Statistical Analysis Plan Amendment 6

Study ID: 215336

Official Title of Study: 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

NCT number: NCT05298254

Date of Document: 17 April 2025

Note: The title page of the document records an incorrect NCT number. The correct NCT ID is NCT05298254 and is included in the cover letter

Information Type:	Statistical Analysis Plan for Part I of the study (SAP)

TITLE PAGE

Protocol Title:	A Phase I/II, observer-blind, randomised, placebo-controlled, multi-country study to evaluate reactogenicity, safety, immune response, and efficacy of an HSV vaccine in healthy participants aged 18-40 years or in participants aged 18-60 years with recurrent HSV-2 genital herpes
Study Number:	**215336**
Compound Number:	GSK3943104A
Abbreviated Title:	TH HSV REC-003

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	08 Mar 2022	Amendment 1 (07 Jan 2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses for PART I of TH HSV REC-003 (215336). Details of the planned interim analysis, as well as the final analyses for PART I are provided. There are separate SAPs for PART II and for the analyses of the internal Safety Review Committee (iSRC) that will oversee this study.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints and Estimands
Primary	
To evaluate the reactogenicity and safety of the vaccine candidate.	• 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 study end (Day 394). • Percentage of participants reporting SAEs from Dose 1 (Day 1) up to study end (Day 394). • Percentage of participants reporting pIMDs from Dose 1 (Day 1) up to study end (Day 394). • Percentage of participants reporting any haematological and biochemical laboratory abnormalities at pre-vaccination (Day 1), post-Dose 1 (Day 8 and Day 29), post-Dose 2 (Day 36 and Day 64).
Secondary	
To evaluate the humoral immune response induced by the vaccine candidate.	• Anti-gE-gI antibody GMC and seropositivity rate (assessed by ELISA) at pre-vaccination (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).
To evaluate the cellular immune response induced by the vaccine candidate.	• 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-vaccination (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).

Primary estimand

The primary clinical question of interest for PART I is to assess the reactogenicity and safety of the vaccine candidate among eligible participants who received at least one dose of the study product (i.e., the Exposed Set for all PART I [ES_P1]).

The estimand is described by the following attributes:

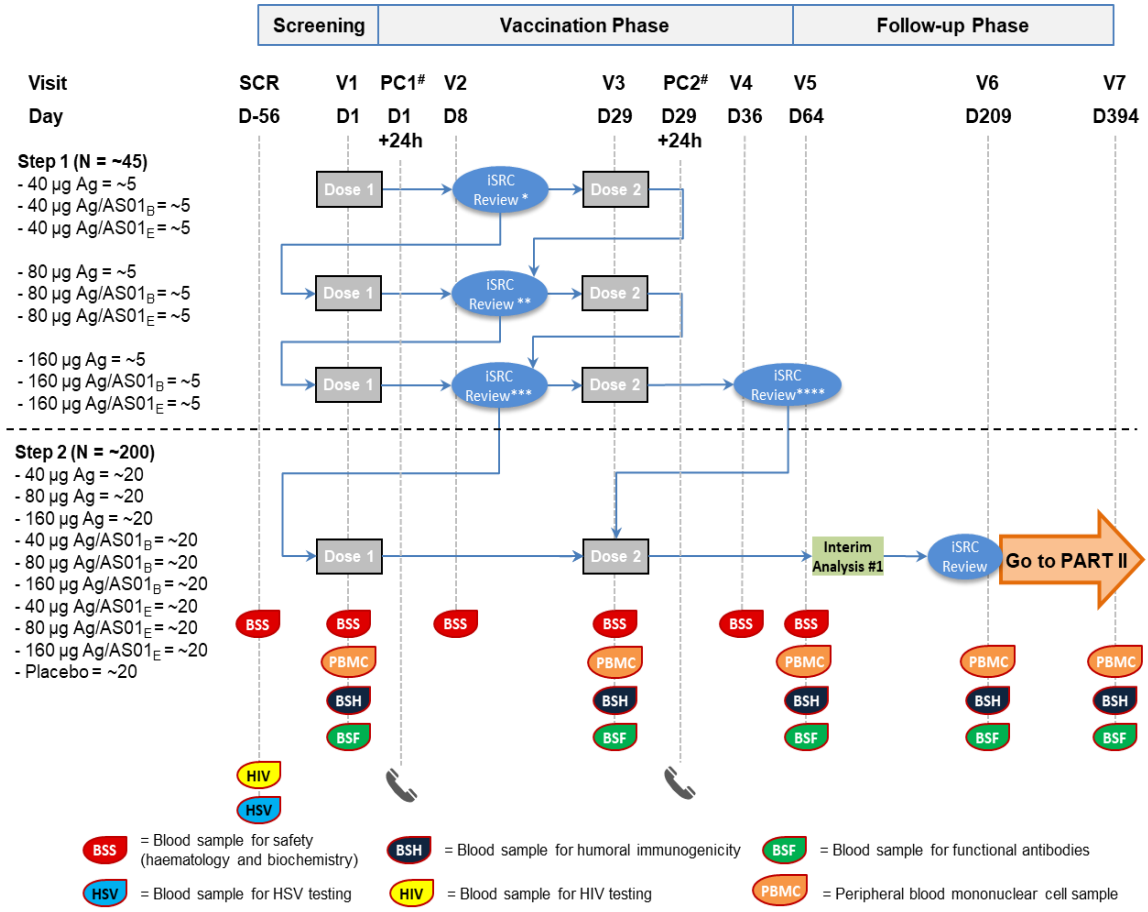
- Population: ES_P1.
- Treatment condition: 9 formulations of the vaccine candidate.
- Variable / endpoint: occurrence of events reported within protocol-defined safety follow-up period.
- Summary measure: percentage of participants reporting events within protocol-defined safety follow-up period.
- Intercurrent events: Study treatment discontinuation – treatment policy strategy

1.2. Study Design

The study will be conducted in 2 parts: PART I will be a 2-step design to assess the reactogenicity, safety, and immunogenicity of up to 9 formulations of the vaccine candidate (refer to Figure 1).

- In PART I, ~245 healthy participants aged 18 to 40 years will receive the vaccine candidate 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 $AS01_E$) glycoprotein E-glycoprotein I (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 iSRC evaluation. 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.
- At the time of the PART I Interim Analysis to be performed when all participants will have attended 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 .
- The safety, reactogenicity, and immunogenicity data from these 2 steps will allow selection of a vaccine candidate formulation for evaluation in the target population in PART II.

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



SCR = screening; **V** = visit; **D** = day; **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. 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 AS01B or AS01E) 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 AS01B or AS01E will be enrolled and vaccinated 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 AS01B or AS01E) 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 AS01B or AS01E will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first vaccine dose will receive their second vaccine dose and participants who will receive the 160 µg formulation non-adjuvanted or adjuvanted with either AS01B or AS01E will be enrolled and vaccinated with the first vaccine dose.

***An iSRC will occur as soon as all 15 participants (who received the 160 µg formulation non-adjuvanted or adjuvanted with either AS01B or AS01E) 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 AS01B or AS01E will be reviewed. If the outcome of the iSRC evaluation is favourable, participants who received the first vaccine dose will receive their second vaccine dose and participants of Step 2 will be enrolled and vaccinated with the first vaccine dose.

****An iSRC will occur as soon as all 15 participants (who received the 160 µg formulation non-adjuvanted or adjuvanted with either AS01B or AS01E) will have been followed-up for 7 days post-Dose 2. In addition, all available safety data of participants enrolled and vaccinated in Step 1 and in Step 2 (with the first vaccine dose) will be reviewed.

If the iSRC evaluation outcome is favourable, participants enrolled in Step 2 will be administered their second vaccine dose. No Dose 2 will be administered in Step 2 until all data from Step 1 (including post-Dose 2) are reviewed.

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses are to be tested in PART I.

2.1. Multiplicity Adjustment

No formal statistical hypotheses are to be tested. In general, test statistics will not be adjusted for multiple comparisons, except for an additional sensitivity analysis comparing pooled adjuvant and pooled antigen groups using Dunnett's test [Dunnett, 1955].

3. ANALYSIS SETS

Analysis Set	Definition / Criteria
Screened Set	All participants who signed the ICF.
Enrolled set	All participants who entered the study (i.e. who were randomised or received study intervention). Note: screening failures are excluded from the Enrolled set as they did not enter the study.
ES_P1	All participants of PART 1 with at least one study intervention administration documented i.e., ES_P1S1 and ES_P1S2.
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 humoral immunogenicity (PPS__HI__P1)	All participants from the ES: • Who received the study intervention according to their random assignment and the expected vaccination schedule, • With at least one post-vaccination humoral immunogenicity data available, • Who had no Protocol deviations during vaccination 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 vaccination schedule, • With at least one post-vaccination CMI data available, • Who had no Protocol deviations during vaccination phase that lead to exclusion.

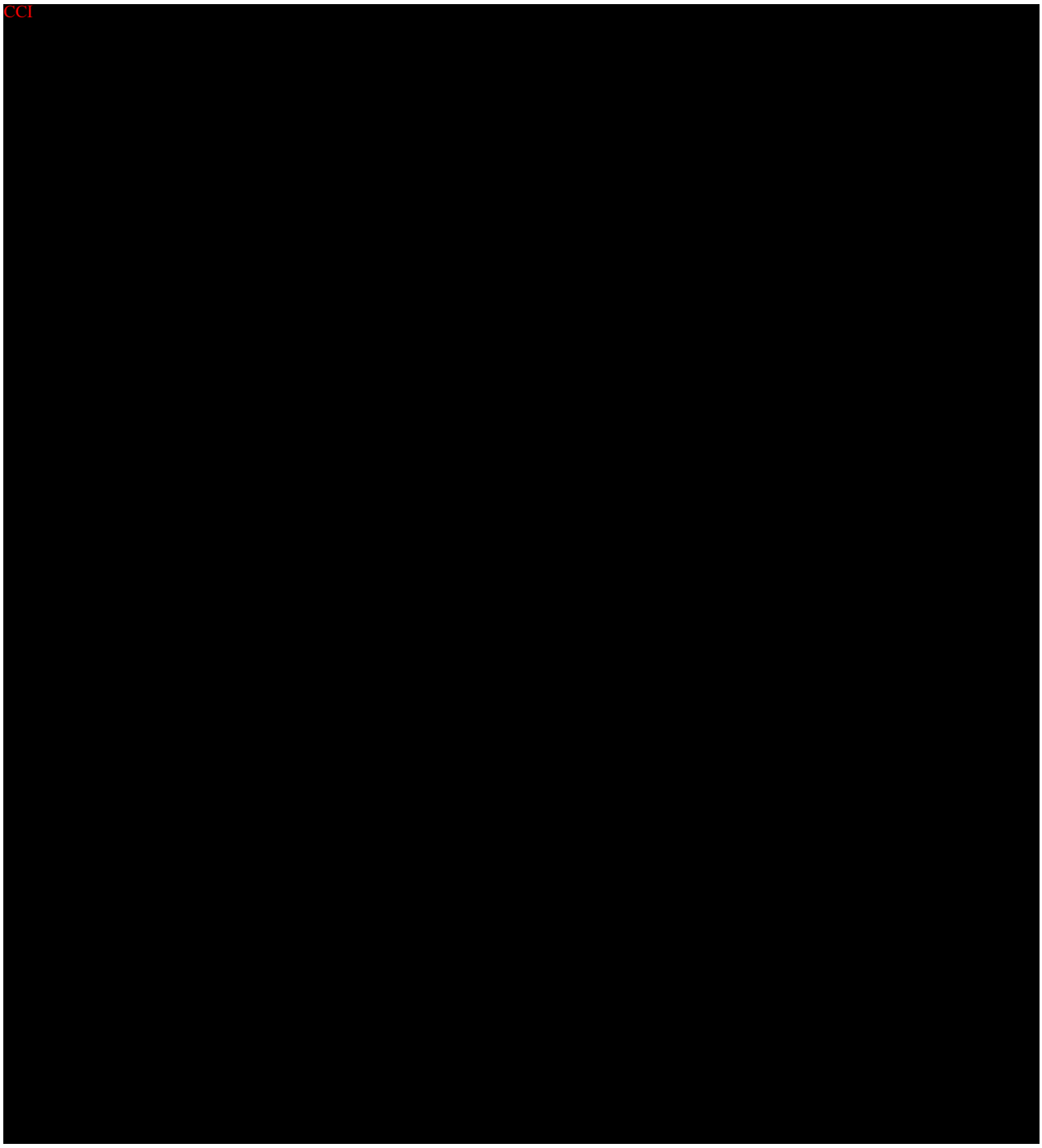
ES = Exposed Set; **PPS** = Per-Protocol Set

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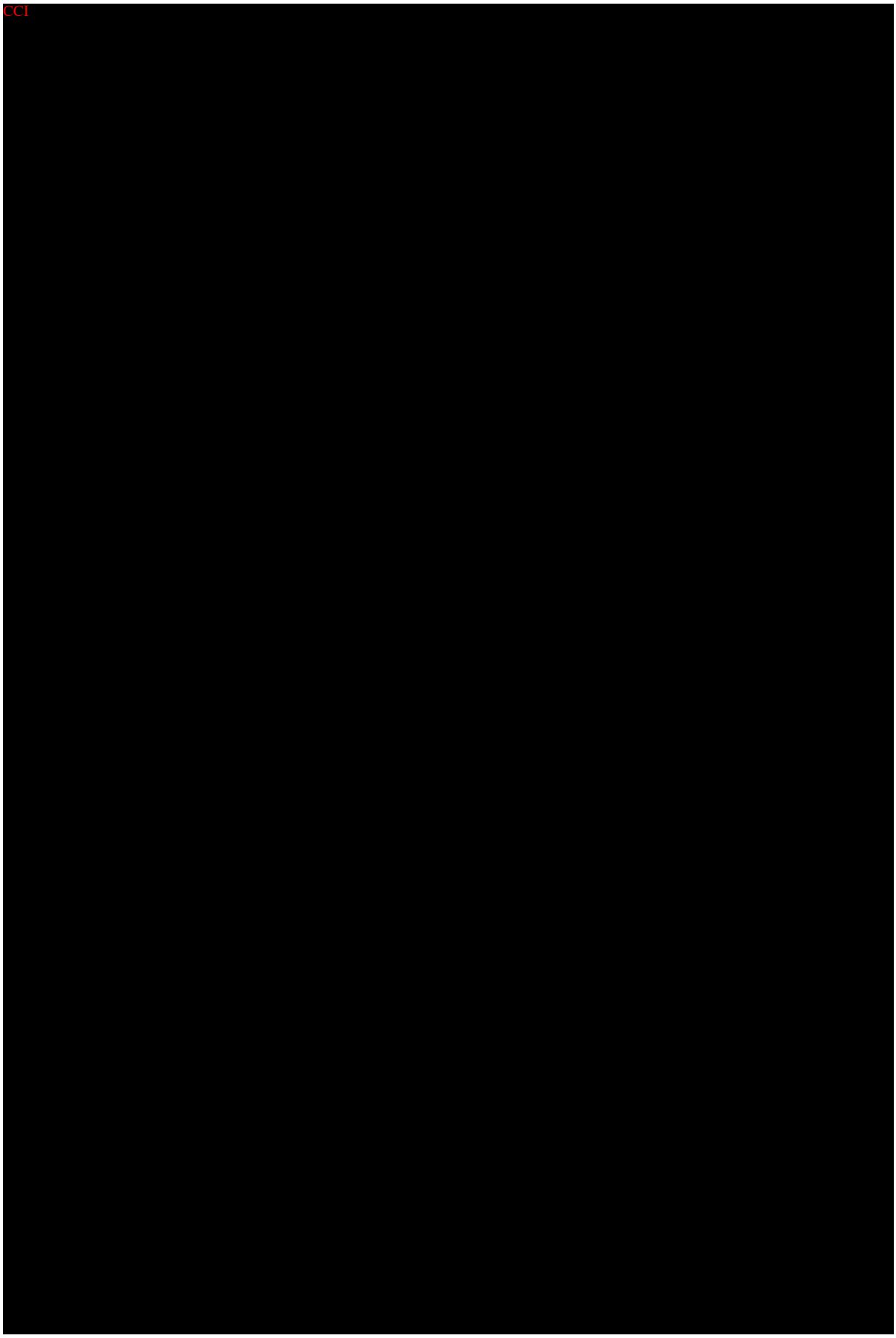
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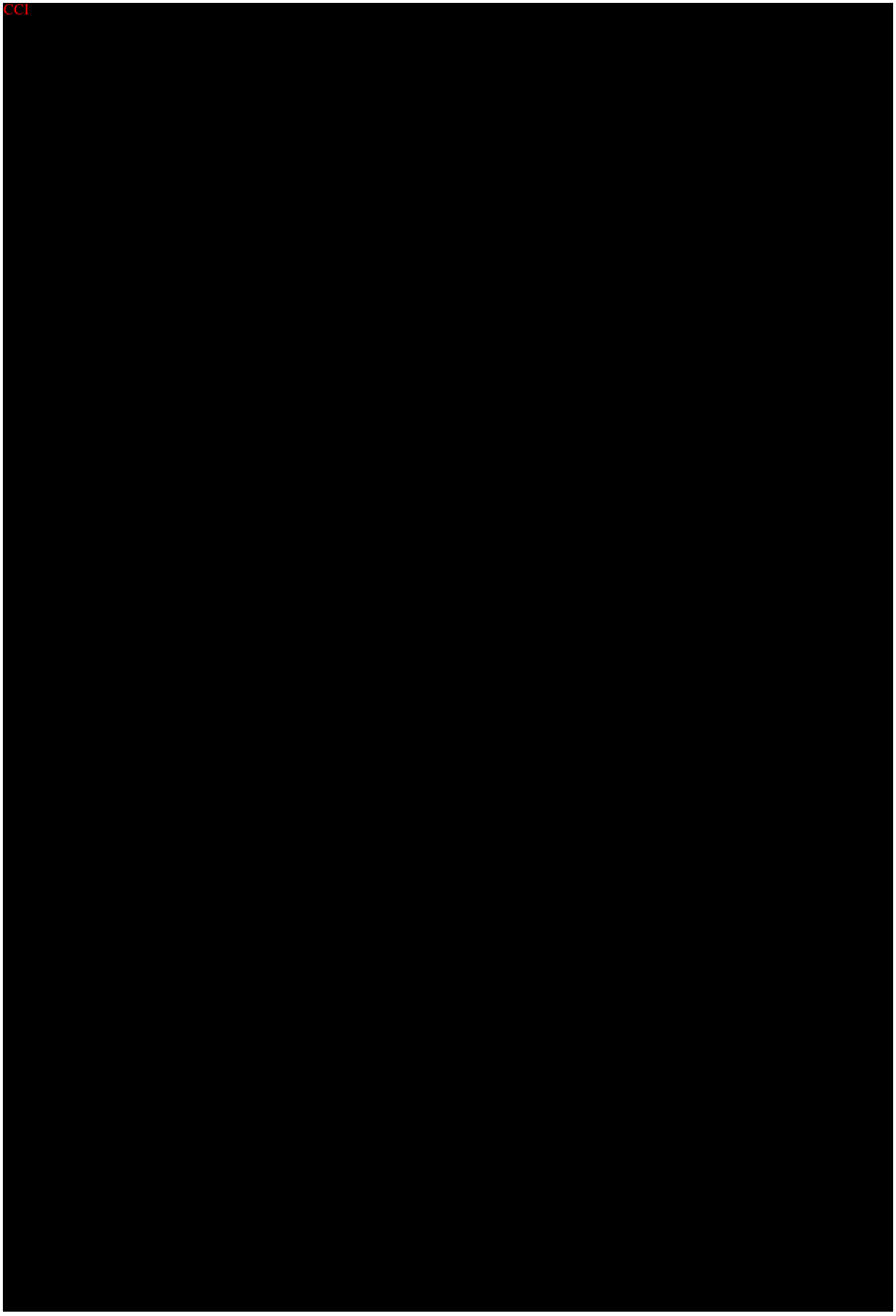
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4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Enrolled participants who prematurely withdraw from study will not be replaced.

In the case of the wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the electronic Case Report Form (eCRF).

Confidence intervals (CIs) will use 95% confidence levels, unless otherwise specified.

In general, CIs for proportions will be calculated using the Clopper-Pearson interval method [Clopper, 1934]. All continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum) and categorical data will be summarized using the number and percentage of participants in each category.

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4.2. Primary Endpoints Analyses

The primary endpoints will be based on the reactogenicity and safety objectives and will be performed on the ES_P1.

- The percentage of participants reporting at least one solicited adverse event (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. For solicited AEs, percentages will be computed based on the total number of solicited symptoms screens completed.
- The number and percentage of participants reporting each individual solicited AE during the 7-day follow up period post-vaccination (i.e., the day of vaccination and 6 subsequent days) will be tabulated with exact 95% CI and descriptive statistics for each group, after each dose and overall.
- The number and percentage of participants reporting each individual unsolicited AE during the 28-day follow up period post-vaccination (i.e., the day of vaccination and 27 subsequent days) will be tabulated with exact 95% CI by event category (e.g., all, grade 3, related, grade 3 related, SAEs, fatal etc.) with descriptive statistics for each group, after each dose and overall. 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 number and percentage of participants reporting each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 7-day follow-up period (i.e. the day of vaccination and 6 subsequent days) will be tabulated for each group, after each dose and overall. The number and percentage of doses that preceded each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 7-day follow-up period (i.e. the day of vaccination and 6 subsequent days) will be tabulated with exact 95% CI for each group, after each dose and overall.
- The number and percentage of participants with each solicited administration site event and separately, solicited systemic event (any grade and grade 3) within the 7-day follow up period will be represented graphically with a bar plot for each group and after each dose.

- The number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e. the day of vaccination and 6 subsequent days) will be tabulated for each group and after each dose.
- The duration of each individual solicited AE during the 7-day follow-up period will be tabulated using descriptive statistics (mean, minimum, Q1, median, Q3, maximum). The same computations will be done for Grade 3 solicited events. This analysis will be done for each group after each dose.
- The prevalence of each solicited AE by day during the 7-day follow up period will be presented graphically.
- The number and percentage of participants with any unsolicited AEs during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) will be tabulated with exact 95% CI by study group and categorized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (i.e. the table will be grouped by SOC and then preferred terms will be included within each group). 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 physician 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 preferred term. This will be done by group, after each dose and overall.
- The number of percentage of participants reporting each individual unsolicited AE during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) will be tabulated and ranked by MedDRA PT with the most common appearing first. This analysis will be done for each group after each dose.
- The number and percentage of participants with at least one solicited or unsolicited medically attended event (MAE) reported during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) and separately, any time between the day of vaccination (Day 1) and the end of the study period post vaccination (up to Day 394) will be classified by MedRA SOC and PT and tabulated with exact 95% CI. This analysis will be done by group and after each dose.
- The number and percentage of participants with at least one serious adverse event (SAE) reported during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) and separately, any time between the day of vaccination (Day 1) and the end of the study period post vaccination (up to Day 394) will be classified by MedRA SOC and PT and tabulated with exact 95% CI. This analysis will be done by group and after each dose. The same tabulation will be presented for causally related SAEs, fatal SAEs and causally related fatal SAEs.

- The number and percentage of participants with at least one potential immune-mediated disease (pIMD) (selection defined by GSK list of terms AND/OR investigator tick box) reported during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) and separately, any time between the day of vaccination (Day 1) and the end of the study period post-vaccination (up to Day 394) will be classified by MedRA SOC and PT and tabulated with exact 95% CI. This analysis will be done by group and after each dose. The same tabulation will be presented for causally related pIMDs.
- The number and percentage of participants reporting each individual pIMD, SAE, or MAE that occurred in the study up to the point of the DBF prior to the interim analysis will be tabulated and categorized by MedDRA SOC and preferred term with exact 95% CIs, after each dose and overall. Note: different groups and doses will have different amounts of follow up time.
- All SAEs/MAEs/pIMD will be described in detail in a tabular listing.
- All AEs/SAEs leading to study/intervention discontinuation from dose 1 up to study end will be tabulated and described in detail in a tabular listing.
- All participants taking concurrent medication/vaccines will be described in a detailed listing
- All SAEs related to study participation (not due to vaccination) will be described in detail in a tabular listing.
- The percentage of participants with any AEs (solicited and unsolicited) resulting in a medically attended visit from Dose 1 up to study end (Day 394) will also be tabulated after each dose and overall.
- For each group and for each haematology and biochemistry parameter:
  - Comparison of changes since baseline i.e., summary of absolute and relative differences for each parameter by timepoint, by group and after each dose will be tabulated with descriptive statistics.
  - The number and percentage of participants having haematology and biochemistry results below or above the central laboratory defined normal ranges will be tabulated with exact 95% CI by timepoint [pre-vaccination (Day1), post-dose 1 (Day 8 and Day 29), post-dose 2 (Day 36 and Day 64)]. This will be done for each group and overall.
  - The summary of grading post-study intervention administration will be tabulated vs. baseline. Grades will be based on the Food and Drug Administration (FDA) Guidance for Industry “Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”; see Section 10.2.2 of the protocol). The laboratory parameters not included on FDA Toxicity Grading Scale will not be graded.
- Compliance in completing solicited events information will be tabulated after each dose and overall.
- Pregnancy and pregnancy outcomes will be listed (if applicable).

- 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.
- Number and percentage of participants meeting each holding rule will be tabulated with exact 95% CI. This analysis will be done by group and after each dose. Furthermore, it will done separately by step 1, step 2 and all part I (step 1 and step 2 combined).
- To examine the generalizability of results, key safety endpoints (specified below) will also be calculated by HSV-1 status at baseline (only if at least 20% of the included subjects are in each HSV-1 strata i.e., ≥20% positive and ≥20% negative) and sex (only if at least 30% of the included subjects are in each sex strata):
  - The number and percentage of participants reporting each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 7-day follow-up period (i.e. the day of vaccination and 6 subsequent days) will be tabulated with exact 95% CI for each group after each dose and overall.
  - The number and percentage of participants with any unsolicited AEs during the 28-day follow-up period (i.e. the day of vaccination and 27 subsequent days) will be tabulated with its exact 95% CI by group after each dose and overall and by MedDRA SOC and PT.

4.3. Secondary Endpoints Analyses

The analysis of the secondary objective on humoral immune response will be performed on the PPS for analysis of immunogenicity (PPS_HI_P1). The analysis of the secondary objective on cellular immune response will be performed on the PPS for analysis of CMI (PPS_CMI_P1). Step 1 and Step 2 data will also be combined for this portion of the analysis. No alpha adjustment is planned for the interim analyses.

4.3.1. Within group evaluation

4.3.1.1. Humoral immune response

4.3.1.1.1. Analytical Approach

The within-group evaluation will derive unadjusted Geometric Mean Concentrations (GMCs) based on the anti-log of the mean of anti-gE-gI concentrations.

Geometric mean fold increase will be calculated by dividing the post-vaccination anti-gE-gI concentrations of individuals at a given time point by the pre-vaccination concentrations and then taking the geometric mean of all individual fold increases.

Note: Unless otherwise specified, results below the cut-off of the assay at baseline will be replaced by half the value of the cut-off.

95% CIs for GMCs will be based on a back-transformation of student CIs for the mean log-transformed anti-gE-gI concentrations.

4.3.1.1.2. Main Outputs

The following will be tabulated for each group, and at each timepoint that blood samples are collected for the humoral immune response (anti-gE-gI antibody):

- Percentage of participants above the pre-defined assay cut-off (i.e., seropositive participants) and their exact 95% CI will be tabulated by baseline seropositivity status and overall.
- Total N, GMCs and their 95% CI will be tabulated by baseline seropositivity status and overall. Study groups (i.e., not split by baseline seropositivity status) will be represented graphically over time. In addition, GMCs over time combining all groups in a single plot will also be produced.
- Total N, distribution of geometric mean fold increase values i.e., antibody concentration at each post-vaccination timepoint over pre-vaccination (Day 1) for each group will be tabulated with 95% CI..
- Geometric mean fold increase values and their 95% CI will be represented graphically

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4.3.1.2. Cell-mediated immune response

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4.3.1.2.2. Main outputs

The following variables will be tabulated and summarised by group using descriptive statistics (Total N, GM, SD, min, Q1, median, Q3 and max) and displayed graphically using boxplots (min, Q1, median, Q3, max) or frequency plots at each timepoint that blood samples are collected for CMI. T cell frequencies will be measured by intracellular cytokine staining (ICS) using peripheral blood mononuclear cells (PBMCs). CCI

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- Frequency of T-cells expressing at least 2 markers including at least 1 cytokine* among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17.

  **Cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17.*

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Note: values in graphs will be displayed on the log10 scale.

4.3.2. Between-group evaluation

4.3.2.1. Humoral immune response

4.3.2.1.1. Analytical approach

A statistical analysis will be performed to compare the vaccine formulation groups in terms of anti-gE-gI antibody concentrations at the one-month post-Dose 2 (Day 64) timepoint.

The difference between groups will be evaluated using an ANCOVA model: Day 64 log_{10} (concentrations or frequencies) will be modelled as a function of the adjuvant ($AS01_B$, $AS01_E$, no adjuvant) and the antigen dose (40 µg, 80 µg, 160 µg) with the pre-vaccination antibody concentration as covariates. CCI [redacted]

- To assess the adjuvant effect, the overall test of difference (to reject the null hypothesis of no difference) will be conducted at significance level 0.10.
  - CCI [redacted]
- To assess the antigen dose effect, the overall test of difference (to reject the null hypothesis of no difference) will be conducted at significance level 0.10.
  - CCI [redacted]
- The interaction between pooled adjuvant groups and pooled antigen doses will also be assessed at significance level 0.10.

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4.3.2.1.2. Main outputs

- Model parameters and associated p-values will be tabulated for the main model (specified in 4.3.2.1.1), the main model with interaction term and the main model with HSV-1 status.
- Individual study group GM values will be displayed for the main model.

- The model adjusted GMs of each of the 3 adjuvant groups and their 95% CI will be presented. Additionally, if calculated, the 3 adjusted GM ratios of the different pairwise comparisons ($AS01_B$ vs no adjuvant, $AS01_E$ vs no adjuvant, $AS01_B$ vs $AS01_E$) with their 95% CI and p-values will be presented.
- The global model adjusted GMs of each of the 3 antigen-dose groups and their 95% CI will be presented. Additionally, if calculated, the 3 adjusted GM ratios of the different pairwise comparisons (160 µg vs 80 µg, 160 µg vs 40 µg, 80 µg vs 40 µg) with their 95% CI and p-values will be presented.
- The Dunnett's test will be performed comparing antigen and adjuvant groups (i.e., 160 µg vs. 40 µg and 80 µg vs. 40 µg and AS01E vs. non-adjuvanted formulation and AS01B vs. non-adjuvanted formulation) and and results will be tabulated to adjust for multiple comparisons as a sensitivity analysis.

4.3.2.2. Cell-mediated immune response

4.3.2.2.1. Analytical approach

The frequencies of gE-gI-specific CD4+ and CD8+ T-cells expressing at least 1 marker among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17 will be assessed using the ANCOVA model.

4.3.2.2.2. Main outputs

- The Main outputs presented here will be the same as 4.3.2.1.2.

4.3.2.2.3. Sensitivity analyses

If more than 10% of participants are eliminated from any of the PPS in any treatment group, a sensitivity analysis will be carried out using the ES.

4.4. Candidate formulation selection rules

Refer to the study protocol for details on selection of the final formulation.

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4.6. Safety Analyses

The main safety analyses are described in Section 4.2

4.6.1. Additional Safety Assessments

4.6.1.1. Vital signs

Vital signs (systolic/diastolic blood pressure, and heart rate) and pre-vaccination temperature reported before each study intervention administration (Visit 1 [Day 1] and Visit 3 [Day 29]) will be summarized by group using descriptive statistics.

4.6.1.2. COVID-19 Assessment

The follow analyses will be conducted on COVID-19 data:

- Summary of participant's COVID-19 vaccination status before or after the study vaccination will be tabulated by group.
- Number and percentage of participants tested for COVID-19 with results and final diagnosis will be tabulated by group.
- Participant answers to additional COVID-19 assessments (e.g., contact with COVID-19 case) will be tabulated (number and percentage) for each group.
- Number and incidence of COVID-19 reported as unsolicited AE and SAE with be tabulated by group with exact 95% CI and categorized by MeDRA SOC and PT.
- Severity and outcome of COVID-19 AEs will be tabulated (number of percentage) by group.
- Summary of study completion with reasons for withdrawal related to COVID-19 will be tabulated by group.

4.7. Other Analyses

Not applicable.

4.8. Analyses

An 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] and CMI results) data will be performed after all participants from PART I (Step 1 and Step 2) have completed their Visit 5 (i.e. 1 month post-Dose 2 [Day 64]). This analysis will also generate all standard outputs for the next iSRC meeting (e.g., safety assessments and holding rules) – See the iSRC SAP for more details. This analysis will allow the vaccine candidate 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 not individual listings. The GSK study personnel, investigators and study participants will stay blinded (i.e., will not have access to the individual participant treatment assignment) until end of PART I. 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 interim analysis could become unblinded regarding those few specific cases.

As Stated in the Response-To-Question document submitted to Belgian Authorities (FAMHP) in December 2021 a statistical report including the unblinded data analysis will be generated and submitted to the FAMHP. No clinical study report will be generated at this stage.

The interim analysis planned in PART I will be only descriptive.

4.9. Changes to Protocol- Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2

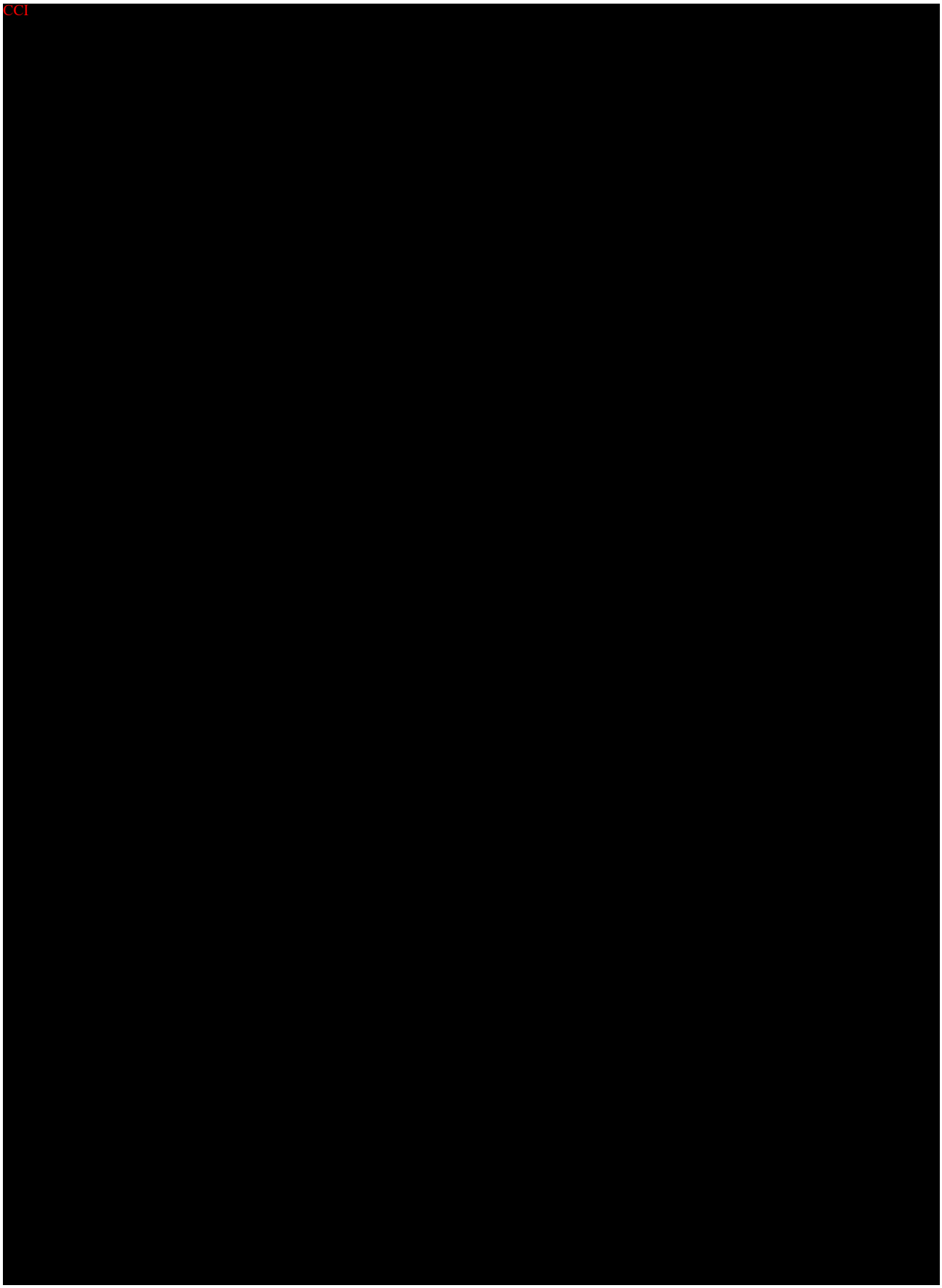
Table 2 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
There are two exposed sets ES_P1S1 (for Part 1, Step 1) and ES_P1S2 (for Part 1, Step 2)	Added ES_P1 which is for all Part 1 participants	Due to the 07 Jan 2022 protocol amendment, data is now being pooled across Steps in PART 1 for both the safety and immunogenicity analyses
No adjustment for multiple comparisons	Conducting Dunnett's Test to adjust for multiple comparisons in ANCOVA model as sensitivity analysis	To check if conclusions change when we adjust for multiple comparisons

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

The number of participants who are enrolled, vaccinated and in each study group will be tabulated.

In addition, the number of participants in each analysis set will be described, e.g., including the number of participants excluded from the PPS and the number who withdraw and reason for dropout.

6.1.2. Demographic and Baseline Characteristics

The median, mean, range and SD of age (in years) at first vaccination, height (cm), weight (kg), and BMI (kg/m²) will be computed by group, distribution of participants in each HSV-1 category (positive/negative), race, ethnicity, and sex composition will be summarised overall and by vaccine group. This analysis will be based on the ES_P1, the PPS_HI_P1 and the PPS_CMI_P1.

6.1.3. Subject exposure:

The number and percentage of participants who received each vaccine formulation or the placebo will be tabulated by group and by dose for the ES.

6.1.4. Concomitant Medications

Medications will be coded using the GSKDRUG dictionaries.

The number and percentage of participants using concomitant medication (any medication and any antipyretic) during the 7-day and the 28-day follow-up period after each dose and overall will be tabulated with exact 95% CI.

6.2. Appendix 2 Data Derivations Rule

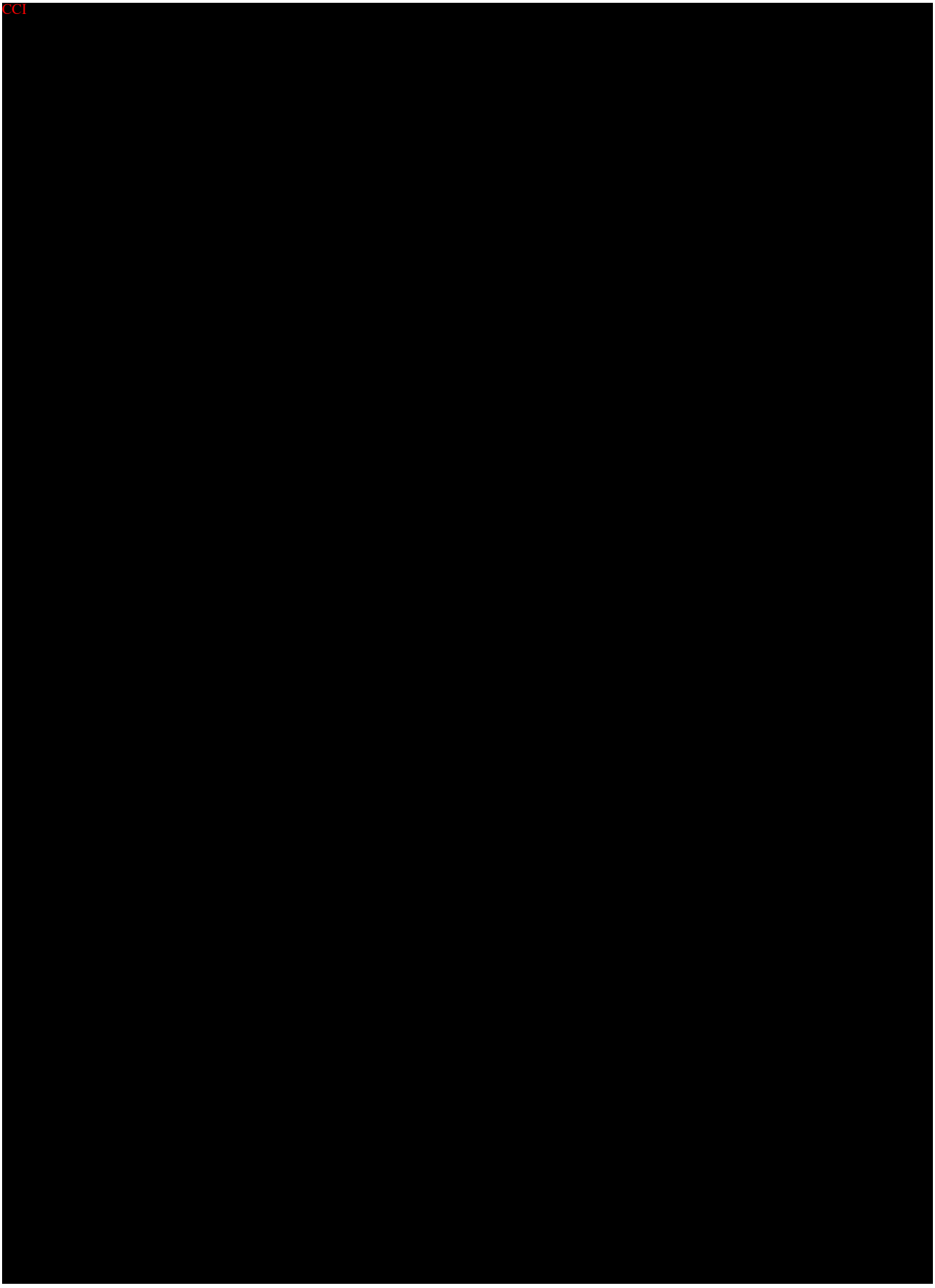
This section contains standard rules for data display and derivation for clinical and epidemiological studies.

6.2.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an AE is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after study dose. If ‘after study dose’ is selected, the relative dose for the event will be the one administered on the start day of the event. If ‘before study dose’ is selected, the relative dose for the event will be the dose prior to this one.

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6.2.3. Data derivation

6.2.3.1. Age at first dose in years

Age will be calculated as the number of years between the date of birth and the date of first vaccination.

In case of partial dates, the following 2 dates will be used as replacement dates:

- 15th of month, if the day is missing.
- 30th of June, if day and months are missing.

6.2.3.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

6.2.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	Value
"value" and value is > ULOQ	ULOQ
All other cases	missing

6.2.3.4. Geometric mean titers (GMTs) and concentrations (GMCs)

Geometric Mean Titer (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titer or concentration transformations. Non quantifiable antibody titers or concentrations will be converted as described in section 6.2.3.3 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.3.5. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the last (i.e., most recently received) study dose (i.e., it may be dose 1 or dose 2 of the vaccine) and the start date of the event plus one day. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose) and e.g., 2 for an event occurring on the day after the study dose was given.

6.2.3.6. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 3 March 2018 and ends on 12 March 2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the AE reported at grade 1 or higher during the solicited event period.

6.2.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs will be considered systemic events since the administration site flag is not included in the expedited AE eCRF pages. Unsolicited AEs with missing administration site flag will also be considered systemic.

Multiple events with the same PT which start on the same day are counted as only one occurrence.

6.2.3.8. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

Table 8 Intensity grading scale 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

*The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C regardless of the location of measurement.

6.2.3.9. Counting rules for occurrence of unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the AEs domain but they do not contribute to the summaries of unsolicited AEs.

Missing severity, relationship with study vaccine, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

6.2.4. Display of decimals

6.2.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.2.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.4.3. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, body mass index (BMI), pre-dose body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.2.4.4. Serological summary statistics

For each assay, GMTs or GMCs and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-dose.

GMT or GMC group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

Dunnett, Charles W. "A multiple comparison procedure for comparing several treatments with a control." *Journal of the American Statistical Association* 50.272 (1955): 1096-1121.

Information Type:	Statistical Analysis Plan (SAP) for PART II of the study

TITLE PAGE

Protocol 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
Study Number:	215336
Compound Number:	GSK3943104A
Abbreviated Title:	TH HSV REC-003

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Numbers:

Registry	**ID**
EudraCT	2021-003586-35
IND	29696
Clintrials.gov	NCT04762511
EU CT	2024-510571-37-00

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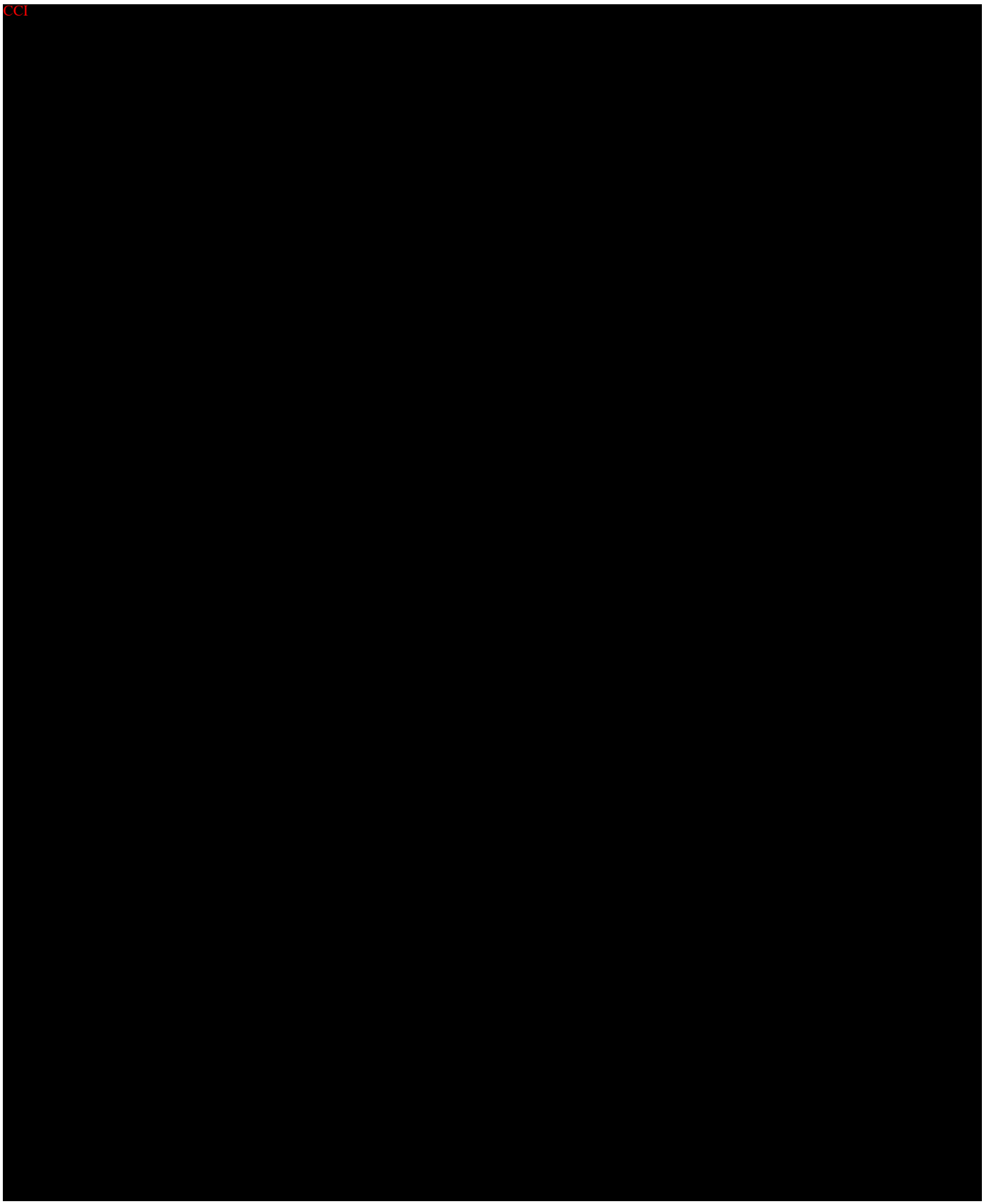
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Figure 1 Study Design Overview of PART II for Participants in the Shedding Sub-cohort 15

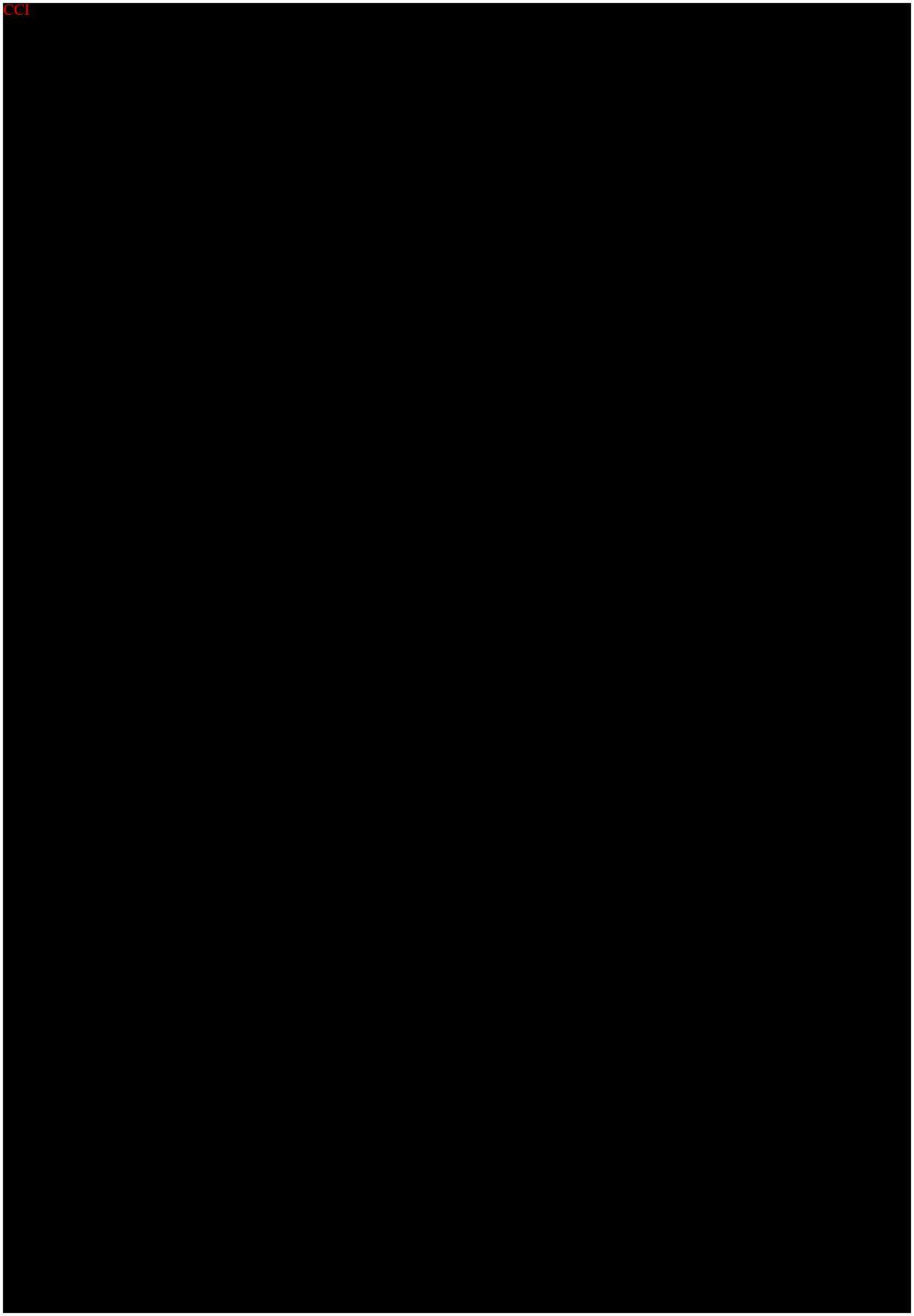
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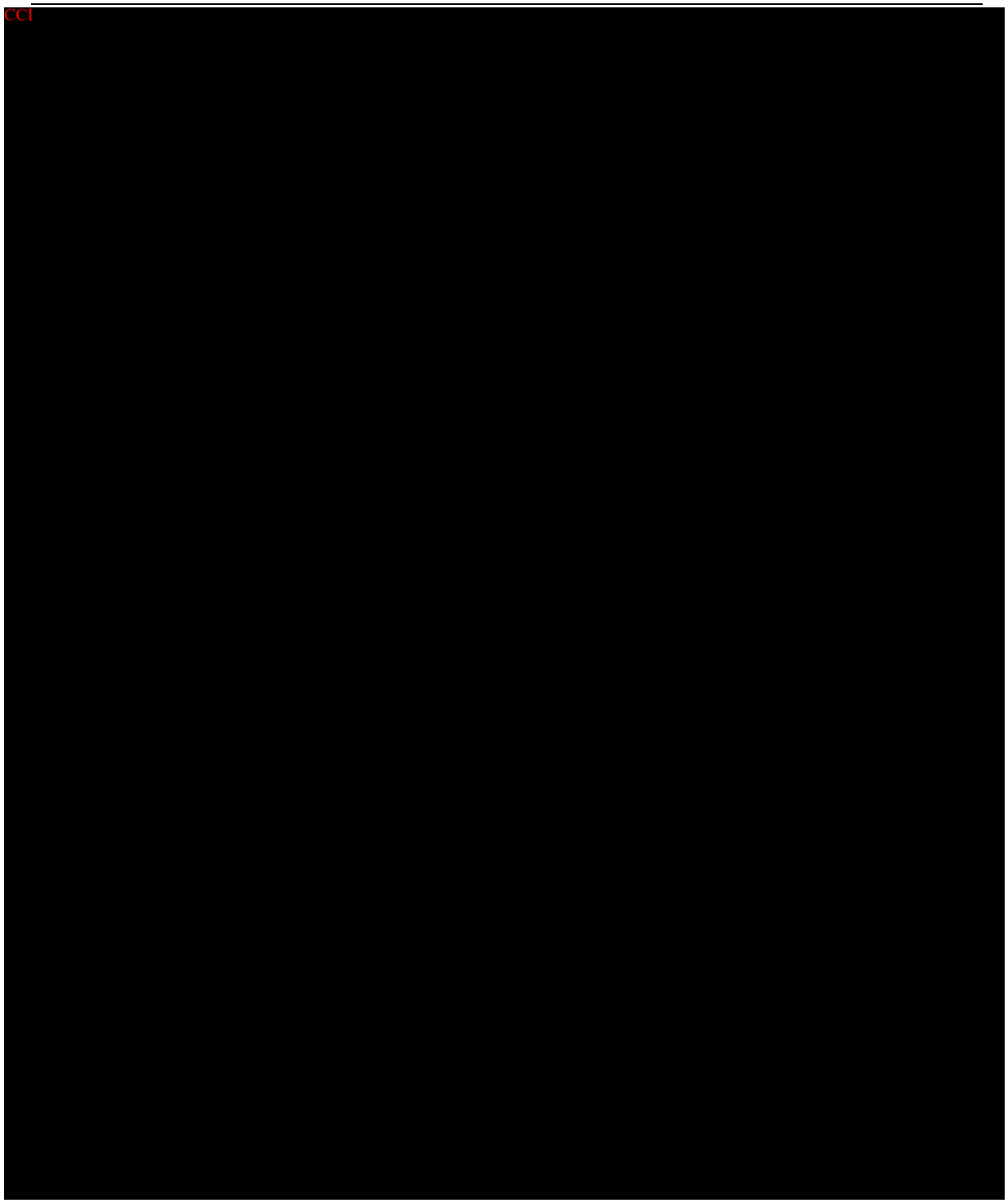
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1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses for PART II of the TH HSV REC-003 study (215336). There are separate SAPs for PART I analyses and the analyses of the internal Safety Review Committee.

1.1. Objectives, Estimands and Endpoints

Table 1 PART II 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). • 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	
To demonstrate the efficacy of the HSVTI in reducing the risk of having confirmed HSV-2 RGH episodes.	• Time-to-first confirmed HSV-2 RGH episode.
Secondary	
Efficacy	
To compare the HSVTI to placebo in terms of incidence rate of RGH episodes.	• Number of confirmed HSV-2 RGH episodes divided by the number of days of follow-up assessed until end of RGH event reporting period.
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 HSV2 RGH episode at 6 months after the last dose of study intervention.
To compare the HSVTI to placebo in terms of severity of RGH episode-associated symptoms during each RGH episode.	• HSC total score during each confirmed HSV-2 RGH episode assessed until end of RGH event reporting period.

Objectives	Endpoints and Estimands
To compare the HSVTI to placebo in terms of duration of RGH episode-associated symptoms, as assessed by the participant.	• Number of days with RGH-associated symptoms during each confirmed HSV-2 RGH episode assessed until end of RGH event reporting period.
To evaluate the lesion rate after administration of the last dose of the HSVTI.	• 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 shedding sub-cohort: To evaluate the effect of the HSVTI, about 6 weeks after the last dose of the HSVTI on shedding rate.	• HSV-2 shedding rate reduction (overall, asymptomatic and symptomatic) from baseline to about 6 weeks post-Dose 2 (Day 71).
Only for 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.	• 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.	• 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, IL17, 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).
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] CCI [redacted]

Primary estimand

The primary clinical question of interest for PART II is to evaluate the clinical efficacy of HSV targeted immunotherapy (HSVTI) from 14 days post-Dose 2 onwards.

The estimand is described by the following attributes:

- Population: Eligible immunocompetent 18 to 60-year-old being HSV-2 positive by University of Washington Western Blot (UWWB) with a history recurrent genital herpes
- Treatment condition: HSVTI_F1 vs. placebo or HSVTI_F2 vs. placebo.
- Variable/Endpoint: Time-to-first confirmed HSV-2 RGH episode

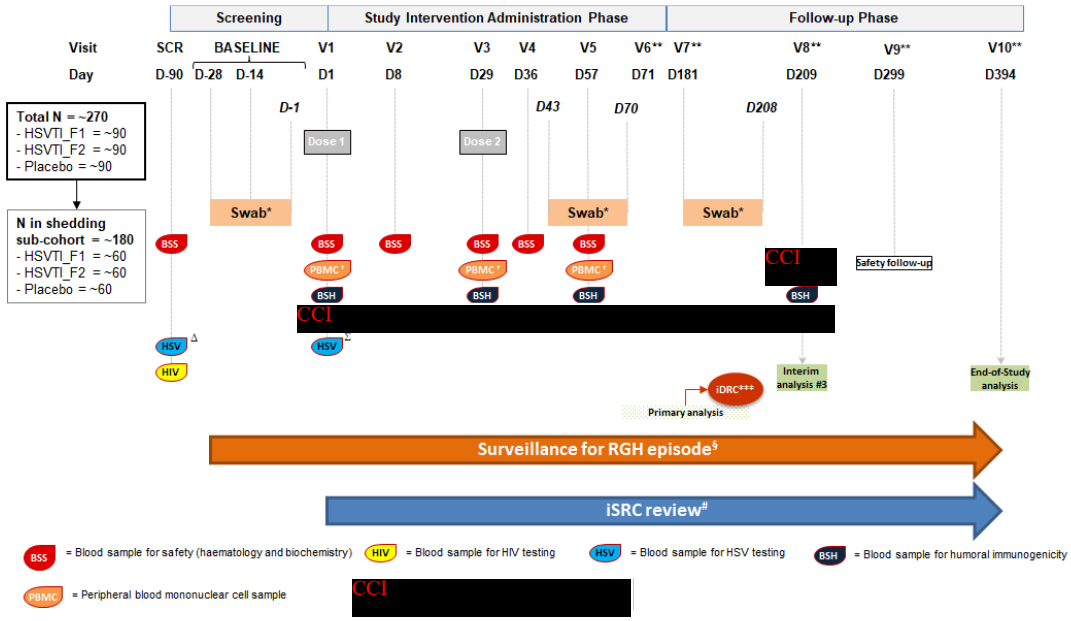
- Summary measure: The hazard ratio comparing survival time (in days) from 14 days post Dose 2 up to the first confirmed HSV-2 RGH episode.
- Intercurrent events: Participants whose treatment is not given according to protocol (e.g., study intervention temperature excursion), or taking chronic suppressive therapy during the dosing period will be excluded from the primary estimand. On the other hand, participants who switch to chronic suppressive therapy or take any concomitant or immune-modifying drugs over the course of the RGH follow-up observation period (see Appendix Section 6.3.3 for more details) will be included in the primary analysis regardless of these intercurrent events – treatment policy strategy.

Rationale for estimand: The interest lies in the effect of HSVTI when it is administered according to protocol (e.g., participants must receive both doses). Use of chronic suppressive therapy (CST) will not be considered during the RGH follow-up observation period (see Appendix Section 6.3.3 for more details), because CST will likely only be initiated after the first recurrence (i.e., after a participant counts towards the primary endpoint). Therefore, the modified exposed set will be used instead of the per protocol set which will help maintain the effects of the randomization. For additional information about estimands included in this analysis, see Appendix 1 (Section 6.1).

1.2. Study Design

Overview of Study Design and Key Features

Figure 1 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 Protocol 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.

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

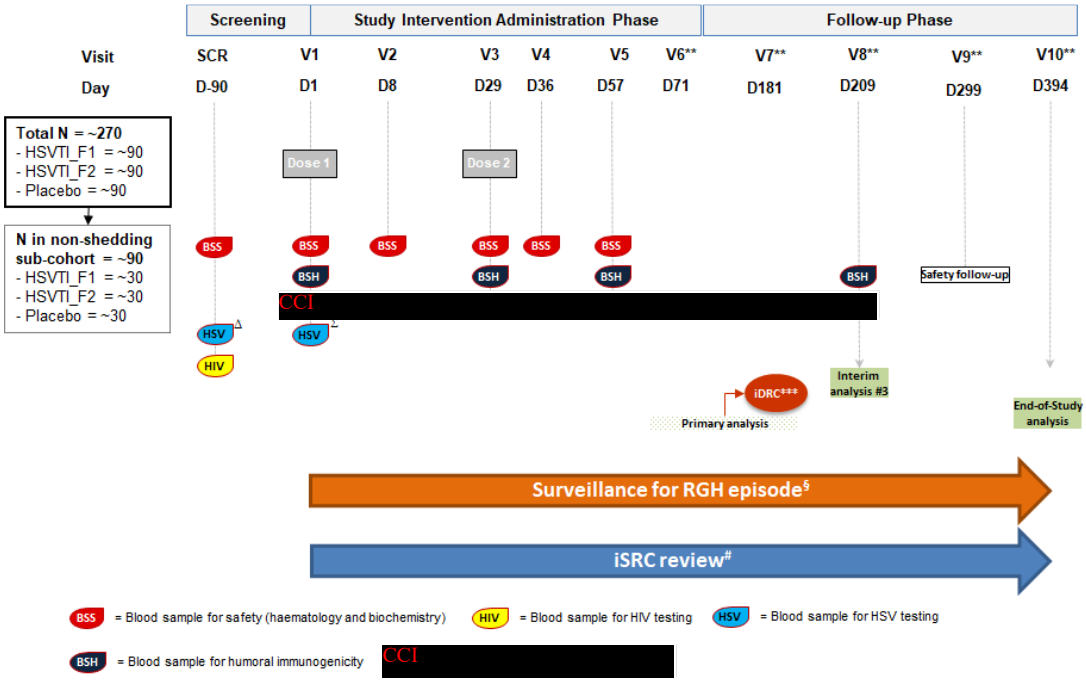
Δ If no documentation of laboratory-confirmed HSV-2 genital herpes.

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

§ Refer to Protocol 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.

Overview of Study Design and Key Features

Figure 2 **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 Protocol Section 8.2.2.1.
**These visits might be replaced by a virtual contact.
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Δ If no documentation of laboratory-confirmed HSV-2 genital herpes.
 For all enrolled participants except for those who were already tested by UWWB during the Screening visit.
§ Refer to Protocol 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.

Design Features	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), was a 2-step design to assess the reactogenicity, safety, and immunogenicity of up to 9 formulations of the HSVTI; • 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. 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 Protocol Section 8.2.2) CCI CCI
Study intervention	Participants 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)
Study intervention Assignment	The randomization algorithm will use a minimization procedure accounting for • Study site • Inclusion in the shedding sub-cohort (yes vs. no) • Sex (females vs. males), • Historical genital herpes frequency (< 6 episodes vs. ≥ 6 episodes) in the relevant 12-month time period defined at screening (see Protocol Section 5.1).

Overview of Study Design and Key Features	
Interim Analysis	This SAP covers the first 3 interim analyses: • Interim analysis #2 will be triggered when there are CCI CCI • Interim analysis #3 will be triggered when (1) all participants under follow up have completed Visit 8 (Day 209), (2) all samples are received and tested, and (3) after Protocol Amendment 7 is implemented in all countries • The primary analysis will be triggered when there are CCI CCI

*the Primary analysis was combined with Interim analysis #2

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3. ANALYSIS SETS

Analyses will be conducted using the analysis sets described below. There are additional details about the primary and secondary estimands in Section 6.1.

Table 3 Analysis Sets for PART II (Patients With HSV Genital Herpes, Aged 18 to 60 Years)

Analysis Set	Description	Analyses evaluated
Screened Set	All participants who signed the ICF.	• Demography
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.	• Demography
ES_P2 (PART II)	All participants with at least one study intervention administration documented.	• Demography • Safety • Clinical efficacy (sensitivity analysis) • Virological efficacy (sensitivity analysis) • Immunogenicity if >10% are eliminated from PPS_I_P2 • Cell Mediated Immunity, if >10% are eliminated from PPS_CMI_P2
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.	• Demography • Immunogenicity
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, • Who were part of the CMI sub-cohort, • 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.	• Demography • Cell-mediated immunity
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,	• Demography • Clinical efficacy

Analysis Set	Description	Analyses evaluated
	• 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 evaluable anogenital swabs within the window of the given swabbing period. • Who are determined to be HSV-2 seropositive by UWWB.	• Demography • Virological efficacy • Tertiary analyses

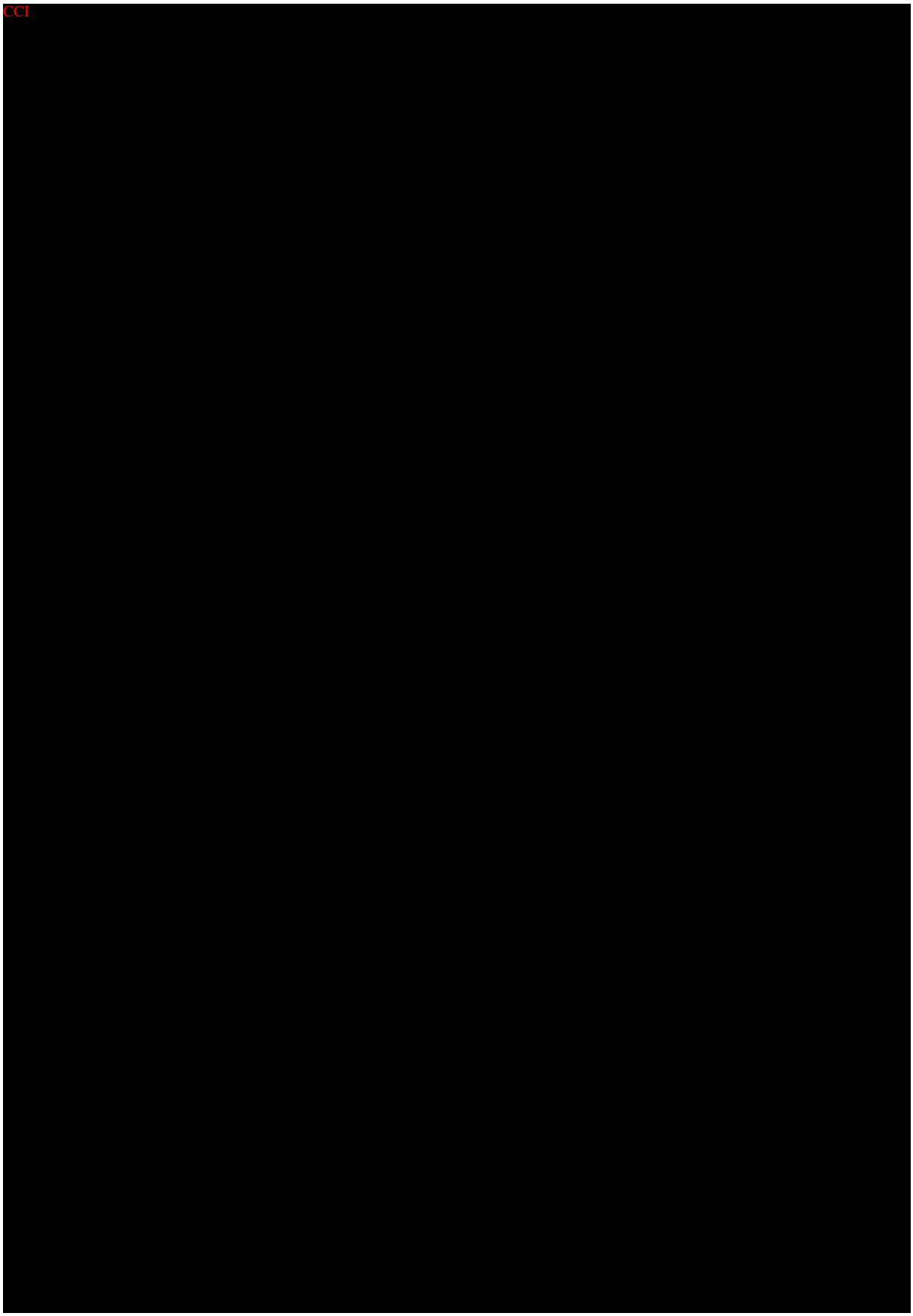
ICF = informed consent form; ES = Exposed Set; PPS = Per-Protocol Set; UWWB = Western Blot from the University of Washington; mES = modified Exposed Set

Note: the additional estimands analysis (see Section 4.3.13) will be conducted on the intersection of relevant analysis sets as specified.

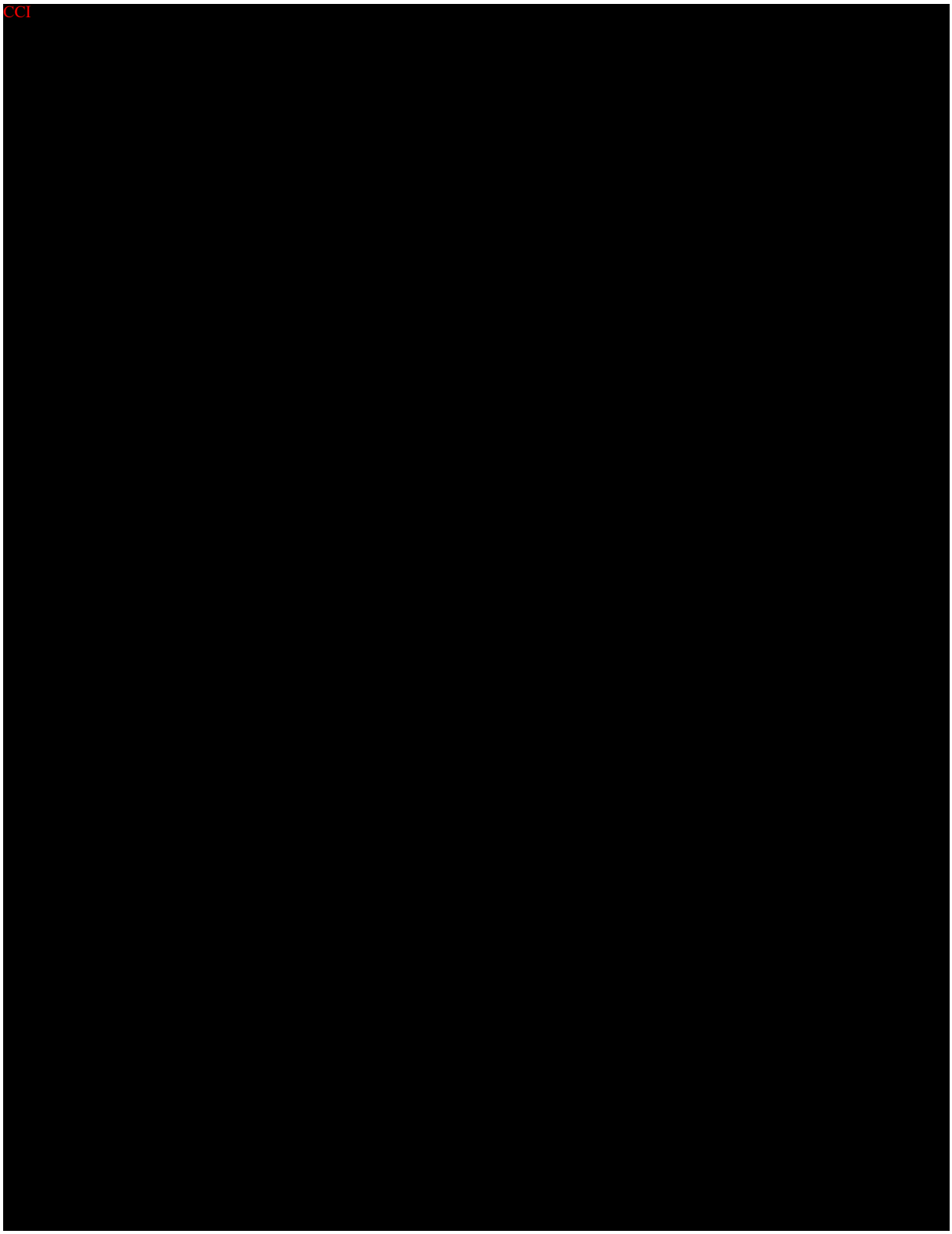
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4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Enrolled participants who prematurely withdraw from study will not be replaced.

In the case of the wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the electronic Case Report Form (eCRF).

Confidence intervals (CIs) will use 95% confidence levels, unless otherwise specified.

In general, CIs for proportions will be calculated using the Clopper-Pearson interval method [Clopper, 1934]. All continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum (min) and maximum (max)) and categorical data will be summarized using the number and percentage of participants in each category.

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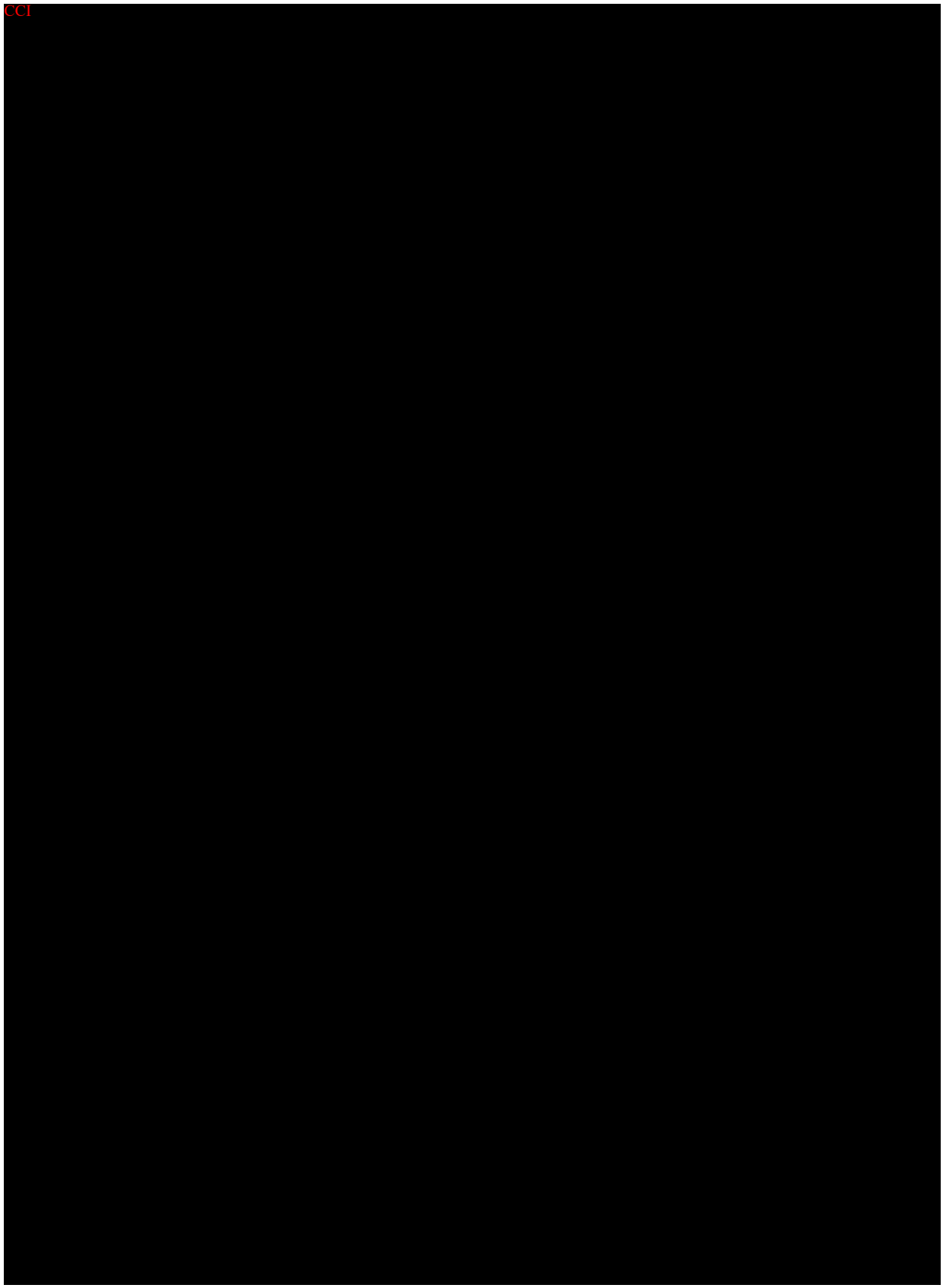
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4.2. Primary Endpoints Analyses

4.2.1. Definition of reactogenicity and safety endpoints

The analysis of the primary reactogenicity and safety objectives will be performed on the ES_P2. Main analytical approach of reactogenicity and safety endpoints

- The percentage of participants reporting at least one solicited adverse event (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. For solicited AEs, percentages will be computed based on the total number of solicited symptoms screens completed.
- The number and percentage of participants reporting each individual solicited AE (any grade, Grade 1, Grade 2, Grade 3 and resulting in medically attended visit) during the 7-day follow up period post- study intervention administration (i.e., the day of study intervention administration and 6 subsequent days) will be split by systemic and administration site AEs and tabulated with exact 95% CI for each group, after each dose and overall.
- The number and percentage of participants reporting each individual unsolicited AE during the 28-day follow up period post- study intervention administration (i.e., the day of study intervention administration and 27 subsequent days) will be tabulated with exact 95% CI by event category (e.g., all, grade 3, related, grade 3 related, SAEs, fatal etc.) for each group, after each dose and overall. For unsolicited AEs, percentages will be computed based on the total number of exposed participants.
- The number and percentage of participants with each solicited administration site event and separately, solicited systemic event (any grade and grade 3) within the 7-day follow up period will be represented graphically with a bar plot for each group and after each dose.

- The duration of each individual solicited AE (not limited to the 7-day post-study intervention period) will be tabulated using descriptive statistics (mean, minimum, Q1, median, Q3, maximum). The same computations will be done for Grade 3 solicited events. This analysis will be done for each group after each dose.
- The number and percentage of participants with any unsolicited AEs during the 28-day follow-up period (i.e., the day of study intervention administration and 27 subsequent days) will be tabulated per participant and after each dose with exact 95% CI by study group and categorized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). This will also be tabulated per participant and split by Grade 3 unsolicited AEs, causally related unsolicited AEs and Grade 3 causally related unsolicited AEs. The verbatim reports of unsolicited AEs will be reviewed by a physician 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 preferred term.
- The number of percentage of participants reporting each individual unsolicited AE during the 28-day follow-up period (i.e., the day of study intervention administration and 27 subsequent days) will be tabulated and ranked by MedDRA PT with the most common appearing first. This analysis will be done for each group after each dose.
- The number and percentage of participants with at least one solicited or unsolicited medically attended event (MAE) will be classified by MedRA SOC and PT and tabulated with exact 95% CI. This analysis will be done by group and after each dose.
- The number and percentage of participants with at least one serious adverse event (SAE) reported at any time between the day of study intervention administration (Day 1) and 12 months after last study intervention administration (Day 394) will be classified by MedRA SOC and PT and tabulated with exact 95% CI. This analysis will be done by participant and split by group.
- The number and percentage of participants with at least one potential immune-mediated disease (pIMD) (selection defined by GSK list of terms AND/OR investigator tick box) reported at any time between the day of study intervention administration (Day 1) and 12 months after last study intervention administration (Day 394) will be displayed by newly diagnosed, exacerbation of pre-existing events and overall. pIMDs will be classified by MedRA SOC and PT and tabulated with exact 95% CI.
- All SAEs and MAEs will be described in detailed in a tabular listings.
- All pIMDs will be described in detail in a tabular listing. Note, there will be a column distinguishing between pIMDs that are newly diagnosed vs. exacerbated.
- All unsolicited AEs leading to study/intervention discontinuation from Dose 1 up to study end will be tabulated and described in detail in a tabular listing. This information will be retrieved from the DS domain.
- All participants taking concurrent medication/vaccines will be described in a detailed listing.

- All SAEs related to study participation (not due to study intervention administration) or concurrent GSK medications will be presented based on the enrolled set and described in detail in a tabular listing.
- For each group and for each hematology and biochemistry parameter:
  - The number and percentage of participants having hematology and biochemistry results below or above the central laboratory defined normal ranges will be tabulated with exact 95% CI by timepoint [pre- study intervention administration (Day1), post-dose 1 (Day 8 and Day 29), post-dose 2 (Day 36 and Day 57)]. This will be done for each group and overall.
  - The summary of grading post-study intervention administration will be tabulated vs. baseline. Grades will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"; see Section 10.2.2 of the protocol). The laboratory parameters not included on FDA Toxicity Grading Scale will not be graded.
- Compliance in completing solicited events information will be tabulated after each dose and overall (for details on how solicited AE compliance is being assessed, see Section 6.3)
- Proportion of eDiary days completed by participants or investigators will be tabulated after each dose and overall.
- Reason for missed eDiary entries will be tabulated after each and overall.
- Pregnancy and pregnancy outcomes will be listed (if applicable).

4.2.2. Sensitivity analyses

Not applicable.

4.2.3. Definition of clinical efficacy endpoints

The time-to-first confirmed HSV-2 RGH episode analysis will be performed on the mES_CE (see Section 4.7 for specific triggers for each case-driven analysis). Unless otherwise specified, the recurrence analysis will include all cases from 14 days post-Dose 2 onwards. Participants will be censored at the last timepoint in which they have data. For instance, the date of censoring may occur on the date in which they withdraw or the RGH reporting end date (see Section 6.3.3 for more information).

Hazard ratios comparing survival time in days between each HSVTI group and placebo 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) CCI [redacted]
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† This variable represents recurrence history

The hazard ratio and 90% CI will be calculated for each comparison of HSVTI group-to-placebo by exponentiating the treatment group parameter estimate and their associated confidence limits. The null hypothesis will be rejected if the 2-sided p-value is below 0.1.

To check the proportional hazards assumption, a plot displaying log(-log(survival)) vs. time will be generated for each treatment group. If the hazards are proportional, the lines should be parallel (these results will not be displayed).

4.2.4. Main analytical approach of clinical efficacy endpoints

The following outputs will be generated for each comparison (HSVTI_F1 vs. placebo and HSVTI_F2 vs. placebo), for the main analysis (on mES_CE) CCI
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- If hazard ratios are proportional, *the model will be run* and a table displaying number (and percentage) of cases, mean follow-up time, hazard ratios, 90% Cis and p-values split by treatment group for time to first confirmed RGH episode will be generated.

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- At the Primary Analysis, a table presenting the results of the re-randomization sensitivity analysis will display the number and percentage of participants with cases, the observed chi-square value (vs. placebo) and the re-randomization p-value for each comparison (see Section 4.2.5 for more details). This will only be conducted on the main analysis.
- Kaplan-Meier plots displaying time to first RGH episode displayed by treatment group.

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4.3. Secondary Endpoints Analyses

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4.3.2. Main analytical approach of clinical efficacy endpoints

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Incidence rate

- The following output will be generated from the model for the main analysis (on mES_CE), and for each comparison). The Poisson model will be run on each comparison separately (HSVTI_F1 vs. placebo and HSVTI_F2 vs. placebo) for the main analysis (on mES_CE) and the number of confirmed recurrences, total amount of follow-up time (in person-years), incidence rates (or lesion rates), incidence rate ratios (or lesion rate ratios), 90% CIs and p-values will be tabulated. CCI
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- Total number of confirmed recurrences, total amount of follow up time (in person-years), incidence rates and 90% CIs will be displayed by treatment group CCI [redacted] CCI [redacted]
- Descriptive statistics (n, mean, SD, median, Q1, Q3) on the incidence rates will be CCI [redacted] CCI [redacted] displayed by treatment group. This analysis will be repeated for lesion rates.
- CCI [redacted] CCI [redacted].
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Lesion rate

- Days with confirmed lesions, total amount of follow up time (in person-years), lesion rates and 90% CIs will be displayed by treatment group.

%RGH-free up to 6MPD2

- Number and percentage of participants free from RGH episodes, CCI [redacted] CCI [redacted] from 14 days post-Dose 2 to 6-months post-Dose 2 will be tabulated by study group with exact 90% CIs. This output will not be generated for the primary analysis. The following definitions will be used for this table:
  - "Free from RGH episode" will include participants who either had no suspected RGH episode or in which all events they reported were determined as non-RGH by PCR

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Severity

- Descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) on the duration in days of each confirmed HSV-2 genital herpes recurrence starting 14 days post-Dose 2 will be tabulated by treatment group. CCI

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- Descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) of the HSC total scores will be presented per recurrence by treatment group for each confirmed HSV-2 recurrence starting 14 days post Dose 2.

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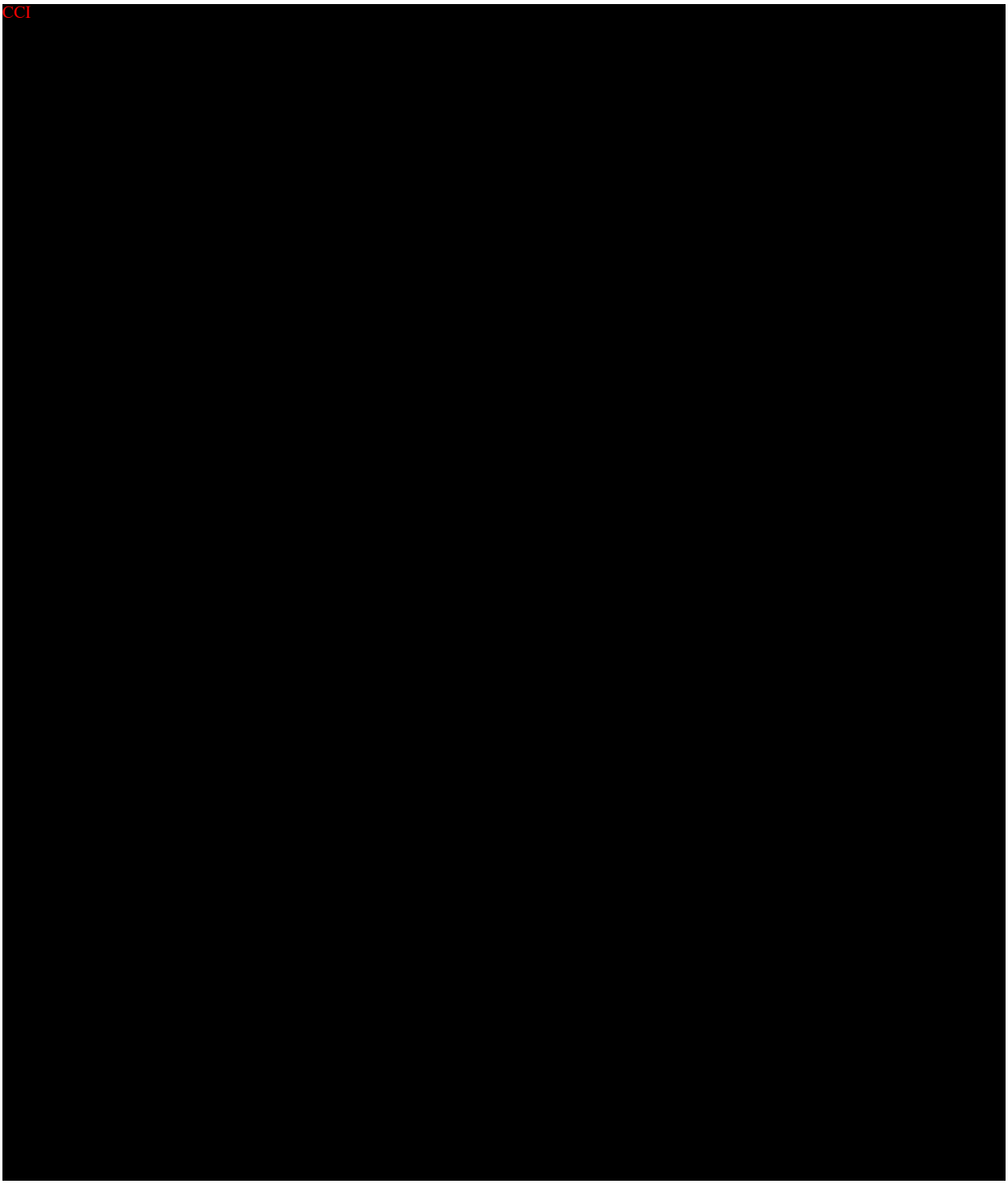
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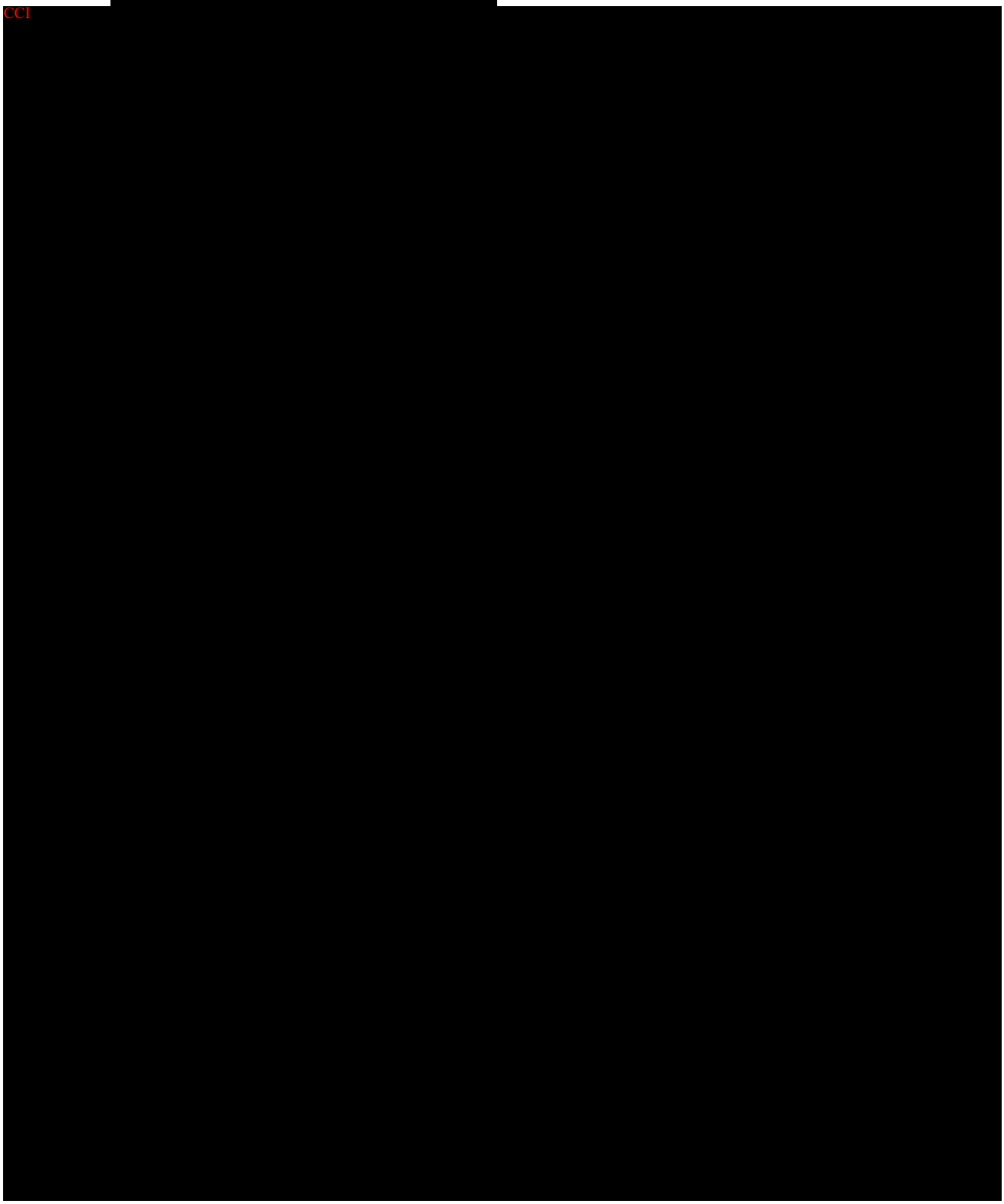


4.3.5. Main analytical approach of virological efficacy endpoints

- For each model run, the following model outputs will be generated: Model estimated shedding rate reduction will be tabulated with 90% CI by study group and swabbing period.

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- Number and descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) on the duration of HSV-2 shedding episodes will be displayed by treatment group, and swabbing period (See Appendix 2 Section 6.2.6 for details on shedding episode duration) CCI [redacted]



4.3.8. Main analytical approach of humoral immune response endpoints

The following will be tabulated for each group, and at each timepoint that blood samples are collected for the humoral immune response (anti-gE-gI antibody):

- Number and percentage of participants above the pre-defined assay cut-off (i.e., seropositive participants), GMCs and their exact 95% CI will be tabulated and split by sex and overall.
- GMCs and their 95% CIs will be displayed graphically
- Distribution of geometric mean fold increase values i.e., antibody concentration at each post-vaccination timepoint over pre-vaccination (Day 1) for each group will be tabulated with 95% CI. CCI [redacted]
- GMCs and GMRs will be tabulated and split by treatment group and timepoint.

CCI [redacted].

Note: values in graphs will be displayed on the $\log_{10}$ scale.

4.3.9. Sensitivity analyses

If more than 10% of participants are eliminated from PPS_I_P2 in any treatment group, a sensitivity analysis generating the outputs above may be carried out using the ES_P2.

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4.3.11. Main analytical approach of cell-mediated immune response endpoints

The following variables will be tabulated and summarized by group using descriptive statistics (Total N, GM, SD, min, Q1, median, Q3 and max) at each timepoint that blood samples are collected for CMI.

- Descriptive statistics of the frequency of HSV-2 gE-gI specific CD4+ T-cells expressing at least 2 markers including at least 1 cytokine* among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17 will be split by sex and separately HSV-1 status at baseline and overall and tabulated. The overall tabulation (not split by sex) will be repeated for gE specific CD4+, gI specific CD4+ and gE-gI specific CD8+ T-cells.

  *Cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17.

- Boxplots (min, Q1, median, Q3, max) of the frequency of HSV-2 gE-gI specific CD4+ T-cells expressing at least 2 activation markers including at least 1 cytokine will be displayed.

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γ, 41BB, at each timepoint will be displayed by combination and CCI
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Note: values in graphs will be displayed on the log10 scale.

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4.5. Safety Analyses

The safety analyses will be on ES_P2 unless otherwise specified.

4.5.1. Adverse Events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activity (MedDRA dictionary).

See Section 4.2.1 for details about all safety analyses.

4.5.2. Vital Signs

Vital signs (systolic/diastolic blood pressure, and heart rate) and pre-vaccination temperature reported before each study intervention administration (Visit 1 [Day 1] and Visit 3 [Day 29]) will be summarized by group using descriptive statistics.

4.5.3. Concomitant Medications

Medications will be coded using the GSKDRUG dictionaries.

Concomitant medications will be described in a detailed listing.

4.6. Other Analyses

4.6.1. Screening failures

4.6.2. Demography

Demography will be displayed for the screened set and the exposed set.

The median, mean, range and SD of age (in years) at first study intervention administration (or screening), height (cm), weight (kg), BMI (kg/m^2) center, race, ethnicity, and sex composition will be summarized overall and by study intervention group.

A table displaying a summary of baseline HSV characteristics including HSV-1 serostatus, HSV-2 serostatus by UWWB, historical diagnostic method, duration of HSV-2 infection, number of recurrences prior to enrolment or CST initiation, and on suppressive therapy at study entry will be generated.

4.6.3. Participant disposition

Participant disposition will be displayed for all analysis sets.

- The disposition from screened set to enrolled set with number of screening failures (and reasons) will be tabulated.
- The number of participants who are enrolled, vaccinated and in each study group will be tabulated.
- In addition, the number of participants in each analysis set will be described, e.g., including the number of participants excluded from the PPS and the number who withdraw.

4.6.4. Participant exposure

The number and percentage of participants who received each study intervention formulation or the placebo will be tabulated by group and by dose for the ES_P2.

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4.8. Changes to Protocol Defined Analyses

Table 5 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	CCI
Percentage of recurrent genital herpes free at different time points was specified 95% CIs	This was changed to display 90% CI	
Limited AE reporting compliance tables	Added compliance tables	
Descriptive statistics on number of lesions	This was removed	
Plot displaying the kinetics of individual GMC titers for humoral immunogenicity analysis	This was removed	

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Estimands for Primary and Secondary Objectives

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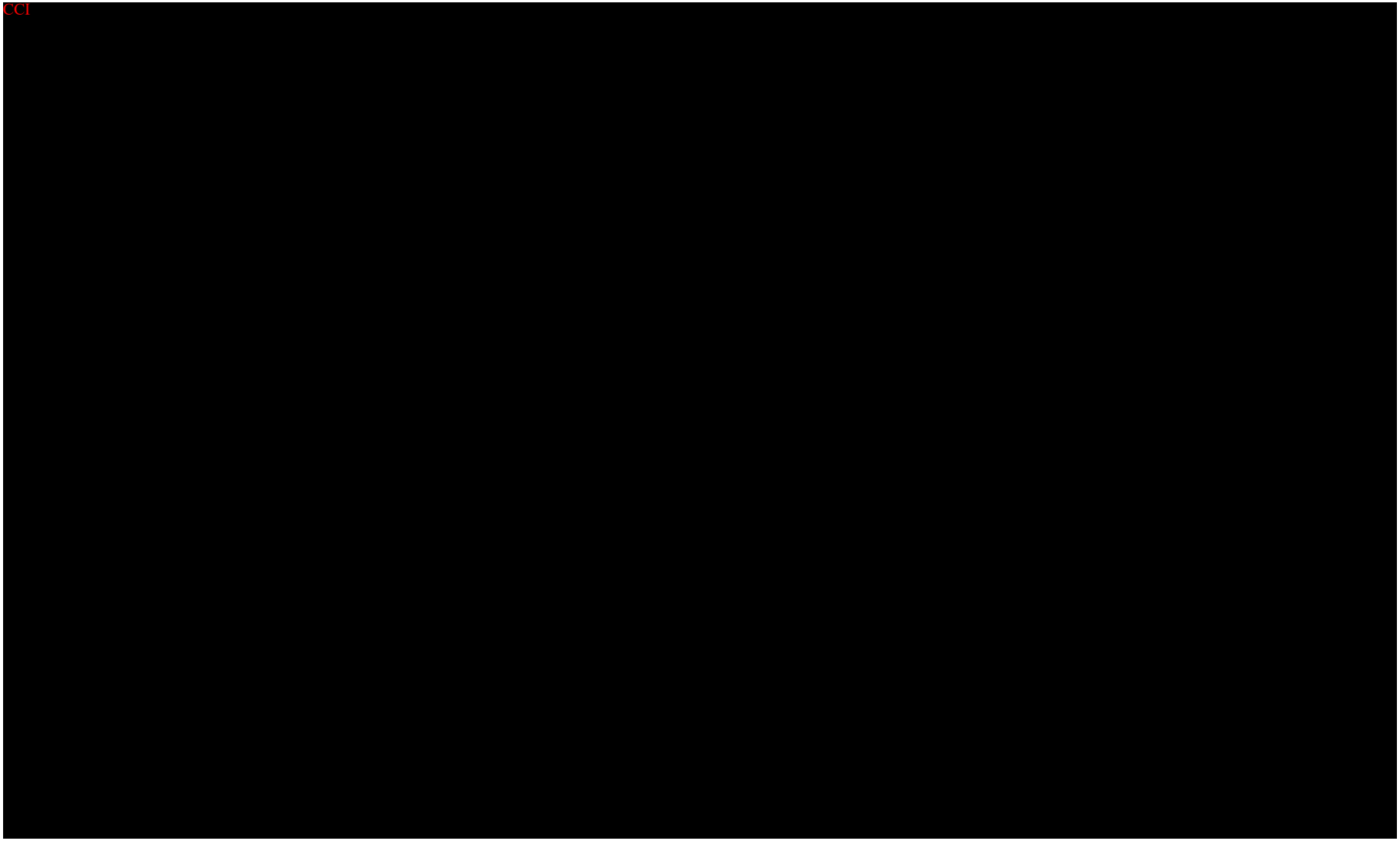
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6.1.1. Protocol deviations

Important protocol deviations will be summarized. Protocol deviations will be tracked and reviewed by the study team throughout the study.

6.2. Appendix 2 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

6.2.1. Attributing events to study intervention doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an AE is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

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6.2.2.3. Dates

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td>General</td><td colspan="2">• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., except for time since HSV-2 diagnosis).</td></tr>
<tr><td>Adverse Events</td><td colspan="2">• Partial dates for AE recorded in the CRF will be imputed using the following conventions:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
• If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
• Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then</td></tr>
</table>

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><td></td><td>If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td></td><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td></td><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td></td><td>Completely missing start/end date</td><td>No imputation</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td colspan="2">Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
If month and year of start date = month and year of study intervention start date, then
If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.</td></tr>
</table>

Element	Reporting Detail	
		Else if study intervention start date is not missing: • *If year of start date = year of study intervention start date, then* • *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.* • *Else set start date = study. intervention start date.* *Else set start date = January 1.*
	Missing end day	*A '28/29/30/31' will be used for the day (dependent on the month and year).*
	Missing end day and month	*A '31' will be used for the day and 'Dec' will be used for the month.*
	Completely missing start/end date	• *For HSV antivirals, the end date will be set to the follow up end date for that participant.* • *For other concomitant medications, no imputation will be done*
Age	For Integrated Data Standards Library (IDSL) reporting, AGE will need to be imputed from year of birth. For CDISC studies AGE is an expected DM variable and this section can be deleted. For date of birth: • A missing day will be imputed to '15' • A missing day and month will be imputed to '30-Jun'	
ICF addendum	For date in which the ICF addendum has been signed • A missing day will be imputed to '1' • Missing month or year will not be imputed	
HSV-2 diagnosis date	• A missing day will be imputed to '01' • A missing day and month will be imputed to '01-Jan' • A missing year will not be imputed	

6.2.2.4. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

6.2.2.5. Daily recording of solicited events

6.2.2.5.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited AEs, a solicited AE will be considered present only when a daily recording of grade 1 or more is present. Missing or non-evaluable measurements will not be replaced.

6.2.2.5.2. Unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

Missing severity, relationship with study intervention, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' in all statistical output.

6.2.3. Data derivation

6.2.3.1. Age at first dose in years

Age will be calculated as the number of years between the date of birth and the date of first vaccination.

6.2.3.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

6.2.3.3. Geometric mean titers (GMTs) and concentrations (GMCs)

Geometric Mean Titer (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titer or concentration transformations. Cut-off values are defined by the laboratory before the analysis.

6.2.3.4. Onset day

The onset day for an event (e.g., AE, concomitant medication/vaccination) is the number of days between the last (i.e., most recently received) study dose (i.e., it may be dose 1 or dose 2 of the study intervention) and the start date of the event plus one day. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose) and e.g., 2 for an event occurring on the day after the study dose was given.

6.2.3.5. Duration of solicited events

The duration of an unsolicited adverse event with a start and end date will be the difference between the start and end date plus one day, i.e., an event that starts on 3 March 2018 and ends on 12 March 2018 has a duration of 10 days.

The duration of solicited events will be calculated in the following manner:

- Start date - End date + 1
- This may include days that are reported as Grade 0 in the middle of an event
- The start date and end date can only start on days that are Grade 1 or higher

6.2.3.6. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs will be considered systemic events since the administration site flag is not included in the expedited AE eCRF pages. Unsolicited AEs with missing administration site flag will also be considered systemic.

Multiple events with the same PT which start on the same day are counted as only one occurrence.

6.2.3.7. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

Table 7 Intensity grading scale 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	0	None

Event	Intensity grade	Parameter
Headache	1	Mild: Symptom that is easily tolerated
Myalgia	2	Moderate: Symptom that interferes with normal activity
Arthralgia	3	Severe: Symptom that prevents normal activity

*The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C regardless of the location of measurement.

6.2.3.8. Counting rules for occurrence of unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the AEs domain but they do not contribute to the summaries of unsolicited AEs.

Missing severity, relationship with study intervention, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

6.2.4. Display of decimals

6.2.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.2.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.4.3. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, body mass index (BMI), pre-dose body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

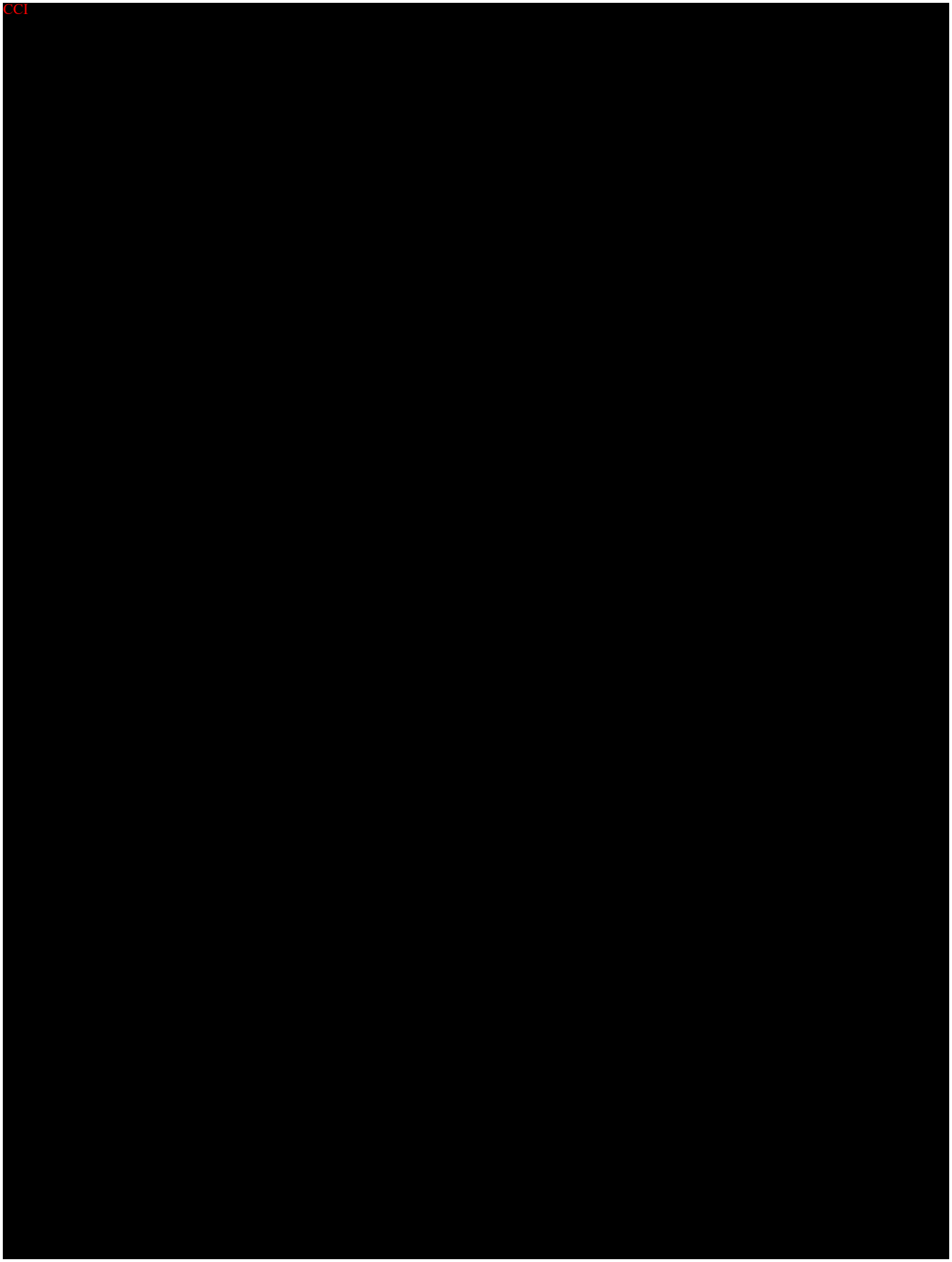
The maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.2.4.4. Serological summary statistics

For each assay, GMTs or GMCs and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-dose.

GMT or GMC group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

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6.3. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance]

Compliance is the state of being in accordance with the established protocol guidelines or specifications: i.e., the overall number of datapoint collected vs the overall number of datapoint expected.

The target compliance threshold for solicited event reporting that will be tracked by the study team during in stream protocol deviation meetings is 90% per participant.

6.3.1. Study Level compliance

Overall eCOA compliance (across all eCOAs and all participants) for the study is calculated as:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs per participant} \times \text{Total number of participants}}$$

An eCOA is considered complete if there are no missing data within the assessment. The study eCOA compliance will be reported for each treatment group. A participant is considered to be compliant with their eCOAs if at least 90% of their eCOAs are complete (have no missing data), i.e., a participant is eCOA compliant if they meet the following criteria:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs}} \times 100 \geq 90\%$$

6.3.2. Endpoint Level Compliance

Solicited AE's:

The study protocol defines a 7-day solicited AE follow-up period.

Participants enter solicited events (administration site events and systemic events) in their eDiary. The occurrence of each solicited events within 7 days after study intervention administration will be captured. In case of a missing eDiary day by a participant, the investigator can enter data via the *Missed Daily Diary* eCRF preferably within 36 hours of the missed entry. In case participants make an error in their reporting, the investigator can correct it via a data correction report. Investigator-entered data will take precedence over participant entered data.

In terms of compliance for each of Day 1-7 the number/ percentage of completed eDiary entries by either a participant or the investigator/study staff will be summarized by study group and by dose. The denominator will be the number of expected completion days.

The reasons for investigator/study staff entry upon missed eDiary on Day 1-Day 7 will be summarized in frequency table.

Reported recurrence eDiary

Participants report recurrence related symptoms in their eDiary during the follow up/observation period for each day during a recurrence.

In terms of compliance for recurrence related symptoms, the number/ percentage of completed eDiary entries by either a participant or the investigator/study staff will be summarized by study group. The denominator will be the number of expected completion days which will be equal to the sum of the duration of all suspected recurrences.

HSC eDiary

When participants reports recurrence related symptoms in their eDiary, they must fill out an HSC questionnaire.

In terms of compliance for the HSC questionnaire, the number/ percentage of completed eDiary entries by either a participant or the investigator/study staff will be summarized by study group. The denominator will be the number of expected completion days which will be equal to the sum of all days in which symptoms are reported.

6.3.3. The RGH event follow up observation period

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 of 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.

The end of the RGH event reporting period date will be taken directly from the eCRF.

7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

Magaret, AS, Stanaway, J. Sample Size for a Binomial Proportion with Autocorrelation. Statistical Communications in Infectious Diseases, 2011, 3(1), 8. http://doi.org/10.2202/1948-4690.1036 (last accessed: 22 September 202107 January 2022).

Magaret A. Models for HSV shedding must account for two levels of overdispersion. UW Biostatistics Working Paper Series. 2016 Working Paper 410. https://biostats.bepress.com/uwbiostat/paper410/ (last accessed: 22 September 202107 January 2022).

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