbing procedures will also be presented and made available to the participants, as applicable (refer to the SPM for details). If deemed necessary, a refresher training (with optional demo swab collection) on the anogenital swabbing process will be provided to participants in the shedding sub-cohort at the beginning of each subsequent swabbing period (or for the second swabbing period, during the previous visit [Visit 4; Day 36]). A refresher training on both processes can be provided at any timepoint to all participants, if deemed necessary.

8.2.1.8. 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).

  Note that in case a study visit is replaced by a virtual contact (see Section 8), the physical examination will not be performed.
- 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 7 [PART I] and Table 8 [PART II]). 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 (including during an 'Unscheduled visit' [only for PART II]) must be performed according to local medical practice outside this study or by referral to an appropriate healthcare provider.

8.2.1.9. Perform Pregnancy Test

Women of childbearing potential must perform a urine/blood (depending on local clinical requirement) pregnancy test at the Screening visit and 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. Collected information will be recorded in the eCRF.

- 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 needs to be documented in the participant's source document. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche and menopause.

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

8.2.1.10. Use of eDiary for Collecting Study Information

8.2.1.10.1. Check Participant's Device Compatibility with the App

At the Screening visit, the study staff will ask the participant if he/she agrees to use their personal mobile phone to record information related to their health and participation in the study and they will check the compatibility of the participant's device with respect to the eDiary application. Note that the compatibility is to be checked anytime during the study in case the participant acquires a new device or if there is an upgrade.

If the participant agrees, he/she will have the opportunity to download the app on their mobile phone during Visit 1 (Day 1)/Baseline Day -28 Visit (PART II; shedding sub-cohort). On the other hand, if the participant disagrees to use their mobile phone or if the device is not compatible with the app, he/she will receive an electronic device for the duration of the study (refer to Section 8.2.1.10.2).

8.2.1.10.2. Download the App or Distribution of Electronic Device and Train Participant on the Use of eDiary

At Visit 1 (Day 1)/Baseline Day -28 Visit (PART II; shedding sub-cohort), participants will download the app on their mobile phone or will receive an electronic device to record information related to their health and participation in the study. Note that the reporting tool, either the app or electronic device, is referred to as 'eDiary' throughout the document (refer to the Glossary of Terms). On that same day, participants will be trained on the use of the eDiary. The following data will be recorded:

- Occurrence of any solicited AEs during a 7-day post-study intervention administration period (see Section 10.3.8). In addition, participants will encode the occurrence (yes/no) of any unsolicited AEs (during the 28-day post-study intervention administration) and the use (yes/no) of concomitant therapy (as per the reporting timings defined in Section 6.8) in the eDiary. This will send an alert to the site staff who will collect the necessary information (e.g., which symptoms/medications, duration of the event/therapy) at the subsequent visit/contact and encode those in the eCRF.

Only for PART II:

- *For participants in the shedding sub-cohort*: Information on the anogenital swab collection performed during the 3 time periods defined in Section 8.1.1.2.
- *For all participants*: Information related to any genital herpes signs and symptoms occurring during the study (from baseline [Day -28] (shedding sub-cohort)/Visit 1 [Day 1] (other participants) until the end of RGH event reporting period), including the use of antivirals (see Section 8.1.5). In case of genital herpes symptoms, the participant will be asked to complete the HSC (see Section 8.1.5.2).

If the data related to study objectives/endpoints to be collected by the participants cannot be encoded in their eDiary (e.g., unresolved technical issues), they can be reported directly to the site staff and submitted via the eCRF.

8.2.1.11. Return of eDiary

Participants will be instructed to bring their device to the study site at each visit to have the opportunity to discuss questions or issues with the eDiary.

At Visit 5 (Day 64) (PART I) or at the end of RGH event reporting period (PART II), participants will deactivate the eDiary by either:

- Return the electronic device to the study site, if used, or,
- Shut down and uninstall the app on their mobile phone.

Refer to the SPM for more details regarding the use and collection of data via the eDiary.

8.2.2. Study Holding Rules and Safety Monitoring

In this study, safety oversight will be ensured by an iSRC (in an unblinded manner) and by a Safety Review Team (SRT) (in a blinded manner). The iSRC is a group of GSK experts (clinicians, safety representatives and statisticians), independent from the ongoing study, with a proper medical and scientific expertise to guarantee the safety of the participants. For more details, refer to the iSRC Charter and to Section 10.1.5.

8.2.2.1. Staggered Administration of Study Intervention

The study will be conducted in 2 parts:

In **PART I**, ~245 healthy participants aged 18 to 40 years will receive the study intervention in 2 steps:

- During **Step 1**, a first wave of ~45 participants (~5 per group) will be enrolled and dosed in a staggered manner.
  - An iSRC* (refer to Figure 1) will occur as soon as all 15 participants who received the 40 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will have been followed-up for 7 days post-Dose 1. If the outcome of the iSRC evaluation is favourable, those participants will receive their second dose and participants who will receive the 80 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be enrolled and dosed with the first dose.
  - An iSRC** (refer to Figure 1) will occur as soon as all 15 participants who received the 80 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will have been followed-up for 7 days post-Dose 1. In addition, all available safety data from participants who received the 40 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first study intervention dose will receive their second dose and participants who will receive the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be enrolled and dosed with the first study intervention dose.

  - An iSRC*** (refer to Figure 1) will occur as soon as all 15 participants who received the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will have been followed-up for 7 days post-Dose 1. In addition, all available safety data from participants who received the 40 µg and 80 µg formulations non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first study intervention dose will receive their second dose and participants of Step 2 will be enrolled and dosed with the first study intervention dose.
  - An iSRC**** (refer to Figure 1) will occur as soon as all 15 participants who received the 160 µg formulation non-adjuvanted or adjuvanted with either $AS01_B$ or $AS01_E$ will have been followed-up for 7 days post-Dose 2. In addition, all available safety data from participants enrolled and dosed in Step 1 and in Step 2 (with their first study intervention dose) will be reviewed. If the iSRC evaluation outcome is favourable, participants enrolled in Step 2 will receive their second study intervention dose.

- During **Step 2**, ~200 healthy participants (~20 per group) will be enrolled and will receive 2 doses of either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI (40 µg, 80 µg or 160 µg) or placebo in a parallel manner (10 groups). Administration of the second dose in Step 2 will depend on the favourable outcome of the iSRC evaluation (iSRC****). No Dose 2 will be administered in **Step 2** until all data from **Step 1** (including post-Dose 2) are reviewed. Ad hoc iSRC meetings can also be convened as needed.

At the time of the PART I Interim Analysis (see Section 9.4.1), to be performed when all participants from PART I will have attended their Visit 5 (Day 64), an iSRC evaluation (refer to Figure 1) on all available safety and reactogenicity data (including safety laboratory data) will be performed before moving to PART II.

The investigator is not permitted to start dosing the participants with the next dose/in the subsequent Step/PART until receipt of the favourable outcome of the safety evaluations by the SRT and iSRC. The SRT will review blinded safety data on a regular basis.

The iSRC will review unblinded safety data between the doses before proceeding to the next dose/Step/PART. Screening procedures may be performed to facilitate enrolment of the remaining participants.

In **PART II**, ~270 participants aged 18 to 60 years with HSV genital herpes will receive 2 doses of the HSVTI formulations selected during the PART I or placebo:

- The first planned iSRC meeting will take place after approximately (but no more than) 10 participants per group (i.e., ~ 30 in total) have completed their 7-day follow-up period after the first dose administration, in order to review solicited AEs data and all other available safety data. If the outcome is favourable, these participants will receive the second dose as scheduled per protocol and other participants will be administered with the first dose.

- The second planned iSRC meeting will take place after the above-mentioned ~30 participants have completed their 7-day follow-up period after the second dose administration to review solicited AEs data and all other available safety data. If the outcome is favourable, the remaining participants will receive the second dose.
- In addition, the iSRC will review all available safety data approximately every month during the study intervention administration period to identify potential safety concerns that will lead to safety hold of study intervention administration. Please note, in addition to periodic iSRC review, the study team led by the CSL will perform instream review of blinded safety data on a weekly basis. If the study team suspects a potential holding rule being met, an ad hoc iSRC review will be requested immediately to ensure the timely study intervention hold, should a safety concern be identified.
- During the follow-up phase, iSRC reviews will be planned every 6 months. Ad hoc iSRC meetings will be conducted should a safety risk/concern be raised.

All participants in both PARTs will be closely observed for a minimum of 60 minutes after each study intervention administration.

All participants in both PARTs will be instructed to contact the study staff immediately should they manifest any signs or symptoms they perceive as severe (Grade 3) or serious.

8.2.2.2. Limited Study Intervention Administration

During **Step 1 of <u>PART I</u>**, study intervention administration will be limited to no more than 2 participants per day during the first 3 days ('sentinel'). These sentinel participants must be dosed sequentially and at least 60 minutes apart. This procedure is applicable for each dose level (40 µg, 80 µg and 160 µg). If no safety concerns are identified for all the dosed sentinel participants within 24 hours after administration of Dose 1, administration of Dose 1 may proceed for the remaining participants*, without the 60-minute interval for study intervention administration between participants and the limitations regarding the number of participants per day. Administration of Dose 2 in this Step will follow the same approach as for Dose 1.

To ensure a close safety follow-up and that all safety data related to the sentinel participants are collected, the study staff will contact them (e.g., via individual phone contact) 24 hours after their study intervention administration to collect any safety concerns they might have*.

**No study intervention can be administered to any participant before the confirmation is received that there are no safety concerns from participants that were dosed in the previous day.*

During **Step 2 of <u>PART I</u>** and during **<u>PART II</u>**, the 60-minute interval for study intervention administration between participants and the limitations regarding the number of participants per day do not apply.

8.2.2.3. Outcome of Safety Evaluation

- If no safety concern is observed, the favourable outcome of safety evaluations will be documented and provided in a written way, authorising the investigator to start the administration of the subsequent dose of study intervention to participants/to start the next Step/PART, as applicable.
- If a safety concern is observed during the safety evaluations or if any of the holding rules 2a-c is met (Table 26), the iSRC Chair (or his/her delegate) is responsible for the urgent communication to GSK's Chief Medical Officer, Head of Global Safety, and Head of Biostatistics to discuss and to decide on the next steps.
  - The study CSL (or his/her delegate) will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.
  - During this review period, the study intervention administration will be temporarily put on hold, while the decision is being made. In case of a decision to stop the study, a letter indicating the reason will be sent to the IEC/IRB by the investigator and to the Regulatory Agency by the Sponsor. If the Sponsor decides that the study can be resumed, this decision will be communicated to the Regulatory Agency(ies) and IEC/IRB, as applicable by national regulations.

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

8.2.2.4. Study Holding Rules

Holding rules to be applied in PART I and in PART II are presented in Table 26:

- 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.

  Therefore, the investigator (or delegate) will be requested to record safety data meeting the criteria of holding rules in the eCRF within 24 hours after reception of the data to ensure that all necessary information is available for iSRC/SRT reviews.
- Holding rules 2a-2c 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.

In addition, the SRT will review blinded safety data on a regular basis.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, 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. 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 26 Study Holding Rules

Holding Rule	Event	Number of Participants per Group		
		PART I Step 1	PART I Step 2	PART II
1a	Death or any life-threatening **SAE**, regardless of causality	≥ 1	≥ 1	≥ 1
1b	Any **non-life-threatening SAE** that can be reasonably attributed to the study intervention administration	≥ 1	≥ 1	≥ 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	≥ 1	≥ 1
1d	Any solicited administration site or solicited systemic AE leading to **hospitalisation**, or **necrosis** at the injection site, with an event onset within the 7-day (Days 1-7) post-study intervention administration period	≥ 1	≥ 1	≥ 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	≥ 2	≥ 25% (and ≥ 2)	≥ 25% (and ≥ 2)
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	≥ 2	≥ 25% (and ≥ 2)	≥ 25% (and ≥ 2)
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-day (Days 1-28) post-study intervention administration period OR Any Grade 3 abnormality* in pre-specified haematological or biochemical **laboratory parameters** in an investigational group, between Day 1 and Day 29 post-study intervention administration period	≥ 2	≥ 25% (and ≥ 2)	≥ 10% (and ≥ 2)

SAE = serious adverse event; **AE** = 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 43).

Figure 6 illustrates the probability to reach the study holding rules following study intervention administration in any of the active arms during PART I (healthy adults aged 18 to 40 years):

- For holding rules 1, using a cut-off of 1/5 (Step 1), there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 28% and there is more than 77% chance that the holding rule is not met for a study intervention with a true incidence rate below 5%.
- For holding rules 1, using a cut-off of 1/10 (as example of about half enrolment in Step 2), there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 15% and there is more than 60% chance that the holding rule is not met for a study intervention with a true incidence rate below 5%.
- For holding rules 1, using a cut-off of 1/20 (Step 2), 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 2/5 (Step 1), there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 49% and there is more than 74% chance that the holding rule is not met for a study intervention with a true incidence rate below 20%.
- For holding rules 2, using a cut-off of 5/20 (Step 2), 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 6 Risk Assessment Curves for Study Holding Rules for PART I (Healthy Adults, Aged 18 to 40 Years)

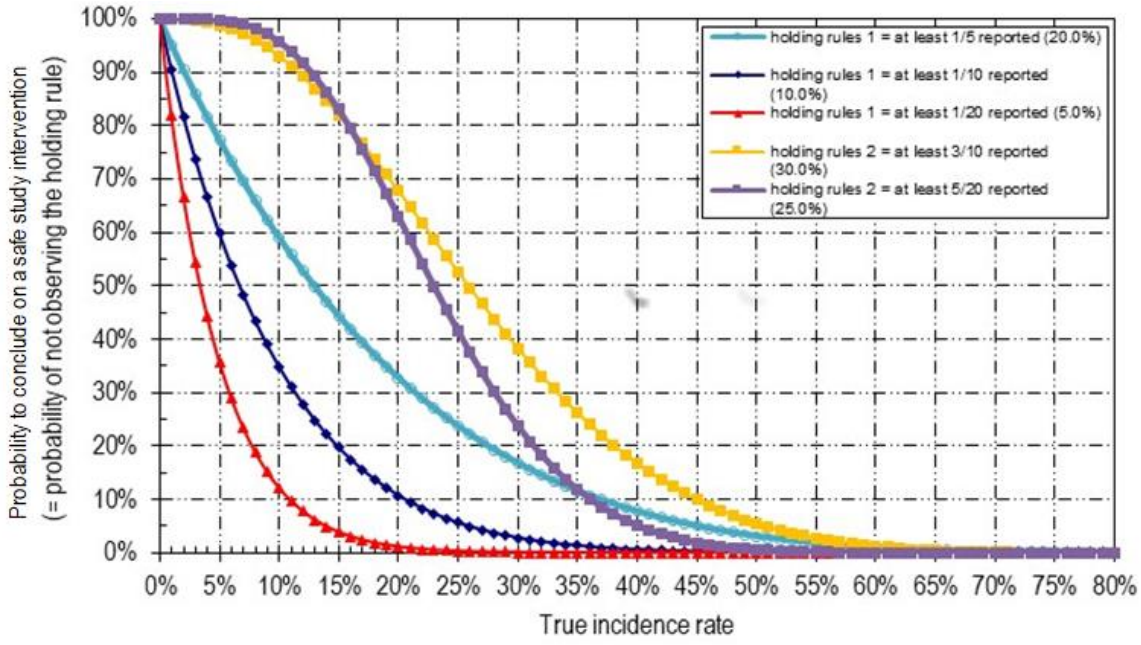
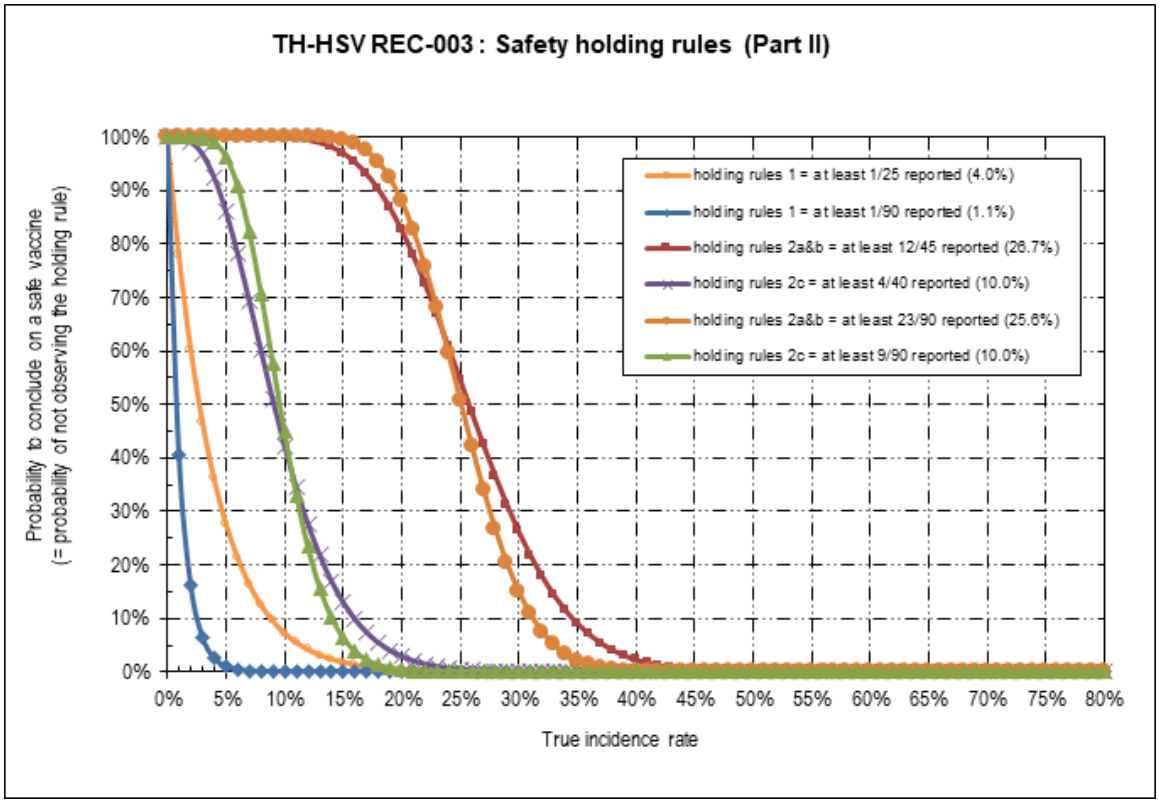


Figure 7 illustrates the probability to reach the study holding rules following study intervention administration in any of the active arms during PART II (patients with HSV genital herpes, aged 18 to 60 years):

- For holding rules 1, using a cut-off of 1/90, there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 2% and there is more than 40% chance that the holding rule is not met for a study intervention with a true incidence rate below 1%.
- For holding rules 2a and 2b, using a cut-off of 23/90, there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 29% and there is more than 80% chance that the holding rule is not met for a study intervention with a true incidence rate below 21%.
- For holding rules 2c, using a cut-off of 9/90, there is more than 80% chance that the holding rule is met for a study intervention with a true incidence rate above 13% and there is more than 80% chance that the holding rule is not met for a study intervention with a true incidence rate below 7%.

Figure 7 Risk Assessment Curves for Study Holding Rules for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)



If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform GSK immediately (e.g., holding rules 1a-d). Refer to Table 30 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 other site(s) of his/her country (if applicable), LML(s) of other country(ies), the iSRC Chair, the SRT lead and the CSL.
- All informed study staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK will further evaluate the case with the iSRC and GSK's GSB and will take the decision to stop or to restart the study intervention administration. 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 7 (PART I) and Table 8 (PART II), all screening procedures as detailed in the SoA (Table 1 [PART I]/Table 2 & Table 3 [PART II]) must be performed again (except for the twice daily anogenital swabbing for participants in the shedding sub-cohort in PART II if ongoing at the time of study hold). Data from this re-screening, if performed, must be encoded in the eCRF.

8.2.2.5. Criteria to go from PART I Step 1 to Step 2

In PART I, each formulation tested in Step 1 (40 µg, 80 µg and 160 µg non-adjuvanted or adjuvanted with $AS01_B$ or $AS01_E$) will be evaluated from a safety perspective before moving to Step 2. The safety assessment will be guided by the methodological considerations described by Tavares *et al.* [Tavares, 2015].

A sample size of 5 participants per group in PART I Step 1 would provide a probability of 23% or 80% to observe at least one AE, if the true AE rate is 5% or 28%, respectively.

To proceed to Step 2, a formulation should present an acceptable safety profile considering the totality of available safety data as assessed by the iSRC assessed 7 days after Dose 1 in 160 µg antigen-dose formulation; refer to Section 4.2).

8.2.3. 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 SoA.

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 27 Timeframes for Collecting and Reporting of Safety Information for PART I (Healthy Adults, Aged 18 to 40 Years)

Event	Screening*	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	Visit 6	Visit 7
		Day 1	Day 7	Day 8	Day 28	Day 29	Day 35	Day 36	Day 57	Day 64	Day 209	Day 394
	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												

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

Table 28 Timeframes for Collecting and Reporting of Safety Information for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Event	Screening*	Baseline**	Visit 1		Visit 2		Visit 3		Visit 4	Visit 5	Visit 10
			Day 1	Day 7	Day 8	Day 28	Day 29	Day 35	Day 36	Day 57	Day 394
	Up to 90 days before Visit 1	Day -28 to Day -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											
SAEs pIMDs MAEs AEs/SAEs leading to withdrawal from the study											
SAEs related to study participation or concurrent GSK medication/vaccine											
Pregnancies											

AE = adverse event; **MAE** = medically attended event; **pIMD** = potential immune-mediated disease; **SAE** = serious adverse event
*i.e., consent obtained
**Only for participants in the shedding sub-cohort

The investigator or designee will record and immediately report all SAEs in enrolled participants to the Sponsor or designee via the Adverse Events Form and the corresponding Expedited Adverse Event Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. 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 27 (PART I) and Table 28 (PART II). 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 he/she considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in Table 30.

8.3.2. Method of Detecting AEs and SAEs, Pregnancies, and Other Events

Detection and recording of AEs/SAEs/pIMDs/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality, and outcome are described in Section 10.3.9.

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 he/she did so, 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 35 days (PART I) or within 28 days (PART II) 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 or LML. Refer to Section 10.3.6 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 aetiology 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 29. This is essential for meeting GSK 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 Section 10.3.9.2.

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

The Sponsor has the legal responsibility to notify local authorities/regulatory agencies, as applicable, 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, IEC/IRB, and investigators.

The sponsor will report SUSAR information to the relevant regulatory authorities (including Eudravigilance). The timelines for reporting SUSARs by the sponsor are:

- In the case of fatal or life-threatening SUSARs, within 7 calendar days after the sponsor became aware of the reaction;
- In the case of non-fatal or non-life-threatening SUSARs, within 15 calendar days after the sponsor became aware of the reaction;
- In the case of a SUSAR which was initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening, within 7 calendar days after the sponsor became aware of the reaction being fatal or life-threatening.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/pIMDs/pregnancies.

Table 29 Timeframes for Submitting Serious Adverse Event, 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 Adverse Events Form and corresponding Expedited Adverse Event Form	24 hours*	Electronic Adverse Events Form and corresponding Expedited Adverse Event Form
Pregnancies	24 hours*	Electronic pregnancy report	24 hours*	Electronic pregnancy report
pIMDs	24 hours**,‡	Electronic Adverse Events Form and corresponding Expedited Adverse Event Form	24 hours*	Electronic Adverse Events Form and corresponding Expedited Adverse Event Form

SAE = serious adverse event; **pIMD** = potential immune-mediated disease
*Timeframe allowed after receipt or awareness of the information by the investigator/study staff.
**Timeframe allowed once the investigator determines that the event meets the Protocol definition of a pIMD (see Section 10.3.5).
‡The investigator will be required to confirm review of the SAE/pIMD causality within 72 hours of submission of the SAE/pIMD.

8.3.3.1. Contact Information for Reporting Serious Adverse Events, potential Immune-mediated Diseases, Pregnancies, and Study Holding Rules

Table 30 Contact Information for Reporting Serious Adverse Events, potential Immune-mediated Diseases, Pregnancies, and Study Holding Rules

Study contact for questions regarding SAEs, pIMDs, and pregnancies	**Study contact for reporting of study holding rules**
Refer to the local study contact information document	As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the LML
Back-up study contact for reporting SAEs, pIMDs, and pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Email address: ogm28723@gsk.com Outside US sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 US sites only: Fax: 1 610 787 7053	**Back-up study contact for escalation of holding rules** Refer to the local study contact information document

SAE = serious adverse event; **US** = United States; **pIMD** = potential immune-mediated disease; **LML** = local medical lead

8.3.4. Treatment of AEs

Any medication administered for the treatment of an SAE/pIMD should be recorded in the eCRF and linked to the corresponding Expedited Adverse Event Form of the participant's eCRF screen (refer to Section 10.3.10.1).

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 his/her possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/care giver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back-up.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics and/or Pharmacogenomics

Pharmacogenomics analysis will be performed on collected samples from participants who have consented to take part in the study and are determined to be eligible to participate in the study. See Section 10.5 for information regarding genetic research.

Only for PART II: Participants who do not wish to participate in the genetic research may still participate in the study, provided they fulfil all eligibility criteria.

8.6. Biomarkers

This section is not applicable.

8.7. Immunogenicity Assessments

Immunogenicity is described in Section 8.1.

8.8. Health Outcomes

This section is not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

In PART I: No formal statistical hypotheses are to be tested.

In PART II: CCI [redacted] The null hypothesis that will be tested for this objective/endpoint is presented in Table 31.

Table 31 Primary Clinical Objective and Null Hypothesis for PART II

Objectives	Null Hypothesis
Primary	
• To demonstrate the efficacy of the HSVTI in reducing the risk of having HSV-2 RGH episodes.	• The hazard ratio comparing HSVTI to placebo for the first confirmed HSV-2 genital herpes recurrence is CCI [redacted]

HSV-2 = herpes simplex virus type 2; **RGH** = recurrent genital herpes

For the primary efficacy objective of time-to-first RGH episode, each HSVTI group will be compared to placebo separately using a 2-sided alpha of 10% for each test.

9.2. Analysis Sets

Table 32 Analysis Sets for PART I (Healthy Adults, Aged 18 to 40 Years)

Analysis Set	Description
Screened Set	All participants who signed the ICF.
Enrolled set	All participants who entered the study (i.e., who were randomised or received a study intervention). Note: Screening failures are excluded from the Enrolled set as they did not enter the study.
ES_P1S1 (PART I, Step 1)	All participants of Step 1 with at least one study intervention administration documented.
ES_P1S2 (PART I, Step 2)	All participants of Step 2 with at least one study intervention administration documented.
PPS for analysis of immunogenicity (PPS_I_P1)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • With at least one post-study intervention administration immunogenicity data available, • Who had no Protocol deviations during study intervention administration phase that lead to exclusion.
PPS for analysis of CMI (PPS_CMI_P1)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • With at least one post-study intervention administration CMI data available, • Who had no Protocol deviations during study intervention administration phase that lead to exclusion.

ICF = informed consent form; **ES** = Exposed Set; **PPS** = Per-Protocol Set

Table 33 Analysis Sets for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Analysis Set	Description
Screened Set	All participants who signed the ICF.
Enrolled set	All participants who entered the study (i.e., who were randomised or received a study intervention). Note: Screening failures are excluded from the Enrolled set as they did not enter the study.
ES_P2 (PART II)	All participants with at least one study intervention administration documented.
PPS for analysis of immunogenicity (PPS_I_P2)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • With at least one post-study intervention administration immunogenicity data available, • Who had no Protocol deviations during study intervention administration phase that lead to exclusion, • Who are determined to be HSV-2 seropositive by UWWB.
PPS for analysis of virological efficacy (PPS_VE)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • Who were part of the shedding sub-cohort, • Who had collected at least 45 anogenital swabs within the window of the given swabbing period. • Who had no Protocol deviations during study intervention administration phase and applicable swabbing period that lead to exclusion. • Who are determined to be HSV-2 seropositive by UWWB.

Analysis Set	Description
PPS for analysis of CMI (PPS_CMI_P2)	All participants from the ES: • Who were part of the shedding sub-cohort, • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • With at least one post-study intervention administration CMI data available, • Who had no Protocol deviations during study intervention administration phase that lead to exclusion. • Who are determined to be HSV-2 seropositive by UWWB.
mES for analysis of clinical efficacy (mES_CE)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • Who were not under or did not switch to chronic suppressive therapy during the period from Dose 1 to 14 days post Dose 2, • With at least 14 days of follow-up after Dose 2, • Who are determined to be HSV-2 seropositive by UWWB.
mES for analysis of virological efficacy (mES_VE)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected study intervention administration schedule, • Who were part of the shedding sub-cohort, • Who had collected at least 45 anogenital swabs within the window of the given swabbing period. • Who are determined to be HSV-2 seropositive by UWWB.

ICF = informed consent form; **ES** = Exposed Set; **PPS** = Per-Protocol Set; **UWWB** = Western Blot from the University of Washington; **mES** = modified Exposed Set

9.2.1. Criteria for Elimination from Analysis

If the participant meets one of the criteria mentioned below or ones listed in Section 7.1.1, he/she may be eliminated from Per-Protocol analysis:

- Receive any of the medications/products/vaccines listed in Section 5.2.2.
- Incur an intercurrent medical condition that could alter their immune response or are confirmed to have an alteration of their initial immune status.
- Major Protocol deviation(s) linked to the eligibility criteria (Sections 5.1 and 5.2).
- Study intervention not administered as specified by the Protocol.
- Failure to comply with the post-dose immunogenicity blood sampling schedule at a given timepoint (Table 1 [PART I] and Table 2 & Table 3 [PART II]).
- Other major Protocol deviation during study intervention administration phase that lead to exclusion.
- Only for PART II (shedding sub-cohort): Insufficient number of anogenital swabs available (44 or fewer out of 56) during a given swabbing period.

The SAP will provide a complete list of criteria for elimination from Per-Protocol analyses.

9.2.2. Case Counting Rules for Primary Efficacy Analysis

In the main analysis based on mES_CE, a confirmed case will be counted when a participant experienced the first PCR-confirmed HSV-2 RGH event with the start day on or later than 14 days post-Dose 2.

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 characterise the safety/reactogenicity, immunogenicity, and efficacy (only for PART II) of each HSVTI group. For PART II, the primary objective on time-to-first- confirmed HSV-2 RGH episode will be confirmatory (see Section 9.1).

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

9.3.1. Participants Disposition

The number of enrolled and dosed (at least one study intervention administration, full study intervention administration course) participants, included in each group and in total, will be described. These might be additionally broken down by site.

9.3.2. Demography and Baseline Characteristics Analyses

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

- Frequency tables will be generated for categorical variables.
- Mean, standard deviation (SD), median, minimum and maximum will be provided for continuous data such as age, height, weight, and BMI.

Withdrawal status will be summarised 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 analysis sets, i.e., modified exposed set (mES) and Per-Protocol Set (PPS) will be tabulated.

9.3.3. Primary Endpoints/Estimands Analyses

9.3.3.1. Reactogenicity and Safety (PART I and PART II)

The analysis of the primary reactogenicity and safety objective will be performed on the Exposed Set (ES). In PART I, Step 1 and Step 2 cohorts will be presented separately.

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 haematology and biochemistry parameter: • The percentage of participants having haematology 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 Day 394 will also be tabulated after each dose and overall. The percentage of participants with at least one report of SAE classified by the MedDRA SOC and PTs reported from Dose 1 up to Day 394 will be tabulated with exact 95% CI. Only for PART I: The percentage of participants with at least one report of causally related SAE and with at least one report of fatal SAE, classified by the MedDRA SOC and PTs reported from Dose 1 up to study end will be tabulated with exact 95% CI. The percentage of participants with at least one pIMD classified by the MedDRA SOC and PTs and reported from Dose 1 up to Day 394 will be split by newly diagnosed vs. exacerbation of pre-existing events and tabulated with exact 95% CI. Only for PART I: The percentage of participants with at least one related pIMD classified by the MedDRA SOC and PTs and reported from Dose 1 up to study end will be split by newly diagnosed vs. exacerbation of pre-existing events and tabulated 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 summarised by group after each dose and overall.

AE = adverse event; **FDA** = Food and Drug Administration; **CI** = confidence interval; **MedDRA** = Medical Dictionary for Regulatory Activities; **PT** = preferred term; **SOC** = System Organ Class; **SAE** = serious adverse event; **pIMD** = potential immune-mediated disease

9.3.3.2. Clinical Efficacy (Only for PART II)

The analysis of time-to-first confirmed RGH episode will be performed on the modified ES for clinical efficacy (mES_CE).

Statistical Analysis Methods
To evaluate time in days from Day 43 (i.e., 14 days post-Dose 2) to the first confirmed HSV-2 RGH episode, hazard ratios will be estimated using a Cox proportional hazards model. The model will be run separately for each comparison (i.e., HSVTI_F1 vs. placebo group, and also HSVTI_F2 vs. placebo group) and will be adjusted for sex (female vs. male) and number of RGH episodes in the 12 months before recruitment (< 6 episodes, ≥ 6 episodes). The hazard ratio, 90% confidence interval and p-value will be calculated for each comparison of HSVTI group-to-placebo by exponentiating the parameter estimates and their associated confidence limits. The null hypothesis will be rejected if the 2-sided p-value is below 0.1. Participants will be censored if, for example, they withdraw from the study before the first PCR-confirmed genital herpes recurrence occurs such that they are included in the analysis until the day they withdraw from the study. As a sensitivity analysis, the above analyses will be rerun on the ES to evaluate time in days from Day 1 to first suspected RGH episode. Other sensitivity analyses will be specified in the SAP.

HSV(-2) = herpes simplex virus (type 2); **RGH** = recurrent genital herpes; **PPS** = Per-Protocol Set; **ES** = Exposed Set; **SAP** = Statistical Analysis Plan

9.3.4. Secondary Endpoints/Estimands Analyses

9.3.4.1. Efficacy (Only for PART II)

The analysis of the shedding rate reduction and other virological endpoints will be performed on the mES for analysis of virological efficacy (mES_VE) for the corresponding swabbing period. Additional sensitivity analyses may be carried out in the PPS for virological efficacy (PPS_VE) and the Exposed Set (ES_P2).

The analyses of secondary clinical efficacy endpoints will be performed on the mES_CE.

Statistical Analysis Methods
Number of positive HSV-2 swabs about 6 weeks after the last dose of the HSVTI will be estimated using a Poisson regression model with a random intercept and empirical variance estimate [Magaret, 2016]. The model will be run separately for each treatment group (i.e., HSVTI_F1, HSVTI_F2, and placebo group) and will be adjusted for sex (female vs. male), and number of RGH episodes in the 12 months before recruitment (< 6 episodes, ≥ 6 episodes), total number of swabs and swabbing period (i.e., baseline or swabbing period 2). The shedding rate* ratio (comparing shedding rates post-study intervention administration to shedding rates pre-study intervention administration) will be estimated by exponentiating the model coefficient for swabbing period and the shedding rate* reduction** will be derived from this ratio. **Shedding rate = number of HSV-2-positive swabs divided by number of swabs during the period.* ***Shedding rate reduction (%) = [1-(shedding rate about 6 weeks post-Dose 2 / baseline shedding rate)]*100.* The treatment effects (shedding rate reduction) and 90% confidence limits for the HSVTI group will be calculated by exponentiating the parameter estimates and their associated confidence limits. The null hypothesis will be rejected for the gE-gI/AS01 group if the 2-sided p-value is below 0.1. The above may be repeated for the shedding rate reduction 6 months after the last dose of the HSVTI (tertiary endpoint). Descriptive statistics (n, mean, SD, median, Q1, Q3) on HSV-2 shedding rate and shedding rate reduction will be displayed by treatment group and shedding period. This analysis will be presented for all days and split by symptomatic vs. asymptomatic days. Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration of shedding episodes will be displayed by treatment group and shedding period. Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration in days (i.e., number of days with RGH associated symptoms) of each genital herpes recurrence will be displayed by treatment group. The incidence rate of HSV-2 recurrences (i.e., number of confirmed HSV-2 RGH episodes divided by the number of days of follow up) as of 14 days post-Dose 2 will be estimated using a Poisson model (or negative-binomial regression model if the data are determined to be over-dispersed). The model will be run separately comparing each HSVTI group to placebo and will be adjusted for sex (female vs. male), and number of RGH episodes in the 12 months before recruitment (< 6 episodes, ≥ 6 episodes). The above model will also be repeated to estimate lesion rates (i.e., number of days with lesions detected during confirmed recurrences divided by the number of days of follow-up). Descriptive statistics (n, mean, SD, median, Q1, Q3) on the number of confirmed HSV-2 genital herpes lesions will be displayed by treatment group as of 14 days post-Dose 2 study intervention administration. Number and percentage of participants free from confirmed HSV-2 RGH episodes at 6 months after the last dose of study intervention will be displayed by study group with exact 95% CIs. The frequency of participants experiencing genital herpes recurrences will be displayed by the maximum severity of each symptom as of 14 days post-Dose 2 of the study intervention administration. The categories will be 'Any severity', 'None', 'Mild', 'Moderate', 'Severe' and 'Unknown'.

Descriptive statistics (n, mean, SD, median, Q1, Q3) on the incidence rates will be displayed by treatment group. Descriptive statistics (n, mean, SD, median, Q1, Q3) of the HSC total scores will be presented per recurrence. Refer to SAP for more details.

HSV-2 = herpes simplex virus type 2; **gE-gI** = glycoprotein E-glycoprotein I; **AS01** = Adjuvant System 01; **n** = number; **SD** = standard deviation; **Q1/Q3** = first/third quartile; **HSC** = Herpes Symptoms Checklist; **SAP** = Statistical Analysis Plan

9.3.4.2. Immunogenicity (PART I and PART II)

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

Statistical Analysis Methods
For each group, at each timepoint that blood samples are collected for immune responses and for each assay (unless otherwise specified): • Percentage of participants above predefined threshold and their exact 95% CI will be tabulated. • GMCs/GMTs and their 95% CI will be tabulated and represented graphically. • Mean geometric fold increases and their 95% CI will be tabulated and represented graphically. • Antibody titre/concentration will be displayed using reverse cumulative curves. • The kinetics of titres 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). Immune responses pre- and post-study intervention administration will be tabulated according to the HSV-1 serostatus (positive vs. negative).

CI = confidence interval; **GMC** = geometric mean concentration; **GMT** = geometric mean titre; **CD4+/CD8+** = cluster of differentiation 4/8; **SD** = standard deviation; **Q1/Q3** = first/third quartile; **CMI** = cell-mediated immunity

9.4. Sequence of Analyses

9.4.1. Interim Analysis #1 (PART I, 1 Month Post-Dose 2)

A first interim analysis of available and as clean as possible reactogenicity/safety (including safety laboratory data) and immunogenicity (including at least enzyme-linked immunosorbent assay [ELISA]) data will be performed after all participants from PART I have completed their Visit 5 (Day 64). This analysis will allow the HSVTI formulation selection before going to the target population in PART II. This analysis will be performed by an independent statistician who will be unblinded for this analysis (i.e., will have access to the individual participant treatment assignment), who will generate a statistical report by group but no individual listings.

9.4.2. Final Analysis (PART I)

The final analysis on primary and secondary endpoints (reactogenicity, safety and immunogenicity) from PART I (Step 1 & Step 2) will be performed when all data up to 12 months post-Dose 2 study intervention administration (Day 394) are cleaned and available. At this stage, PART I of the study will be unblinded.

If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

9.4.3. Interim Analysis #2 (PART II)

The interim analysis will be performed when the required number of first HSV-2 RGH episodes is reached (at least 18 cases for each HSVTI group-to-placebo comparison) among participants who are HSV-2 seropositive by UWWB at the Screening visit or at Visit 1.

This case-driven interim analysis will be performed on all available and as clean as possible reactogenicity/safety (including safety laboratory data), immunogenicity, virological efficacy (shedding) and clinical efficacy data.

The purpose of this analysis is to potentially make early conclusions on futility or efficacy.CCI [redacted]

Note that this analysis was combined with the primary analysis (see Section 9.4.4).

9.4.4. Primary Analysis (PART II)

The primary analysis is a case-driven analysis CCI [redacted]
CCI [redacted]
CCI [redacted]

This case-driven analysis will be performed on all available and as clean as possible reactogenicity/safety (including safety laboratory data), immunogenicity, virological efficacy (shedding) and clinical efficacy data. The purpose of this analysis is to conclude on the confirmatory primary objectives of the study.

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9.4.5. Interim Analysis #3 (PART II, 6 Months Post-Dose 2)

An interim analysis will be performed after (1) all participants have completed Visit 8 (Day 209), (2) all samples are received and tested, and (3) after Protocol Amendment 7 is implemented in all countries, based on all available and as clean as possible safety data and all cleaned and available clinical and virological efficacy, and immunogenicity data. The purpose of this analysis is to report all safety and clinical efficacy data with at least 6 months of follow-up post-Dose 2. The virological efficacy and immunogenicity data up to 6 months post-Dose 2 (Day 209) can be analysed for the tertiary objectives.

9.4.6. End-of-Study (EoS) Analysis (PART II)

- The EoS analysis will be performed when all safety data up to 12 months post-Dose 2 study intervention administration (Day 394) are cleaned and available. At this stage, the study will be unblinded. The purpose of this analysis is to provide long-term safety data.
- If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

9.4.7. Statistical Considerations for Interim Analyses

The interim analysis planned in PART I will be only descriptive (see Section 9.4.1).

The interim analysis #2 (PART II) will be used to inform non-binding recommendations based on the efficacy or futility of the primary efficacy objective (time-to-first confirmed HSV-2 RGH episode). Because the study may be stopped early, an O'Brien-Fleming alpha-spending function [O'Brien, 1979] and a Hwang-Shih-DeCani beta-spending function [Hwang, 1990] are used to allow to distribute the risk of false positives or false negatives based on the amount of information present at the analysis. CCI [redacted]

The primary analysis (PART II) will generate the confirmatory analysis of the primary efficacy objective (time-to-first confirmed HSV-2 RGH episode).

The other interim analyses will be descriptive. If any analysis will occur within a sufficiently short period of time of another analysis, these analyses may be combined.

For PART II, the study statistician(s) and the statistical programmers will have access to the participant-level unblinded data to allow the creation of outputs. The study statistician and statistical programmers will maintain secure custody of unblinded or partially unblinded data to ensure the integrity of the data.

The rest of the study team will have access to statistical outputs by group but will remain blinded to individual treatment assignment until the end of the study. 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 the results could become unblinded regarding those few specific cases.

9.5. Sample Size Determination

9.5.1. PART I (Healthy Adults, Aged 18 to 40 Years)

During **Step 1**, ~45 healthy participants aged 18 to 40 years will receive 2 doses of non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI antigen (40 µg or 80 µg or 160 µg) (9 groups).

During **Step 2**, ~200 healthy participants aged 18 to 40 years will receive 2 doses of either non-adjuvanted or adjuvanted ($AS01_B$ or $AS01_E$) gE-gI antigen (40 µg, 80 µg or 160 µg) or placebo (10 groups).

This sample size is typical for this kind of study where a treatment is tested for the first time in humans, and it has not been based on formal hypothesis testing.

Total enrolment in PART I will be ~245 participants.

The primary objective of the study is to evaluate the reactogenicity and safety of the HSVTI.

Table 34 shows the true proportions associated with a 90% probability to observe an event in 25 participants (e.g., SAE, pIMD) and Table 35 illustrates the 95% confidence interval (CI) for different possible numbers of AEs within each group.

Table 34 True Proportions Associated With a 90% Probability to Observe a Certain Number of Adverse Events Within a Group (25 Participants)

True Proportion	Number of AEs Observed With > 90% Probability
0.147	≥ 1
0.199	≥ 2
0.248	≥ 3

AE = adverse event

Table 35 Two-Sided 95% Exact CIs for the True Adverse Event Rate at Different Possible Observed Adverse Event Rates (25 Participants)

Observed Number of AEs	Observed AE Proportion	95% Exact CI	
		LL	UL
0	0.000	0.000	0.137
1	0.04	0.001	0.204
2	0.08	0.01	0.26
3	0.12	0.026	0.312
4	0.16	0.045	0.361
5	0.20	0.068	0.407

AE = adverse event; **CI** = confidence interval; **LL** = lower limit; **UL** = upper limit

The advantage of adding an adjuvant and the effect of antigen dose will be assessed in terms of immunogenicity, by making use of the factorial nature of the study design,

summarised in Table 36. The anti-gE-gI antibody geometric mean concentration (GMC) by ELISA will be modelled.

SDs of 0.45 and 0.50 were considered in the present power calculations given that these values cannot be obtained at the present stage due to unavailability of the final assay.

Table 36 Factorial Study Design: Repartition of the Participants According to the Antigen Dose and to the Type of Adjuvant

Number of Evaluable Participants	40 µg gE-gI Antigen	80 µg gE-gI Antigen	160 µg gE-gI Antigen	Total
$AS01_B$	25	25	25	75
$AS01_E$	25	25	25	75
No adjuvant	25	25	25	75
Total	75	75	75	225

gE-gI = glycoprotein E-glycoprotein I

The SD of group means associated with 80% power to detect differences among the means vs. the alternative of equal means were obtained using the following assumptions:

- A one-way analysis of variance (ANOVA) power analysis performed in PASS 2019,
- Three pooled groups of size n = 75 participants per group,
- Two-sided $\alpha = 0.10$,
- SD of $\log_{10}$ (concentrations) = 0.45 to 0.50, and,
- A scenario with a maximum difference in GMCs of 4-fold in terms of antigen-dose effect (repartition type 1-2-4).

This value is then converted in fold-increase according to the scenario. The values are presented in Table 37.

Table 37 Selection of the Dose: Detectable Fold-Increase in GMCs With 80% Power (N/Group = 75, Two-Sided Alpha = 0.10, One-Way ANOVA Power Analysis)

SD of $\log_{10}$ (concentrations)	SD of Group Means	Detectable Fold-Increase
0.45	0.0837	2.19
0.50	0.093	2.39

SD = standard deviation

The SD of group means associated with 80% power to detect differences among the means vs. the alternative of equal means were obtained using the following assumptions:

- A one-way ANOVA power analysis performed in PASS 2019,
- Three pooled groups of size n = 75 participants,
- Two-sided $\alpha = 0.10$,
- SD of $\log_{10}$ (concentrations) = 0.45 to 0.50, and,

- A scenario with a maximum difference in GMCs of 4-fold in terms of adjuvant effect (repartition type 1-5-5),

This value is then converted in fold-increase according to the scenario. The values are presented in Table 38.

Table 38 Selection of the Adjuvant: Detectable Fold-Increase in GMCs With 80% Power (N/Group = 75, Two-Sided Alpha = 0.10, One-Way ANOVA Power Analysis)

SD of log_{10} (concentrations)	SD of Group Means	Detectable Fold-Increase
0.45	0.0837	1.79
0.50	0.093	1.92

SD = standard deviation

9.5.2. PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

The sample size required in PART II will be at least 80 HSV-2-positive (by UWWB at either the Screening visit or Visit 1) participants per treatment group. This will account for potentially high non-evaluable rates over the entire 2-year study and the fact that sufficient numbers of participants are needed to characterize the safety profile of the HSVTI formulations.



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9.5.3. Number of Participants to be Screened

In PART I: Assuming a 20% proportion of screened participants will not meet the study eligibility criteria, the total maximum number of screened participants needed to achieve ~ 245 eligible participants would be ~307.

In PART II: The target sample size is at least 80 participants HSV-2 seropositive by UWWB at either the Screening visit or Visit 1 per group. Considering a limited number of participants may be tested negative by UWWB at Visit 1, ~270 participants will be enrolled. Assuming a 35-40% proportion of screened participants [Wald, 2014] will not meet the study eligibility criteria, the total maximum number of screened participants needed to achieve ~270 eligible participants would be ~450.

The proportion of screening failure and withdrawals prior to study intervention administration will be monitored and re-evaluated during PART II, to potentially adapt the number of participants to be screened and number to be enrolled. Participants who withdraw from the study after study intervention administration will not be replaced.

9.5.4. Candidate Formulation Selection for PART II

The optimal HSVTI will be selected using the safety and immunogenicity data. The final formulation will be the one presenting the best benefit/risk profile.

PART I of the study uses a factorial design with 2 factors (adjuvant and antigen), which allows to study the effect of each factor on the immune response, as well as the effects of interactions between factors on the immune response. Both the antigen-dose response as well as the adjuvant response will be evaluated in terms of anti-gE-gI antibody concentrations and gE-gI-specific CD4+ T-cell at one month post-Dose 2 (Day 64).

The formulation inducing the highest immune response will be selected, provided it has an acceptable safety profile. If several doses show a similar response, the choice will depend on whether a dose-response is demonstrated (or not) and whether the adjuvant added-value is confirmed (or not). Technical or manufacturing constraints may also support guiding the final formulation selection.

9.5.4.1. Safety Assessment

The safety assessment of the 9 formulations tested in PART I will be guided by the methodological considerations described by Tavares *et al.* [Tavares, 2015]*. A sample size of at least 20 participants per group in PART I would provide a probability of 80% or 90% to observe at least one AE, if the true AE rate is 8% or 11%, respectively.

**To be evaluated in PART II, a formulation must present an acceptable safety profile after iSRC assessment in PART I.*

9.5.4.2. Immune Response Assessment

For the assessment of the immune response supportive of the formulation selection, statistical analyses will be performed to compare the HSVTI groups in terms of anti-gE-gI antibody concentrations (primary measure) and gE-gI-specific CD4+ T-cells (supportive information, if available), one month post-Dose 2 (Day 64).

The statistical design of the study (PART I) has been based on a factorial design with 2 factors resulting in 9 HSVTI formulations (~25 participants per HSV non-adjuvanted and adjuvanted formulations), as presented in Table 40. In addition, a placebo group (~20 participants) will be evaluated.

Table 40 Factorial design

		No adjuvant	Factor B: Adjuvant	
			$AS01_B$	$AS01_E$
Factor A: Antigen dose	40 µg	25	25	25
	80 µg	25	25	25
	160 µg	25	25	25

Eligible formulations in terms of induced immune response will be identified through the following process.

The antigen-dose response will be evaluated in terms of anti-gE-gI antibody concentrations (primary measure) and gE-gI-specific CD4+ T-cells (supportive information, if available) at one month post-Dose 2 (Day 64).

The anti-gE-gI antibody concentrations will be modelled using an ANCOVA model. Day 64 $\log_{10}$ (concentrations) will be modelled as a function of the adjuvant ($AS01_B$, $AS01_E$, no adjuvant) and of the antigen dose (40 µg, 80 µg, 160 µg), including the pre-study intervention administration concentration and minimisation factors (except study site) as covariates. The initial analysis will not include any interaction term.

For the parameter related to the antigen dose, the overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10.

As described in the sample size section (see Section 9.5), the detectable fold-increase in GMCs with 80% power (N/group = 75, 2-sided $\alpha = 0.10$, one-way ANOVA Power Analysis) ranges from 2.2 to 2.4 for assumed SD of 0.45 and 0.5, respectively.

If the test is statistically significant at α level of 0.10, the different pairwise comparisons (160 µg vs. 80 µg and 80 µg vs. 40 µg) will be performed at the same α level.

The adjuvant response will also be evaluated in terms of anti-gE-gI antibody concentrations (primary measure) and gE-gI-specific CD4+ T-cells (supportive information, if available) at one month post-Dose 2 (Day 64).

The ANCOVA model described above will be used to assess the adjuvant effect. The overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10.

As described in the sample size section (see Section 9.5), the detectable fold-increase in GMCs with 80% power (N/group = 75, 2-sided $\alpha = 0.10$, one-way ANOVA Power Analysis) ranges from 1.8 to 1.9 for assumed SD of 0.45 and 0.5, respectively.

If the test is statistically significant at α level of 0.10, the different pairwise comparisons ($AS01_B$ vs. no adjuvant, $AS01_E$ vs. no adjuvant, $AS01_B$ vs. $AS01_E$) will be performed at the same α level.

9.5.4.3. Candidate Selection

The dose presenting the highest immune response will be pre-selected. If all/several doses show a similar response, the lowest one will be pre-selected. If an added value of the adjuvant is confirmed, an adjuvanted formulation will be favoured. If there is no significant effect of the adjuvant on the immune response, the non-adjuvanted formulation will be pre-selected.

If the adjuvanted formulation(s) show an added value over non-adjuvanted one, **the selection of $AS01_B$ vs. $AS01_E$** will be confirmed for the dose pre-selected in terms of anti-gE-gI antibody concentrations and gE-gI-specific CD4+ T-cells (supportive information, if available) at one month post-Dose 2 (Day 64).

A sample size of 25 participants per adjuvanted group would provide a power of 80% to detect a difference of at least 2.1 to 2.3 depending on the variability of anti-gE-gI antibody concentrations (alpha = 0.10, SD of $\log_{10}$ concentrations between 0.45 and 0.5) (Pass 2019, 2sample T-tests assuming equal variance).

The Adjuvant System presenting the highest immune response will be chosen. If both Adjuvant Systems show a similar response, $AS01_E$ will be selected.

9.5.4.4. Final formulation selection

Among the eligible candidates, the final formulation will be the one presenting the best benefit (immunogenicity)/risk (safety-reactogenicity) profile considering the totality of available data. To this end, additional considerations will be taken into account:

- If 2 or more formulations show a similar immune response, but a different safety profile, the less reactogenic formulation will be selected.
- If 2 or more formulations show similar safety and immune profiles:
  - A lower dose of antigen is preferred over a higher one.
  - A non-adjuvanted formulation is preferred over an adjuvanted one.
  - $AS01_E$ is preferred over $AS01_B$.

- A better *humoral* immune response is preferred over a better *cellular* immune response.

Other markers may be used to further guide the choice of formulation.

Of note, if the effect of the second dose is not demonstrated for any of the formulations, one month post-Dose 1 (Day 29) may be considered the most appropriate timepoint to identify a final formulation and/or schedule (1 dose instead of 2).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The names and addresses of all third parties involved in the study are provided in a separate document accompanying this 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 Council for International Organisations of Medical Sciences (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 IEC/IRB by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated, as applicable.
- 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 IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
  - Notifying the IEC/IRB of SAE(s) or other significant safety findings as required by IEC/IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of Title 21 of the Code of Federal Regulations (21 CFR), ICH guidelines, the IEC/IRB, 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 one year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC/IRB or study site.

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 authorised 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 originally signed ICF.

Participants will need to consent on a separate ICF to the use of their samples for the pharmacogenomics testing planned in this study (refer to Section 8.5).

As of Protocol Amendment 7 implementation, participants will be requested to sign an ICF addendum which will provide them with details regarding the revised study design.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. 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.

The participants must be informed that:

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

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, in accordance with the Data Privacy Notice that will be sent to the site staff.

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.

The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

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 and an existing project SRT (refer to Section 8.2.2 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 treatment 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 Chief Medical Officer, Head of Global Safety and Head of Biostatistics.
- The SRT of the TH HSV project includes as core members the GSK's Central Safety product specialists (including a physician), the Clinical Project Lead (CPL), Epidemiologist, Global Regulatory Lead, Global Medical Affairs Lead (GMAL) and Biostatistician of the project, as well as study CSL as ad hoc member. 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).

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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, EU register 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 reasonable 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 randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised 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, CRF), the copy should fulfil 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 in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data, eDiary data). The investigator is responsible for verifying that data entries are accurate and correct by 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, IEC/IRB 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 authorised 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.

Quality tolerance limits (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 summarised 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

10.1.9.1. Study Start *and First Act of Recruitment*

The start of the study and the first act of recruitment are defined as First Subject First Visit (first ICF signature date) at a country-level.

10.1.9.2. 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.

Study sites will be closed 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 may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For site termination:

- Failure of the investigator to comply with the Protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures or GCP guidelines,
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator,
- Total number of participants included earlier than expected.

For study termination:

- Discontinuation of further study intervention development,

If the study is prematurely terminated or temporarily suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or temporary 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 LSLV for interventional studies and follows the guidance from the International Committee of Medical Journal Editors (ICMJE).

10.1.11. Recruitment strategy

Printed and digitalised advertising and recruitment materials may be used to support recruitment.

All advertisement and participant-facing materials will be approved as per local regulations before their use.

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. Assay Standard Operating Procedures (SOPs) and qualification/validation reports will be submitted upon availability.

HSV serology by Western blot

HSV-1 and HSV-2 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 HSV-1 or HSV-2 are then incubated with the participant's serum. Antibodies, which bind to the viral proteins, are then detected by an enzyme-mediated colour change. The pattern of staining on the 2 blots (HSV-1 and HSV-2) is dictated by the number and identity of the HSV proteins to which the patient's immune system has responded. Thus, a predominance of staining on either the HSV-1 or HSV-2 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 HSV-1 and HSV-2 proteins, and re-run on fresh blots to obtain clearer profiles (essentially removing type common antibody) [Ashley, 1988].

HSV serology for screening

The final CE-marked serology assay to be used for screening is not yet selected and is subject to change. The assay principle will be based on either an enzyme like immunosorbent assay (ELISA) or chemoluminescent immunoassay (CLIA) or electrochemiluminescent immunoassay (ECLIA) method.

Below is provided the principle of an ECLIA assay:

- 20 µL of sample, biotinylated recombinant HSV-2-specific antigens, and HSV-2-specific recombinant antigens labeled with a ruthenium complex are mixed. If the sample contains antibody specific to HSV-2, a sandwich complex is formed.
- After addition of streptavidin-coated microparticles, the complex binds to the solid phase (biotin and streptavidin interaction).
- The reaction mixture is transferred into the measuring cell. Microparticles are then magnetically captured onto the surface of the electrode. After a washing step, application of a voltage to the electrode induces chemiluminescent emission which is measured by a photomultiplier.
- Result is compared with the signal of the cutoff value previously obtained by calibration.

Anti-gE-gI testing by ELISA

The gE-gI 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 heterodimer gE-gI in human serum samples.

The principle of this assay will be as follows: the mutated heterodimer gE-gI antigen (which the binding to the Fc-binding has been decreased) 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 horseradish peroxidase (HRP). Bound antibodies will be quantified by the addition of the HRP substrate solution (TMB), whereby a coloured product develops proportionally to the amount of anti-gE-gI IgG antibodies present in the serum sample. The corresponding antibody concentration, corrected for the dilution factor, will be expressed in arbitrary ELISA units per mL of serum (EU/mL), unit 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 PBMCs are stimulated *in vitro* with either gE-gI antigens (peptide pools, 15mer overlapping by 11) 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:

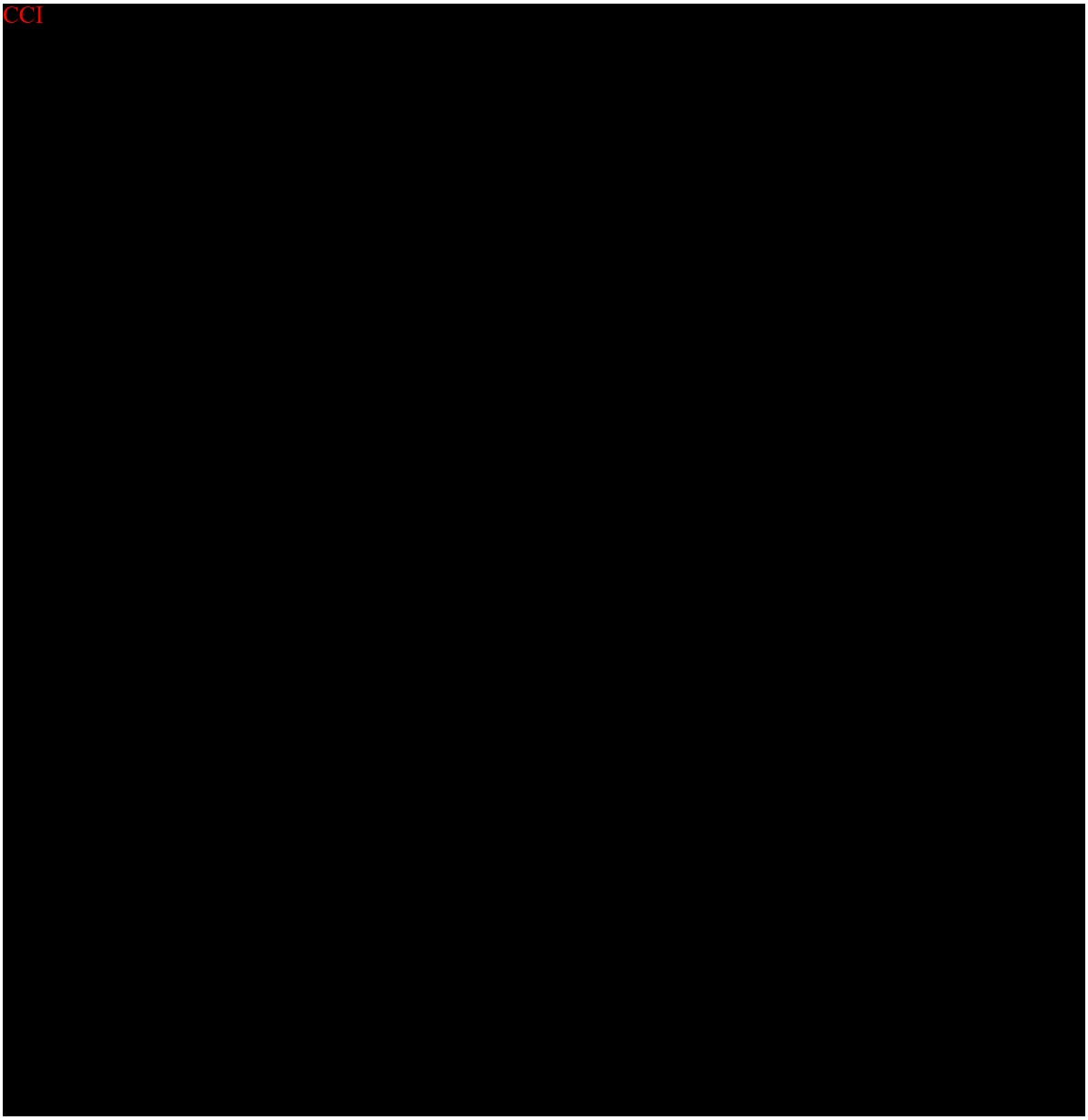
- CD3: phenotyping T-cells,
- CD40L (CD154), 4-1BB: expressed on activated CD4 (or CD8) T-cells [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006],
- Interleukin (IL)-2: key for the development, survival and function of T-cells [Boyman, 2012],
- Tumour necrosis factor-alpha (TNF-α): antiviral/intracellular 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].

Acquisition of data is performed via a flow cytometer, and data analysis is performed on FlowJo software.

HSV DNA testing by qPCR

The DNA from anogenital swabs collected in 1x digestion buffer is extracted using MagNA Pure 96 extraction platform (Roche). After DNA is extracted, real-time TaqMan PCR technology, which utilises fluorescent probes to detect the amplified DNA, is used to amplify, detect and quantify viral DNA in the sample [Wald, 2003; Ryncarz, 1999; Zerr, 2000]. The HSV primers and probes are selected from the highly conserved glycoprotein B gene, and can detect and strain type HSV-1 and HSV-2 [Jerome, 2002; Corey, 2005]. An internal control is spiked into each PCR reaction to ensure that no non-specific inhibition of the reaction has taken place [Limaye, 2001]. A negative result is accepted only if the internal control amplification is detected. Inhibited samples are chelexed or re-extracted and the analysis repeated.

CCI



CCI

[redacted]

β-globin testing by qPCR

To guarantee the quality of the sample, a human housekeeping gene (β-globin) will be assessed by qPCR to ensure that the lesion and anogenital swabbing has been performed appropriately when a RGH episode is suspected. A real-time TaqMan PCR assay detecting the β-globin gene will be used to measure the number of host DNA copies in the samples: ≥ limit of detection will determine positivity for human β-globin DNA.

10.2.2. Protocol-Required Safety Laboratory Assessments

The parameters detailed in Table 41 (PART I) and Table 42 (PART II) will be analysed by a laboratory designated by the Sponsor. The results of each test carried out will be reported in the database.

Table 41 Haematology and Biochemistry Read-Outs for PART I (Healthy Adults, Aged 18 to 40 Years)

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	≥ 245	Haemoglobin WBC differential Platelets ALT AST Creatinine Blood urea nitrogen
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 4 (Day 36) Visit 5 (Day 64)	All participants	~245	

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

Table 42 Haematology and Biochemistry Read-Outs for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Screening	All screened participants	≥ 270	Haemoglobin WBC differential Platelets ALT AST Creatinine Blood urea nitrogen
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 4 (Day 36) Visit 5 (Day 57)	All participants	~270	

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

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" as presented in Table 43.

Table 43 Toxicity Grading Scales for Haematology and Biochemistry Parameters Applicable for this Study

Component	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Haematology (Whole Blood)				
Haemoglobin (g/dL) – female	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Haemoglobin (g/dL) – male	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Haemoglobin (g/dL) – female change from baseline value	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Haemoglobin (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/dL)	23 – 26	27 – 31	> 31	Requires dialysis

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

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 AE

An AE is any untoward medical occurrence (an unfavourable/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 Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.
- 'Lack of efficacy' or 'failure of expected vaccination pharmacological action' *per se* will not be reported as an AE or SAE. Such instances will be captured as an efficacy assessment. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

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. • Worsening of the disease/disorder being studied or expected progression of signs or symptoms of the disease/disorder being studied. Refer to Section 10.3.7 if the progression of signs or symptoms are more severe than expected for the participant's condition or considered clinically significant or serious. • 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. • Hospitalisation 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 hospitalisation or prolongation of existing hospitalisation. Note: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' 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, diarrhoea, 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, foetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g.	Other situations Medical or scientific judgement 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 hospitalisation but may jeopardise 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 hospitalisation.

10.3.3. Solicited Events

10.3.3.1. Solicited Administration Site Events

The following administration site events will be solicited:

Table 44 Solicited Administration Site Events

Pain
Redness
Swelling

10.3.3.2. Solicited Systemic Events

The following systemic events will be solicited:

Table 45 Solicited Systemic Events

Fever
Fatigue
Headache
Myalgia
Arthralgia

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 eDiary.

10.3.4. Unsolicited AEs

An unsolicited AE is an AE that was not included in a list of solicited events using an eDiary. Unsolicited events must have been spontaneously 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 hospitalisation, or an emergency room visit, or visit to/by an HCP). The participants will be instructed to contact the site as soon as possible to report MAE(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. Adverse Events of Special Interest

10.3.5.1. Potential Immune-Mediated Diseases

pIMDs are a subset of AEs of special interest that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 46 (refer to Section 10.3.8.1 for reporting details).

The investigator must exercise his/her medical/scientific judgement 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 categorise 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 46 List of Potential Immune-mediated Diseases

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anaemia	
Autoimmune haemolytic anaemia	• Includes warm antibody haemolytic anaemia and cold antibody haemolytic anaemia
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 anaemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic haemolytic anaemia”
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 hyperlipidaemia	

Medical Concept	Additional Notes
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
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

Medical Concept	Additional Notes
	• Immune-mediated necrotising 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)
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 necrotising myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotising leukoencephalopathy (also known as Weston-Hurst syndrome, acute haemorrhagic leuko-encephalitis, or acute necrotising haemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Post-immunisation encephalomyelitis

Medical Concept	Additional Notes
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 I	• 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
Localised 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	

Medical Concept	Additional Notes
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischaemic 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: • 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 • Necrotising vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute haemorrhagic oedema 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	

Medical Concept	Additional Notes
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.

10.3.6. 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 must exercise his/her medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.7. Events or Outcomes not Qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Women 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 (refer to Section 10.3.2 for the definition of SAE).

10.3.8. 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 in 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.

An eDiary (see Section 8.2.1.10) will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the eDiary. If the data related to the study objectives/endpoints to be collected by the participants cannot be encoded in their eDiary (e.g., unresolved technical issues), they can be reported directly to the site staff and submitted via the eCRF.

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

- Verify completed eDiary during discussions with the participant on timepoints as specified in Table 1 (PART I) and Table 2 (PART II). In case of ongoing administration site or systemic AEs after the solicited period, the eDiary will be verified during discussions with the participant on subsequent visits:
  - For PART I: Visit 2 (Day 8), Visit 3 (Day 29), Visit 4 (Day 36), and Visit 5 (Day 64).
  - For PART II: Visit 2 (Day 8), Visit 3 (Day 29), Visit 4 (Day 36), and Visit 5 (Day 57).

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

Refer to the SPM for more information regarding the eDiary use.

10.3.8.1. Time Period for Collecting and Recording AEs, SAEs, pIMDs, and Pregnancies

All solicited events that occur during 7 days following administration of each dose of study intervention (i.e., on the day of study intervention administration and 6 subsequent days) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within this timeframe should 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 all SAEs will begin at the first receipt of study intervention (Day 1) and will end at Day 394. See Section 10.3.10 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 Day 394.

The time period for collecting and recording MAEs will begin at the first receipt of study intervention (Day 1) and will end at Day 394.

The time period for collecting and recording pIMDs will begin at the first receipt of study intervention (Day 1) and will end at Day 394. See Section 10.3.10 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 Day 394. See Section 10.3.10 for instructions on reporting of pregnancies.

10.3.8.2. 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 Section 10.3.5) will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

10.3.8.2.1. 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 recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. 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 Adverse Events Form and/or corresponding Expedited Adverse Event Form 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.

10.3.8.2.3. 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 Adverse Events Form and/or corresponding Expedited Adverse Event Form 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, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to GSK as described in Section 10.3.10.

10.3.8.3. 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 or mailed to the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK VCSP department within the defined reporting timeframes specified in Table 29).

10.3.9. Assessment of Intensity and Toxicity

10.3.9.1. Assessment of Intensity

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

Table 47 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)
Fatigue Headache Myalgia Arthralgia	0	None
	1	Mild: symptom that is easily tolerated
	2	Moderate: symptom that interferes with normal activity
	3	Severe: symptom that prevents normal activity

*Refer to the SoA (Table 1 and Table 2) 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 48). Where applicable, the assessment will be based on the investigator's clinical judgement.

Table 48 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.
*I.e., when an invasive action to solve a certain condition (e.g., surgery, endoscopy, colonoscopy, paracentesis) or the administration of a corrective therapy is needed.

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 one of the predefined outcomes as described in Section 10.3.2.

10.3.9.2. Assessment of Causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement. 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 to assist in making his/her 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 procedure not required by the Protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (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 Adverse Events Form and corresponding Expedited Adverse Event Form to GSK.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically Attended Visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if he/she received medical attention (defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eDiary.

10.3.9.4. Assessment of Outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

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

10.3.10. Reporting of SAEs, pIMDs, Pregnancies, and Other Events

10.3.10.1. 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 Adverse Events Form and corresponding Expedited Adverse Event Form WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. These forms must be completed as thoroughly as possible, with all available details of the event.

The Adverse Events Form and/or Expedited Adverse Event Form 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 29 for the details on timeframes for reporting of SAEs/pIMDs/pregnancies.

The investigator will be required to confirm the review of SAE causality within 72 hours of submission of the SAE.

Refer to Section 10.3.10.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.10.2. 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 the Sponsor Information) or to GSK's VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Adverse Events Form and corresponding Expedited Adverse Event Form 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 woman with ONE of the following:
  - Documented hysterectomy,
  - Documented bilateral salpingectomy, or,
  - Documented bilateral oophorectomy.

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

- Postmenopausal woman.

  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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Women 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

Women 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 49).

Table 49 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent*
Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only (or progestin-only) hormonal contraception associated with inhibition of ovulation • Injectable • Oral (only if allowed by local regulations or if part of standard medical practice in the country)
Highly Effective Methods That Are User-Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal ligation or occlusion
Vasectomised partner *A vasectomised 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 sterilisation 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

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. Refer to Sections 8.3.1, 8.3.2, 10.3.8.1, 10.3.8.2 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

10.5. Appendix 5: Genetics

Use and analysis of genetic samples

Genetic variation may impact a person's response to a study intervention. Variable response to the study intervention administration may be due to genetic determinants that impact the immune response. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome.

Pending the outcome of primary and secondary objectives of the study, ribonucleic acid (RNA) samples will be analysed for study intervention-specific gene expression. Study intervention platform development, study intervention development and/or research on HSV and related diseases may be investigated. The samples may also be used to develop tests/assays including diagnostic tests related to this research. Additional RNA/DNA analyses may be conducted if it is hypothesised that this may help further understand the clinical data.

Samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to the study interventions or study treatments of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.

The Sponsor will store the genetic samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained no longer than 20 years after the LSLV or other period as per local requirements.

10.6. Appendix 6: Country-specific Requirements

Requirements for EU countries

The sponsor will provide written summaries of the status of the study, information on SAEs or other significant safety findings to the agency in accordance with regulatory requirements.

Requirements for Germany

EXPLANATORY STATEMENT CONCERNING SEX DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

There is no intention to conduct specific analyses investigating the relationship between the sex of the participants and the efficacy, immunogenicity or safety of the GSK's HSVTI gE-gI/AS01. The ratio of male to female participants recruited into the TH HSV REC-003 study is expected to be in line with the demographics of the population infected with HSV-2 and aged 18 to 60 years in the Member State.

Requirements for US

The legal age in some specific US states is above 19 years of age. Therefore, in addition to the ICF, an assent form for these states will be developed and the signature process will be managed by the impacted sites.

Requirements for UK

If the Sponsor decides that the study intervention administration can be resumed after a hold was put in place, this decision will be communicated by substantial amendment to the Competent Authorities (MHRA), as applicable by national regulation.

10.7. Appendix 7: Abbreviations and Glossary of Terms

10.7.1. List of Abbreviations

AE: Adverse Event

ALT: Alanine aminotransferase

ANOVA: Analysis Of Variance

App: Application

AS01: An Adjuvant System containing MPL, QS-21 and liposomes

AS01$_B$: An Adjuvant System containing MPL, QS-21 and liposomes (50 µg MPL and 50 µg QS-21)

AS01$_E$: An Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)

AST: Aspartate aminotransferase

CCI [redacted]

CI: Confidence Interval

CMI: Cell-Mediated Immunity

COVID-19: Coronavirus disease 2019

CSL: Clinical Sciences Lead

CSR: Clinical Study Report

eCRF: electronic Case Report Form

eDiary: electronic Diary

ES: Exposed Set

EoS: End of Study

FDA: Food and Drug Administration, US

FSH: Follicle-Stimulating Hormone

GCP: Good Clinical Practice

CCI [redacted]

GMC: Geometric Mean Concentration

GSB: Global Safety Board

GSK: GlaxoSmithKline

HCP: Healthcare professional

HIV: Human Immunodeficiency Virus

CCI [redacted]

HRP: Horseradish peroxidase

HSC: Herpes Symptoms Checklist

HSVTI: Herpes Simplex Virus-Targeted Immunotherapy

HSV: Herpes Simplex Virus

IB: Investigator's Brochure

ICF: Informed Consent Form

ICH: International Council for Harmonisation

IEC: Independent Ethics Committee

IgG: Immunoglobulin G

IRB: Institutional Review Board

iSRC: Internal Safety Review Committee

LML: Local Medical Lead

LSLV: Last Subject Last Visit

MAE: Medically Attended Event

CCI [redacted]

PBMC: Peripheral Blood Mononuclear Cell

pIMD: potential Immune-Mediated Disease

PPS: Per-Protocol Set

qPCR: quantitative Polymerase Chain Reaction

QS-21: *Quillaja Saponaria* Molina, fraction 21 (licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

QTL: Quality Tolerance Limit

RGH: Recurrent Genital Herpes

CCI [redacted]

SAE: Serious Adverse Event

SAP: Statistical Analysis Plan

SBIR: Source data Base for Internet Randomisation

SD: Standard Deviation

SPM: Study Procedures Manual

SRT: Safety Review Team

SUSAR: Suspected Unexpected Serious Adverse Reaction

CCI [redacted]

US: United States

UWWB: Western Blot from the University of Washington

VCSP: Vaccines Clinical Safety and Pharmacovigilance

10.7.2. Glossary of Terms

Adverse Drug Reaction (ADR)

An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

a. In the context of a clinical study, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition).

b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.

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 unfavourable 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 one 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 SAE. 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. In a single-blind study, the investigator and/or their staff are aware of the intervention assignment but the participant is not.

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.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical study. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
eDiary:	Term used throughout the Protocol to refer to the reporting tools used in this study by the participant to collect data (see Section 8.2.1.10). These tools can be either an app that the participant has downloaded on their mobile phone or an electronic device provided by the study staff.
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. In this study, participants are enrolled when they are randomised or receive a study intervention (see Section 9.2).
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical studies.
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:	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 vaccine/product: (synonym: Investigational Medicinal Product)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including a product already with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about an authorised use.
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: (synonym: subject)	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).
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Pharmacogenomics and Pharmacogenetics:	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.

Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
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 administrative change:	A Protocol administrative change addresses changes to only logistical or administrative aspects of the study.
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.
Randomisation:	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.
Re-screening:	Process which allows a potential eligible participant to have all screening procedures as detailed in the Protocol performed again (except for the twice daily anogenital swabbing for participants in PART II), should the study be put on hold while the participant is in the screening process, and the timing to conduct the first study intervention administration at Visit 1 (Day 1) would exceed the predefined interval. Only one re-screening is allowed per participant.
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).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
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 one 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, study intervention administration schedule, etc.) at the time of enrolment.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	In a clinical study, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All ADRs that are both serious and unexpected are subject to expedited reporting.
Telemedicine:	Telemedicine refers to the use of information technologies and electronic communications to provide clinical services to patients virtually. The digital transmission of medical imaging, virtual medical diagnosis and evaluations, and video consultations with specialists are all examples of telemedicine.

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 AE.
Virtual contact:	This term refers to study visits conducted using multimedia or technological platforms.

10.8. Appendix 8: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 7	18 Sep 2024
Amendment 6	05 October 2023
Amendment 5	28 August 2023
Amendment 4	20 June 2023
Amendment 3	20 October 2022
Amendment 2	9 August 2022
Amendment 1	7 January 2022
Original Protocol	22 September 2021

Detailed description of the current Protocol Amendment:

Cover page, Sponsor Signatory Approval, and Investigator Agreement pages

EU CT number: 2024-510571-37-00

Section 1.3. Schedule of Activities

[…]

Only for PART II: Visit 6 (Day 71), Visit 7 (Day 181), Visit 9 (Day ***299*** ~~366), and Visit 12 (Day 731)~~ ***Visit 10 (Day 394)*** can be replaced by a virtual contact, at the investigator's discretion. ***Visit 10 can be conducted remotely only provided that the ICF addendum has been discussed and signed during a previous on-site visit, at the investigator's discretion*** (see Section 8).

Section 1.3.2.1. Activities to be Performed by Study Staff

Table 2 Shedding Sub-cohort: Activities to be Performed by Study Staff

Type of Contact		Follow-up Phase									
	V6	V7	V8	~~C1~~ V9[15]	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Obtain informed consent (see Section 10.1.3)[11]											
[…]											
Perform physical examination (see Section 8.2.1.8)	○[6]	○[6]	○[6]	○[6]	~~○[6]~~	○[6]		~~○~~		~~○[6]~~	~~○~~
[…]											
Blood sampling for antibody determination (humoral immunogenicity) analysis (~8.5 mL) (see Section 8.1.1)			●[12]			●[12]		●[12]			●[12]
Blood sampling (PBMCs) for CMI response analysis (~30.0 mL) (see Section 8.1.1)			●[12]			●[12]		●[12]			●[12]
Blood sampling (PBMCs) for CCI analysis (~45.0 mL) (see Section 8.1.1)[7]						●[12]					
Blood sampling for exploratory humoral response testing (~34.0 mL) (see Section 8.1.1)			●[12]			●[12]		●[12]			●[12]
Check participant's device compatibility with the app for collecting study information (see Section 8.2.1.10.1)	○	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
Download the eDiary app or distribution of electronic device (see Section 8.2.1.10.2)											
Train participant on the use of eDiary and provide a refresher training if needed (see Section 8.2.1.10.2)	○	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
Lesion swab collection procedure explained to the participant (see Section 8.2.1.7)											
Anogenital swab collection procedure explained to the participant (see Section 8.2.1.7)		○[9]			~~○~~					~~○~~	
Distribution of materials for lesion swabbing (see Section 8.2.1.7)											
Distribution of materials for anogenital swabbing (see Section 8.2.1.7)		○[9]			~~○~~					~~○~~	
Demo anogenital swab collected by the study staff (see Section 8.2.1.7)		○[5, 9]			~~○[5]~~					~~○[5]~~	
First anogenital swab collected by the participant on site (see Section 8.2.1.7)		●[6, 9]			~~●[6]~~					~~●[6]~~	
Return of the collected anogenital swabs (see Section 8.1.1.2)	●		●[9]			●[9]					●[9]
Record the date since when participant has stopped reporting RGH episodes, when applicable		●[10]	●[10]	●[10]		●[10]					
Check if the participant has enough materials for the anogenital and lesion swabbing, as needed	○	○[9]	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
Return of eDiary device or deletion of the app (see Section 8.2.1.11)			○[13]	○[13]	○[13]	○[13]					~~○~~

Type of Contact		Follow-up Phase									
	V6	V7	V8	~~C1~~ V9[15]	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Record concomitant medications/vaccinations (see Section 6.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Record use of any antivirals (see Section 6.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Record any intercurrent medical conditions (see Section 9.2.1)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Review of eDiary data via the web portal, ***as applicable*** (see Section 10.3.8)	○	○	○	○	~~○~~	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~
[…]											
Recording of MAEs (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of SAEs (all) (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of pIMDs (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
~~Recording of SAEs and pIMDs (fatal and related) (see Section 10.3.8)~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Recording of pregnancies (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Study conclusion (see Section 4.4)						●[14]					~~●~~

[…]

[9] Participants may voluntarily participate in the third swabbing period.

[10] As of Protocol Amendment 7 implementation, investigators should record in eCRF the date since when a participant has stopped the reporting of RGH episodes.

[11] The investigator or study staff will contact each participant to discuss the ICF addendum associated with Protocol Amendment 7 as soon as effective. The date of contact should be record in the source document and in the eCRF. The date of ICF addendum signature is to be encoded in the eCRF. This signature must be obtained during the next on-site visit following the approval of the ICF addendum.

[12] On a voluntary basis as of Protocol Amendment 7 implementation.

[13] eDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.

[14] If a participant will have already completed their Visit 10 (Day 394) by the time Protocol Amendment 7 is effective, they will be contacted and instructed by the study staff to come back to the site to sign the ICF addendum related to this amendment.

[15] At Day 299, a phone contact is applicable for sites where Protocol Amendment 7 is not yet implemented; a site visit or virtual contact is applicable for sites where Protocol Amendment 7 is implemented.

Table 3 Non-Shedding Sub-cohort: Activities to be Performed by Study Staff

Type of Contact		Follow-up Phase									
	V6	V7	V8	~~C1~~ V9[11]	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Obtain informed consent (see Section 10.1.3)[7]											
[…]											
Perform physical examination (see Section 8.2.1.8)	○[4]	○[4]	○[4]	○[4]	~~○~~[4]	○[4]		~~○~~		~~○~~[4]	~~○~~
[…]											
Blood sampling for antibody determination (humoral immunogenicity) analysis (~8.5 mL) (see Section 8.1.1)			●[8]			~~●~~		~~●~~			~~●~~
Blood sampling for exploratory humoral response testing (~34.0 mL) (see Section 8.1.1)			●[8]			~~●~~		~~●~~			~~●~~
Check participant's device compatibility with the app for collecting study information (see Section 8.2.1.10.1)	○	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
Download the eDiary app or distribution of electronic device (see Section 8.2.1.10.2)											
Train participant on the use of eDiary and provide a refresher training if needed (see Section 8.2.1.10.2)	○	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
[…]											
Record the date since when participant has stopped reporting RGH episodes, when applicable		●[6]	●[6]		●[6]	●[6]					
Check if the participant has enough materials for the anogenital and lesion swabbing, as needed	○	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~	
Return of eDiary device or deletion of the app (see Section 8.2.1.11)		○[9]	○[9]	○[9]		○[9]					~~○~~
Record concomitant medications/vaccinations (see Section 6.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Record use of any antivirals (see Section 6.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Record any intercurrent medical conditions (see Section 9.2.1)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Review of eDiary data via the web portal, ***as applicable*** (see Section 10.3.8)	○	○	○	○	~~○~~	○	~~○~~	~~○~~	~~○~~	~~○~~	~~○~~
[…]											
Recording of MAEs (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of SAEs (all) (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of pIMDs (see Section 10.3.8)	●	●	●	●	~~●~~	●					
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
~~Recording of SAEs and pIMDs (fatal and related) (see Section 10.3.8)~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Recording of AEs leading to withdrawal from the study (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~

Type of Contact		Follow-up Phase									
	V6	V7	V8	~~C1~~ V9[11]	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Recording of pregnancies (see Section 10.3.8)	●	●	●	●	~~●~~	●	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~
Study conclusion (see Section 4.4)						●[10]					~~●~~

[…]

[6] As of Protocol Amendment 7 implementation, investigators should record in eCRF the date since when a participant has stopped the reporting of RGH episodes.
[7] The investigator or study staff will contact each participant to discuss the ICF addendum associated with Protocol Amendment 7 as soon as effective. The date of contact should be record in the source document and in the eCRF. The date of ICF addendum signature is to be encoded in the eCRF. This signature must be obtained during the next on-site visit following the approval of the ICF addendum.
[8] On a voluntary basis as of Protocol Amendment 7 implementation.
[9] eDiary app must be deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.
[10] If a participant will have already completed their Visit 10 (Day 394) by the time Protocol Amendment 7 is effective, they will be contacted and instructed by the study staff to come back to the site to sign the ICF addendum related to this amendment.
[11] At Day 299, a phone contact is applicable for sites where Protocol Amendment 7 is not yet implemented; a site visit or virtual contact is applicable for sites where Protocol Amendment 7 is implemented.

Table 4 Activities to be Performed by Study Staff During the Unscheduled Visit (Planned in Case of Genital Herpes Recurrence) ***until end of RGH event reporting period***

[…]

Section 1.3.2.2. Activities to be Performed by the Participant

Table 5 Shedding Sub-cohort: Activities to be Performed by the Participant

Type of Contact	Screening			Study Intervention Administration Phase							Follow-up Phase										
	Scr	Baseline		V1	V2	V3	V4	-	V5	V6	V7	V8	C1 V9	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D -90	D -28	D -14	D1	D8	D29	D36	D43	D57	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Twice daily anogenital swabbing […]		From D-28** to D-1						From D43 to D70			From D181** to D208#			~~From D366** to D393~~					~~From D731** to D758~~	
Recording of the use of antivirals […]		Each time genital herpes symptoms/lesions are reported by the participant***																		
Recording of genital herpes recurrence information […]		Each time genital herpes symptoms/lesions are reported by the participant***																		
Completion of HSC […]		Once daily, each time genital herpes symptoms are reported by the participant***																		
Collection of lesion and anogenital […]		Once per new recurrence, when the participant reports the appearance of genital herpes lesions***																		
Return of the anogenital swabs […]			X	X					X	X		X#			~~X~~					X§
[…]																				
Return of eDiary […]			X	X	X	X	X		X	X	X	X^Δ	X^Δ	X^Δ			~~X~~		~~X~~	~~X~~

[…]

******As of Protocol Amendment 7 implementation, reporting of suspected RGH episodes and related procedures will be on a voluntary basis until Day 209 Visit.***

^Δ eDiary app must deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.

 # As of Protocol Amendment 7 implementation, participants may voluntarily participate in the third swabbing period.

§ Not required as of Protocol Amendment 7 implementation.

Table 6 Non-Shedding Sub-cohort: Activities to be Performed by the Participant

Type of Contact	Screening	Study Intervention Administration Phase							Follow-up Phase									
	Scr	V1	V2	V3	V4	-	V5	V6	V7	V8	~~C1~~ V9	~~V9~~	V10	~~C2~~	~~V11~~	~~C3~~	~~V12~~	~~V13~~
Timepoints	D -90	D1	D8	D29	D36	D43	D57	D71	D181	D209	D299	~~D366~~	D394	~~D484~~	~~D574~~	~~D664~~	~~D731~~	~~D759~~
Recording of the use of antivirals in eDiary (yes/no)		Each time genital herpes symptoms/lesions are reported by the participant*																
Recording of genital herpes recurrence information […]		Each time genital herpes symptoms/lesions are reported by the participant*																
Completion of HSC […]		Once daily, each time genital herpes symptoms are reported by the participant*																
Collection of lesion and anogenital swabs […]		Once per new recurrence, when the participant reports the appearance of genital herpes lesions*																
[…]																		
Return of eDiary […]			X	X	X		X	X	X	X**	X**	~~X~~	X**		~~X~~		~~X~~	~~X~~

[…]

As of Protocol Amendment 7 implementation, reporting of suspected RGH episodes and related procedures will be on a voluntary basis until Day 209 Visit.

****eDiary app must deactivated/device must be returned as soon as the participant decides to stop collecting suspected RGH episodes.***

Table 8 Intervals Between Study Visits for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Interval	Planned Visit Interval	Allowed Interval Range
[…]	[…]	[…]
~~Visit 3 (Day 29) → Visit 9 (Day 366)~~	~~337 days~~	~~330 – 344 days~~
Visit 3 (Day 29) → Visit 8 (Day 209)	***180 days***	***165 – 195 days******
Visit 7 (Day 181) → Visit 8 (Day 209)	28 days**	28** – 33 days***
Visit 3 (Day 29) → ~~Contact 1~~ ***Visit 9*** (Day 299)	270 days	~~263 – 277~~ ***256 – 284*** days
Visit ~~9~~ ***3*** (Day ~~366~~ ***29***) → Visit 10 (Day 394)	~~28 days**~~ ***365 days***	~~28** – 33 days***~~ ***337 – 393 days***
~~Visit 10 (Day 394) → Contact 2 (Day 484)~~	~~90 days~~	~~83 – 97 days~~
~~Visit 10 (Day 394) → Visit 11 (Day 574)~~	~~180 days~~	~~173 – 187 days***~~
~~Visit 11 (Day 574) → Contact 3 (Day 664)~~	~~90 days~~	~~83 – 97 days~~
~~Visit 11 (Day 574) → Visit 12 (Day 731)~~	~~157 days~~	~~150 – 164 days~~
~~Visit 12 (Day 731) → Visit 13 (Day 759)~~	~~28 days**~~	~~28** – 33 days***~~

Section 2.3.1. Risk Assessment

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

Important / … / Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Intervention (HSVTI)		
[…]	[…]	[…]
Potential immune-mediated diseases	pIMDs are a theoretical concern with adjuvanted study interventions [Tavares, 2013].	[…] ~~Only for PART II: pIMDs assessed as related to the study intervention and/or with a fatal outcome will be collected up to study end (Day 759)~~.

No new safety risks have been characterized for the HSVTI up to the proof-of-concept analysis conducted in August 2024.

Section 2.3.2. Benefit Assessment

[…]

Only for PART II: ***The primary analysis results failed to demonstrate the superiority of HSVTI over placebo in prolonging the time to first PCR-confirmed genital herpes event up to ~2 months of follow-up starting 14 days post-Dose 2. Therefore, the anticipated benefit was not demonstrated. Participants may gain information and medical advice on genital herpes management through the continuous monitoring of their genital herpes events and clinical evaluation in the study***. ~~After receiving the HSVTI, participants may potentially have fewer genital HSV recurrences. There could also be a potential effect on the severity and duration of possible recurrences. However, the efficacy of the study intervention has not been assessed yet in humans.~~ In addition, for participants included in the shedding sub-cohort, they may gain information […].

Section 2.3.3. Overall Benefit/Risk Assessment

The HSVTI is currently in ***Phase 2*** ~~a very early stage~~ of clinical development~~ and no efficacy has been demonstrated in humans~~. ***All participants have completed the HSVTI or placebo administration in this study***. ~~Considering the measures taken to minimise the risk to participants taking part in this study, the potential risks identified in association with the HSVTI are justified by the potential benefits linked to the development of the HSVTI~~.

Considering the lack of anticipated clinical efficacy but no observed additional safety risks up to the ~2-months of follow-up starting 14 days post-Dose 2, it is no longer justified for further follow-up until 2 years post-Dose 2 and withholding the chronic suppressive therapy. Participants may continue the monitoring of genital herpes events, viral shedding (for shedding sub-cohort only) and immune responses up to 6 months post-Dose 2 on a voluntary basis. To observe the long-term safety risk associated with HSVTI administration, participants will be monitored for 12 months post-last dose.

Section 3. Objectives, Endpoints, and Estimands

Table 9 Study Objectives, Endpoints, and Estimands

Objectives	Endpoints and Estimands
[…]	
Secondary	
Efficacy	
Only for PART II: To compare the HSVTI to placebo in terms of incidence rate of RGH episodes. […] ***Refer to Section 8.1.5 for the definition of end of RGH event reporting period.***	• Number of confirmed HSV-2 RGH episodes divided by the number of days of follow-up assessed until ~~study end (Day 759)~~ ***end of RGH event reporting period***.
Only for PART II: To compare the HSVTI to placebo in terms of percentage of RGH-free participants at 6~~, 12, 18, and 24~~ months after the last dose […].	• Percentage of participants free from confirmed HSV-2 RGH episode at 6~~, 12, 18, and 24~~ months after the last dose of study intervention.
Only for PART II: To compare the HSVTI to placebo in terms of severity of RGH episode-associated symptoms during each RGH episode. ***Refer to Section 8.1.5 for the definition of end of RGH event reporting period.***	• HSC total score during each confirmed HSV-2 RGH episode assessed until ~~study end (Day 759)~~ ***end of RGH event reporting period***.
Only for PART II: To compare the HSVTI to placebo in terms of duration of RGH episode-associated symptoms, as assessed by the participant. ***Refer to Section 8.1.5 for the definition of end of RGH event reporting period.***	• Number of days with RGH-associated symptoms during each confirmed HSV-2 RGH episode assessed until ~~study end (Day 759)~~ ***end of RGH event reporting period***.
Only for PART II: To evaluate the lesion rate after administration of the last dose of the HSVTI. […] ***Refer to Section 8.1.5 for the definition of end of RGH event reporting period.***	• Number of days with confirmed HSV-2 genital herpes lesions divided by the number of days of follow-up assessed until ~~study end (Day 759)~~ ***end of RGH event reporting period***.

Objectives	Endpoints and Estimands
Only for PART II (shedding sub-cohort): To evaluate the effect of the HSVTI, about 6 weeks~~, 6, 12, and 24 months~~ after the last dose of the HSVTI on shedding rate. Refer to Section 9.3.4.1 for the definitions of shedding rate reduction.	• HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to about 6 weeks post-Dose 2 (Day 71). • ~~HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to 6 months post-Dose 2 (Day 209).~~ • ~~HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to 12 months post-Dose 2 (Day 394).~~ • ~~HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to 24 months post-Dose 2 (Day 759).~~
Only for PART II (shedding sub-cohort): To evaluate the HSV shedding.	• Number and duration of HSV-2 DNA shedding episodes during the 28-day periods starting at baseline (Day -28), Day 43, Day 181~~, Day 366, and Day 731~~ (overall, asymptomatic and symptomatic).
Immunogenicity	
To evaluate the humoral immune response induced by the HSVTI.	• Only for PART I: […]. • Only for PART II: Anti-gE-gI antibody GMC and seropositivity rate […], and 1 month post Dose 2 (Day 57)~~, 6 months (Day 209), 12 months (Day 394), 18 months (Day 574) and 24 months (Day 759) post-Dose 2~~.
To evaluate the cellular immune response induced by the HSVTI.	• Only for PART I: […]. • Only for PART II: Geometric mean of gE-gI-specific CD4+/CD8+ T-cells frequency […], and 1 month post-Dose 2 (Day 57) ~~6 months (Day 209), 12 months (Day 394), 18 months (Day 574) and 24 months (Day 759) post-Dose 2~~.
~~**Safety**~~	
~~Only for PART II: To evaluate the long-term safety of the HSVTI.~~	• ~~Only for PART II: Percentage of participants reporting SAEs related to study intervention from Dose 1 (Day 1) up to study end (Day 759).~~ • ~~Only for PART II: Percentage of participants reporting fatal SAEs from Dose 1 (Day 1) up to study end (Day 759).~~ • ~~Only for PART II: Percentage of participants reporting pIMDs (classified as newly diagnosed or exacerbation of pre-existing events) related to study intervention from Dose 1 (Day 1) up to study end (Day 759).~~

Objectives	Endpoints and Estimands
Tertiary *(Note that tertiary objectives, endpoints, and estimands are optional and might be assessed only if needed; therefore, not all testings might be performed and reported)*	
CCI [redacted]	

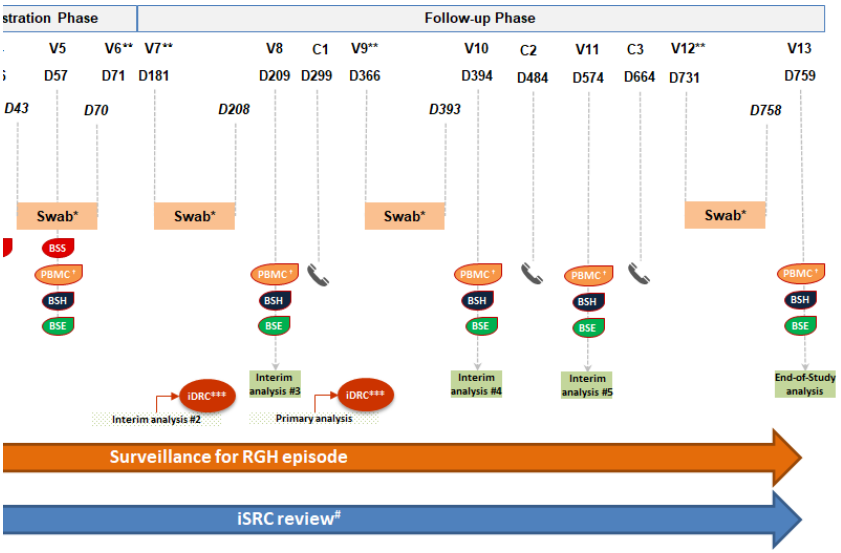
Section 4.1. Overall Design

[…]

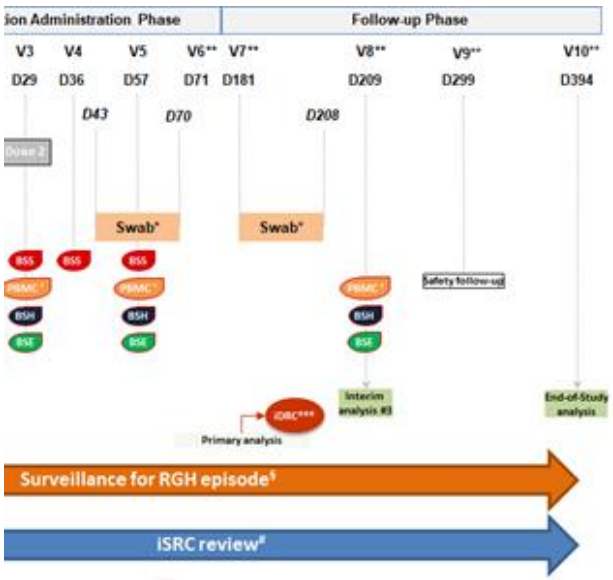
Day 394 of PART II ~~or the date on which the final data are available to trigger the primary clinical efficacy analysis (refer to Section 9.4.3), whichever occurs later,~~ will be considered as the Primary Completion Date.

Figure 2Study Design Overview of PART II for Participants in the Shedding Sub-cohort

Old figure



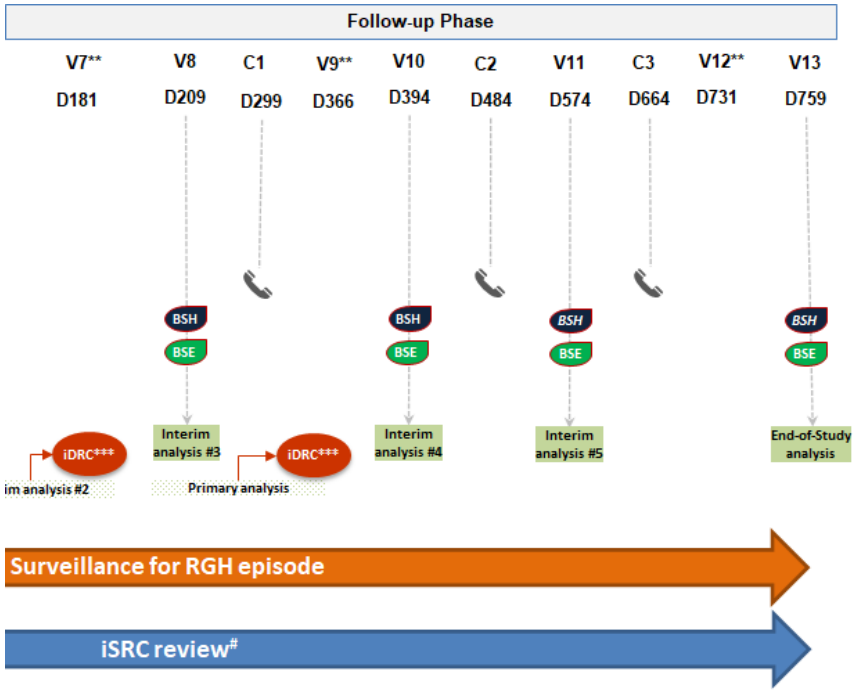
New figure



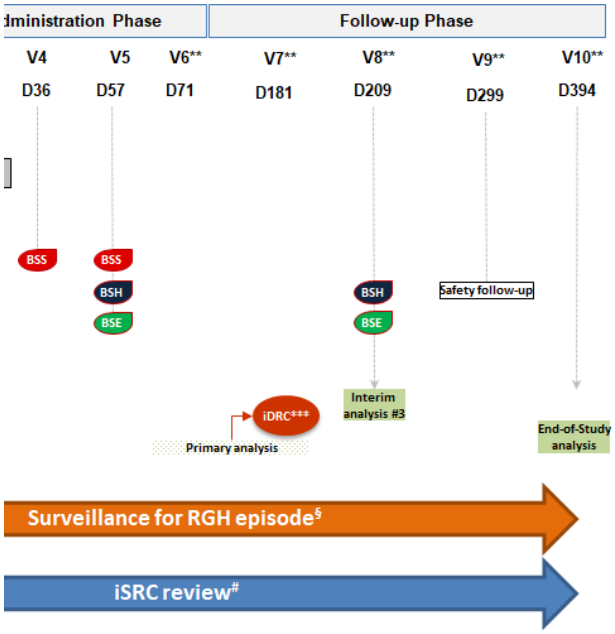
§ Refer to Section 8.1.5 for the definition of end of RGH event reporting period following Protocol Amendment 7 approval by relevant IECs/IRBs and Regulatory Authorities.

Figure 3Study Design Overview of PART II for Participants Not in the Shedding Sub-cohort

Old figure



New figure



§ Refer to Section 8.1.5 for the definition of end of RGH event reporting period following Protocol Amendment 7 approval by relevant IECs/IRBs and Regulatory Authorities.

Table 10 Study Groups, Intervention, and Blinding

PART II				
Study Groups	Number of Participants	Age (Min-Max)	Study Interventions	Blinding Visit 1 → Visit ~~13~~ *10* (Observer-blind)
[…]	[…]	[…]	[…]	X

Section 4.2. Scientific Rationale for Study Design

[…]

Randomisation is used to reduce bias of selection and the placebo group is included as a control ***in an observer-blinded manner to allow the discrimination of the HSVTI treatment effect*** for reactogenicity, safety, immunogenicity, and efficacy assessments ***while avoiding placebo effect*** ~~since there are currently no existing HSV immunotherapy that could be used as control~~. ***In the context of lack of efficacy, the study duration is shortened from 24 months to 12 months post-Dose 2 to allow the observation of safety risk beyond 1 month post-Dose 2. The blinding is remained till end of 12 months post-Dose 2 to minimise the potential confounding factors for safety signals and risk identification***.

Section 4.2.1. Participant Input Into Design

An epidemiological study (EPI-HSV-006 BOD TH) ~~is currently ongoing to confirm~~ ***has been completed to assess*** genital herpes recurrence rates and to assess […].

Section 4.4. End of Study Definition

[…] A participant of PART II is considered to have completed the study if he/she returns for the last visit (Visit ~~13~~ ***10*** [Day ~~759~~ ***394***]) as described in the Protocol.

The End of Study (EoS) is defined as the date of the ~~last testing released of the human biological samples, related to primary and secondary endpoints for PART I~~ and ~~PART II. The EoS must be achieved no later than 8 months after~~ Last Subject Last Visit (LSLV).

Section 5. Study Population

[…]

Note that the eligibility criteria defined below were those applied at the time of enrolment and were not updated in Protocol Amendment(s) developed after enrolment completion.

[…]

33. Only for PART II: Planned use of any episodic antiviral medications during the ~~5~~ swabbing periods (including the baseline period) (*only for the shedding sub-cohort*).

NOTE:

In case of genital herpes recurrence, up to 5 days of oral antiviral treatment are permitted (in accordance with a medical prescription), except during the ~~5~~ swabbing periods *(only for the shedding sub-cohort)* (*see bullet just above*)**.**

Section 6.8. Concomitant Therapy

[…]

- All concomitant medications leading to discontinuation of the study intervention or elimination from the analysis, […] until Day 394 ~~(PART I)/Day 759 (PART II)~~ (refer to Sections 5.2.2 and 9.2.1 for further details).
- […]
- ~~Only for PART II: All concomitant medications which may explain/cause/be used to treat an SAE/pIMD assessed as related to study intervention and/or with a fatal outcome, including vaccines/products, administered after the first dose of study intervention (Day 1) until Day 759 (refer to Sections 8.3.1 and 10.3.8).~~
- […]
- Only for PART II: All ***anti-herpetic antivirals (including the treatment for oral herpes, genital herpes, etc.) and*** concomitant medications ***other than anti-herpetic antivirals*** managing the recurrent genital herpes, ~~including but not limited to, anti-herpetic antivirals~~ administered during the baseline period (only for the shedding sub-cohort) and from Visit 1 (Day 1) until ***the end of RGH event reporting period*** ~~study end (Visit 13 [Day 759])~~.

NOTES:

- **Suppressive antiviral medications *and tenofovir (e.g., in case of pre-exposure prophylaxis to prevent HIV infection)* are ~~not~~ permitted *at the discretion of the investigator after acknowledgment of the unsuccessful primary analysis outcomes* ~~during the entire study period (from the Screening visit until study end [Visit 13/Day 759]).~~**
- **In case of genital herpes recurrences, the participant is allowed to take up […], except during the ~~5~~ swabbing periods *(only for the shedding sub-cohort)*.**
- […]

Table 15 Timeframes for Collecting and Reporting of Concomitant Medication(s)/Product(s)/Vaccine(s)

Event	Baseline					
	Day -28 to Day -1	Day 1	Day 29	Day 64	Day 394	~~Day 759~~
		Dose 1	Dose 2		*Study conclusion*	~~Study conclusion~~
All concomitant medications/vaccines/products leading to discontinuation of the study intervention or elimination from the analysis						
					~~PART II~~	
~~All concomitant medications/vaccines/products which may explain/cause/be used to treat an SAE/pIMD (related and/or fatal only)~~						
					~~PART I~~	
					~~PART II~~	
Only for PART II: All ***anti-herpetic antivirals and other*** medications managing the recurrent genital herpes						
					***	

[…]

****Until end of RGH reporting period.***

The ~~Local Medical Lead (LML)~~ ***Clinical Sciences Lead (CSL)*** should be contacted if there are any questions regarding concomitant or prior therapy.

Section 7.2. Participant Discontinuation/Withdrawal From the Study

[…]

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

- […],
- ***Acknowledgement of failure in primary efficacy analysis,***
- Other (specify).

Section 8. Study Assessments and Procedures

[…]

Only for PART II: Participants can be offered virtual contacts for Visit 6 [Day 71], Visit 7 [Day 181], ***Visit 8 [Day 209]***, Visit 9 ***[Day 299], and Visit 10 [Day 394]*** ~~[Day 366], and Visit 12 [Day 731]~~, ***when applicable, provided that the participant has reconsented on the ICF addendum during a previous on-site visit (see Section 10.1.3)*** […]. Contacts may be via telephone, video conference, telemedicine, or other means, depending on local best practice~~*~~. If the study site is the participant's primary healthcare facility, […].

~~*Note that the format will be the same for the study contacts (Contact 1, Contact 2, and Contact 3) planned at Day 299, Day 484, and Day 664, respectively.~~

Section 8.1.1.1. Blood Samples

Table 17 Biological Samples for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Sample Type	Quantity	Unit	Timepoint	Sub-cohort Name
[…]	[…]	[…]	[…]	[…]
Blood sample for antibody determination (humoral immunogenicity) analysis	Approximately 8.5	mL	Days 1, 29, 57, 209#, ~~394, 574 and 759~~	All participants
Blood sample (PBMCs) for CMI response analysis	Approximately 30.0	mL	Days 1, 29, 57, 209#, ~~394, 574 and 759~~	Shedding sub-cohort**
Blood sample (PBMCs) for […]	Approximately 45.0	mL	Days 1, 29, 57, ~~394~~	Shedding sub-cohort**
Blood sample for exploratory humoral response analysis	Approximately 34.0	mL	Days 1, 29, 57, 209#, ~~394, 574 and 759~~	All participants

[…]

#On a voluntary basis as of Protocol Amendment 7 implementation.

Note that by Protocol Amendment 7 implementation, only a few participants might have already completed Visit 10 (Day 394). Those blood samples may not be tested.

An overall blood volume of up to ~~346~~ ***218.5**** mL (or up to ~~736~~ ***473.5**** mL if part of the shedding sub-cohort and agreed to the optional blood sampling) will be collected […].

****If a participant does not opt for the optional blood sampling at Day 209, these volumes will be decreased to 176 mL and 401 mL, respectively.***

Section 8.1.1.2. Only for PART II: Anogenital Swabs (Shedding Sub-cohort)

[…]

Participants in the shedding sub-cohort will be instructed to self-collect anogenital swabs twice a day (i.e., one in the morning and one in the evening) for **28 consecutive days** (in order to have 56 swabs), during ~~5~~ ***3*** time periods:

- […]
- Period 3: Day 181 to Day 208 (***on a voluntary basis***);
- ~~Period 4: Day 366 to Day 393.~~
- ~~Period 5: Day 731 to Day 758.~~

  For swabbing period~~s~~ 3~~, 4 and 5~~, if the investigator thinks the participant needs to be retrained on the swabbing process, a demo swab can be collected […].
- ***By Protocol Amendment 7 implementation, only a few participants might have already completed Period 4 (Days 366 to 393). Those samples may not be tested.***
- […];

- ~~For period 4: At Visit 10 (Day 394).~~
- ~~For period 5: At Visit 13 (Day 759).~~

Section 8.1.3.2. For PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Table 23 Immunological Read-outs for PART II

Blood Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
Humoral Immunity			
[…] Visit 8 (Day 209)** ~~Visit 10 (Day 394)~~ ~~Visit 11 (Day 574)~~ ~~Visit 13 (Day 759)~~	All participants	~270	Anti-gE-gI
Cell-mediated Immunity			
[…] Visit 8 (Day 209)** ~~Visit 10 (Day 394)~~ ~~Visit 11 (Day 574)~~ ~~Visit 13 (Day 759)~~	Shedding sub-cohort*	~180	gE-gI-specific (CD4+/CD8+) T-cells

[…]
On a voluntary basis and might be tested for the tertiary objectives

Table 24 Read-outs for Molecular Biology Tests for PART II

Sampling Timepoint Type of Contact and Timepoint	Sub-cohort Name	Number of Participants	Component
[…] Day 181 to Day 208*,# ~~Day 366 to Day 393*~~ ~~Day 731 to Day 758*~~	Shedding sub-cohort	~180	HSV DNA
In case of genital herpes recurrence is suspected anytime as of Baseline Day -28 (shedding participants)/Day 1 (non-shedding participants) until ~~study end~~ ***the end of RGH event reporting period****	All participants with suspected genital herpes recurrences	-	HSV DNA β-globin gene

[…]
****Refer to Section 8.1.5.***
#***On a voluntary basis and might be tested for the tertiary objectives***

Section 8.1.5. For PART II Only: Procedures When a Genital Herpes Recurrence is Suspected

RGH event reporting period: As of baseline (from Baseline Day -28) (for the shedding sub-cohort)/as of Day 1 (for non-shedding sub-cohort) and until ***end of RGH event reporting period*** ~~study end (Day 759)~~.

The end of RGH event reporting period is defined as:

- ***Day 209 (for participants who have not yet completed Visit 8 [Day 209] at the time the ICF addendum (associated with Protocol Amendment 7) is signed <u>and</u> consented voluntary to RGH event reporting till Day 209); or***
- ***The date on which the participants decided to stop RGH reporting following the acknowledgement of the unsuccessful primary analysis outcomes before ICF addendum consent (associated with Protocol Amendment 7); or***
- ***The day the investigator deactivates the eDiary for participants who have continued RGH event reporting beyond Day 209 at the time the ICF addendum (associated with Protocol Amendment 7) is signed.***

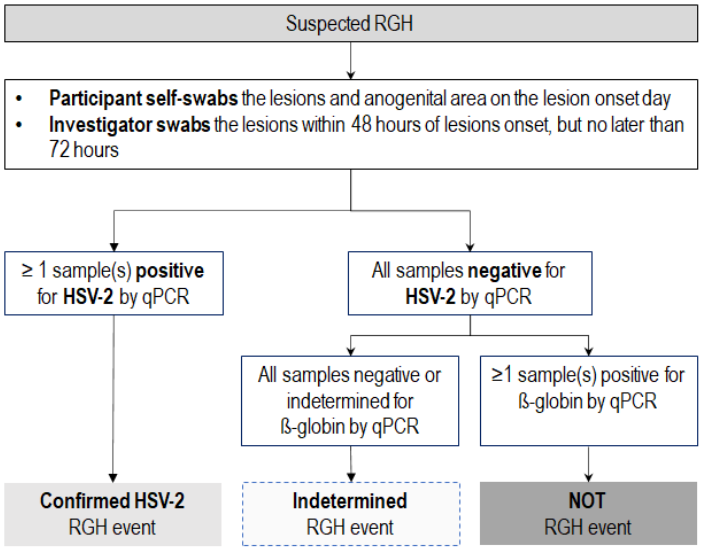
P~~p~~articipants will be asked to report the presence of genital herpes symptoms and genital herpes lesions, using the eDiary […].

<u>Section 8.1.5.1. Algorithm for Recurrent Genital Herpes Episode Determination</u>

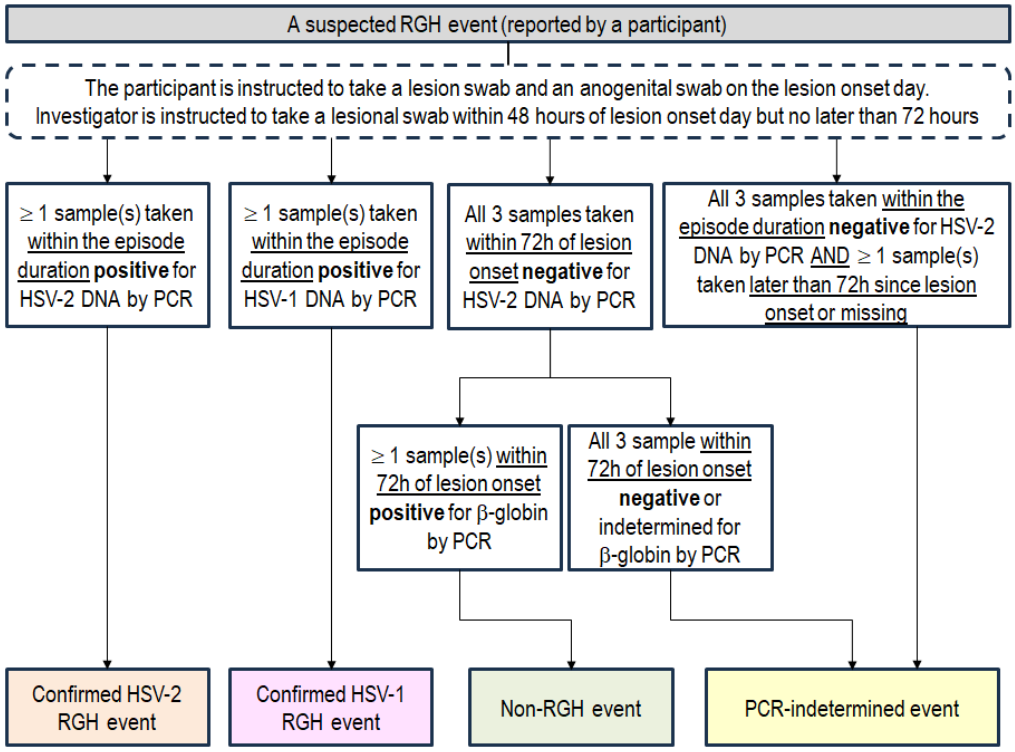
[…]

Figure 4Recurrent Genital Herpes Episode Determination Algorithm

Old figure:



New figure:



Section 8.2.1.1. Collection of Demographic Data

[…]

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

Section 8.2.1.10.2. Download the App or Distribution of Electronic Device and Train Participant on the Use of eDiary

[…]

Only for PART II:

- *For participants in the shedding sub-cohort*: Information on the anogenital swab collection performed during the ~~5~~ ***3*** time periods defined in Section 8.1.1.2.
- *For all participants*: Information related to any genital herpes signs and symptoms […] (other participants) until ***the end of RGH event reporting period*** ~~study end [Day 759]~~), including the use of antivirals […].

Section 8.2.1.11. Return of eDiary

[…]

At Visit 5 (Day 64) (PART I) or ***at the end of RGH event reporting period*** ~~study end (Visit 13 [Day 759])~~ (PART II), participants will ***deactivate the eDiary by*** either:

- […]

Section 8.3.1. Time Period and Frequency for Collecting AE, SAE and Other Safety Information

Table 28 Timeframes for Collecting and Reporting of Safety Information for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Event	[…]	Visit 5	Visit 10	~~Visit 13~~
	[…]	Day 57	Day 394	~~Day 759~~
	[…]	28 days post-Dose 2	***Study conclusion***	~~Study conclusion~~
SAEs pIMDs MAEs ***AEs/SAEs leading to withdrawal from the study***				
~~SAEs (fatal, related)~~ ~~pIMDs (fatal, related)~~ ~~AEs/SAEs leading to withdrawal from the study~~				

Section 8.3.3. Regulatory Reporting Requirements for SAEs, Pregnancies and Other Events

[…]

The sponsor will report SUSAR information to the relevant regulatory authorities (including Eudravigilance). The timelines for reporting SUSARs by the sponsor are:

- ***In the case of fatal or life-threatening SUSARs, within 7 calendar days after the sponsor became aware of the reaction;***
- ***In the case of non-fatal or non-life-threatening SUSARs, within 15 calendar days after the sponsor became aware of the reaction;***
- ***In the case of a SUSAR which was initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening, within 7 calendar days after the sponsor became aware of the reaction being fatal or life-threatening.***

Section 9.2. Analysis Sets

Table 33 Analysis Sets for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Analysis Set	Description
[…]	[…]
~~PPS for analysis of clinical efficacy (PPS_CE)~~	~~All participants from the ES:~~ ~~• Who received the study intervention according to their random assignment and the expected study intervention administration schedule,~~ ~~• With follow-up until at least the first recurrence post-Day 43 (i.e., 14 days post-Dose 2) or with follow up until at least 6 months post-Day 43 in the absence of any recurrence,~~ ~~• Who had no Protocol deviations during study intervention administration phase and follow-up period that lead to exclusion,~~ ~~• Who did not take any suppressive therapy during the follow-up period,~~ ~~• Who are determined to be HSV-2 seropositive by UWWB at either the Screening visit or Visit 1.~~
PPS for analysis of immunogenicity (PPS_I_P2)	All participants from the ES: • […] • Who are determined […] by UWWB ~~at either the Screening visit or Visit 1~~.
PPS for analysis of virological efficacy (PPS_VE)	All participants from the ES: • […] • ~~Who collected at least 45 out of 56 anogenital swabs in the given shedding period,~~ • ***Who had collected at least 45 anogenital swabs within the window of the given swabbing period.*** • […] • Who are determined […] by UWWB ~~at either the Screening visit or Visit 1~~.
PPS for analysis of CMI (PPS_CMI_P2)	All participants from the ES: • ***Who were part of the shedding sub-cohort,*** • […] • Who are determined […] by UWWB ~~at either the Screening visit or Visit 1~~.
mES for analysis of clinical efficacy (mES_CE)	All participants from the ES: • […] • ***Who were not under or did not switch to chronic suppressive therapy during the period from Dose 1 to 14 days post Dose 2***, • With at least 14 days of follow-up after Dose 2, • Who are determined […] by UWWB ~~at either the Screening visit or Visit 1~~.
mES for analysis of virological efficacy (mES_VE)	All participants from the ES: • […] • Who ~~collected~~ at least 45 ~~out of 56~~ anogenital swabs in the given shedding period. • ***Who had collected at least 45 anogenital swabs within the window of the given swabbing period,*** • Who are determined […] by UWWB ~~at either the Screening visit or Visit 1~~.

Section 9.2.2. Case Counting Rules for Primary Efficacy Analysis

In the main analysis based on mES_CE, a confirmed case will be counted when a participant experienced the first PCR-confirmed HSV-2 RGH event with the start day on or later than 14 days post-Dose 2.

~~RGH episodes will be counted as follows for the PPS_CE and the mES analyses:~~

- ~~The first suspected RGH episode will be counted as of 14 days post-Dose 2 for each participant. Participants not having experienced any episode will be censored at the time of last information.~~
- ~~The first confirmed HSV-2 RGH episode is the first suspected episode positive for HSV-2 by PCR.~~
- ~~The first indeterminate RGH episode is the first suspected episode negative for HSV-2 by PCR and β-globin by PCR.~~

~~RGH episodes will be counted as follows for the ES analysis:~~

- ~~RGH episodes will be counted as above, but the counting will start at randomization for each participant.~~

Section 9.3.2. Demography and Baseline Characteristics Analyses

[…]

- The number of participants enrolled into the study as well as the number of participants excluded from analysis set***s, i.e., modified exposed set (mES)*** and Per-Protocol Set (PPS) will be tabulated.

Section 9.3.3.2. Clinical Efficacy (Only for PART II)

The analysis of time-to-first confirmed RGH episode will be performed on the modified ES for clinical efficacy (mES_CE).

Statistical Analysis Methods
To evaluate time in days from Day 43 (i.e., 14 days post-Dose 2) to the first confirmed HSV-2 RGH episode, hazard ratios will be estimated using a Cox proportional hazards model. The model will be run separately for each comparison (i.e., HSVTI_***F1*** ~~group 1~~ vs. placebo group, and also HSVTI_***F2*** ~~group 2~~ vs. placebo group) and will be adjusted for sex (female vs. male) and number of RGH episodes in the 12 months before recruitment (< 6 episodes, ≥ 6 episodes). […] ~~The log rank test will be conducted to compare study groups in case of non-proportional hazards.~~ ~~As a sensitivity analysis, the time to first confirmed HSV-2 RGH episode analysis may be repeated on the PPS for clinical efficacy.~~ […].

Section 9.3.4.1. Efficacy (Only for PART II)

[…]

Statistical Analysis Methods
Number of positive HSV-2 swabs about 6 weeks after the last dose of the HSVTI will be estimated […]. The model will be run separately for each treatment group (i.e., HSVTI_***F1*** ~~group 1~~, HSVTI_***F2*** ~~group 2~~, and placebo group) and will be adjusted for sex (female vs. male), […]. The shedding rate* ratio (comparing shedding rates post-study intervention administration to shedding rates pre-study intervention administration) will be estimated by ~~taking the antilogarithm of~~ ***exponentiating*** the model coefficient for swabbing period and the shedding rate* reduction** will be derived from this ratio. **Shedding rate = number of HSV-2-positive swabs divided by number of swabs during the period.* ***Shedding rate reduction (%) = [1-(shedding rate about 6 weeks post-Dose 2 / baseline shedding rate)]*100.* The treatment effects (shedding rate reduction) and 90% confidence limits for the HSVTI group will be calculated by ~~taking the antilogarithm of~~ ***exponentiating*** the parameter estimates and their associated confidence limits. The null hypothesis will be rejected for the gE-gI/AS01 group if the 2-sided p-value is below 0.1. The above ~~will~~ ***may*** be repeated for the shedding rate reduction 6~~, 12 and 24~~ months after the last dose of the HSVTI (***tertiary endpoint***). Descriptive statistics […]. This analysis will be presented for all days and ~~broken down~~ ***split*** by symptomatic vs. asymptomatic days. ***Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration of shedding episodes will be displayed by treatment group and shedding period.*** ***Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration in days (i.e., number of days with RGH associated symptoms) of each genital herpes recurrence will be displayed by treatment group.*** The incidence rate of HSV-2 recurrences (i.e., number of confirmed HSV-2 RGH episodes divided by the number of days of follow up) ***as of 14 days post-Dose 2*** ~~from Day 1 to study end~~ will be estimated […]. The above model will also be repeated to estimate lesion rates (i.e., number of days with lesions detected ***during confirmed recurrences*** divided by the number of days of follow-up). ~~Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration of shedding episodes will be displayed by treatment group and shedding period.~~ Descriptive statistics (n, mean, SD, median, Q1, Q3) on the number of confirmed HSV-2 genital herpes lesions will be displayed by treatment group as of ~~28~~ ***14*** days post-Dose 2 study intervention administration ~~up to study end (Day 759)~~. Number and percentage of participants free from confirmed HSV-2 RGH episodes at 6, ~~12, 18, and 24~~ months after the last dose of study intervention will be displayed by study group with exact 95% CIs. ~~Descriptive statistics (n, mean, SD, median, Q1, Q3) on the number of suspected genital herpes recurrences from Day 1 up to study end (Day 759) will be displayed by treatment group.~~ ~~Descriptive statistics (n, mean, SD, median, Q1, Q3) on the duration in days (i.e., number of days with RGH associated symptoms) of each genital herpes recurrence) will be displayed by treatment group.~~ The frequency of participants experiencing genital herpes recurrences will be displayed by the maximum severity of each symptom as of ~~28~~ ***14*** days post-Dose 2 ***of the*** study intervention administration ~~up to study end (Day 759)~~. The categories will be 'Any severity', 'None', 'Mild', 'Moderate', 'Severe' and ~~'Missing'~~ ***'Unknown'***. […].

Section 9.3.4.3. Safety (Only for PART II)

~~In PART II, the analysis of the secondary safety objectives will be performed on the ES.~~

~~Statistical Analysis Methods~~
~~The percentage of participants with at least one report of causally related SAE and with at least one report of fatal SAE, classified by the MedDRA SOC and PTs reported from Dose 1 up to study end will be tabulated with exact 95% CI.~~ ~~The percentage of participants with at least one related pIMD classified by the MedDRA SOC and PTs and reported from Dose 1 up to study end will be split by newly diagnosed vs. exacerbation of pre-existing events and tabulated with exact 95% CI.~~

Section 9.4.3. Interim Analysis #2 (PART II)

[…]

Note that this analysis was combined with the primary analysis (see Section 9.4.4).

Section 9.4.4. Primary Analysis (PART II)

[…]

CCI [redacted]

Section 9.4.5. Interim Analysis #3 (PART II, 6 Months Post-Dose 2)

An interim analysis ~~of available and as clean as possible reactogenicity/safety (including safety laboratory data), virological efficacy (shedding), immunogenicity and clinical efficacy data~~ will be performed after ~~a minimum of 28 participants per group have completed their swabbing period #3 (Day 181 to Day 208)~~ ***(1) all participants have completed Visit 8 (Day 209), (2) all samples are received and tested, and (3) after Protocol Amendment 7 is implemented in all countries, based on all available and as clean as possible safety data and all cleaned and available clinical and virological efficacy, and immunogenicity data***. The purpose of this analysis is to report ***all safety and clinical efficacy data with at least 6 months of follow-up post-Dose 2. The virological efficacy and immunogenicity data*** ~~the shedding rate reduction from baseline~~ up to 6 months post-Dose 2 (Day 209) ***can be analysed for the tertiary objectives***.

- ~~All data up to 6 months post-Dose 2 study intervention administration (Day 209) will be cleaned. At this stage, the study will be unblinded. The purpose of this analysis is to provide long-term safety, immunogenicity and efficacy.~~
- ~~If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.~~

~~Section 9.4.6. Interim Analysis #4 (PART II, 12 Months Post-Dose 2)~~

~~An interim analysis of available and as clean as possible safety, immunogenicity, virological (shedding) and clinical efficacy data will be performed after all participants from PART II have completed their 12 months post-Dose 2 follow-up (Day 394). The purpose of this analysis is to assess safety, and 12-month sustained immunogenicity and efficacy.~~

~~Section 9.4.7. Interim Analysis #5 (PART II, 18 Months Post-Dose 2)~~

~~An interim analysis on all available and as clean as possible safety, immunogenicity, and clinical efficacy data will be performed when all participants from PART II have completed their 18 months post-Dose 2 follow-up (Day 574). The purpose of this analysis is to assess long-term safety, and 18-month sustained immunogenicity and efficacy.~~

Section 9.4.8. End-of-Study (EoS) Analysis (PART II)

- The EoS analysis ~~on safety, immunogenicity, virological (shedding) and clinical efficacy data from PART II~~ will be performed when all ***safety*** data up to

12 ~~24~~ months post-Dose 2 study intervention administration (Day ~~759~~ ***394***) are cleaned and available. At this stage, the study will be unblinded. The purpose of this analysis is to provide long-term safety~~, immunogenicity and efficacy~~ ***data***.

Section 10.1.3. Informed Consent Process

[…]

As of Protocol Amendment 7 implementation, participants will be requested to sign an ICF addendum which will provide them with details regarding the revised study design.

Section 10.1.4. Data Protection

[…]

GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

Section 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, EU register*** and/or GSK Clinical Study Register […].

Section 10.3.8.1. Time Period for Collecting and Recording AEs, SAEs, pIMDs, and Pregnancies

[…]

~~The time period for collecting and recording SAEs assessed as related to study intervention and/or with a fatal outcome will begin at the first receipt of study intervention (Day 1) and will end at Day 394 (PART I)/Day 759 (PART II).~~

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 Day 394 ~~(PART I)/Day 759 (PART II)~~.

[…]

~~The time period for collecting and recording pIMDs assessed as related to study intervention and/or with a fatal outcome will begin at the first receipt of study intervention (Day 1) and will end at Day 394 (PART I)/Day 759 (PART II).~~

The time period for collecting and recording pregnancies will begin at the first receipt of study intervention (Day 1) and will end at Day 394 ~~(PART I)/Day 759 (PART II)~~. See Section 10.3.10 for instructions on reporting of pregnancies.

Section 10.6.Appendix 6: Country-specific Requirements

Requirements for EU countries

The sponsor will provide written summaries of the status of the study, information on SAEs or other significant safety findings to the agency in accordance with regulatory requirements.

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