Statistical Analysis Plan Amendment 2

Study ID: 219075

Official Title of Study: A Phase 2 randomized, active-controlled, observer-blind study to assess the safety, reactogenicity, and immunogenicity of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults who previously received a complete primary vaccination series with or without booster dose(s)

NCT number: NCT05960097

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TITLE PAGE

Protocol Title:	A Phase 2 randomized, active-controlled, observer-blind study to assess the safety, reactogenicity, and immunogenicity of a booster dose of investigational COVID-19 mRNA vaccines in healthy adults who previously received a complete primary vaccination series with or without booster dose(s)
Study Number:	219075
Compound Number:	GSK4396687A
Abbreviated Title:	CV2 SARS-COV2-013 BST

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) Not applicable

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	28 April 2023	Clinical Study Protocol (27 April 2023)	Not Applicable	Original version
SAP Amendment 1	07 October 2023	Clinical Study Protocol amendment 1 (26 September 2023)	Added mapping of solicited AEs to MedDRA	Clarify MEDRA mapping for solicited adverse events
			Added statistical analysis for Part B	Protocol Amendment 1
			Clarification on the other variants planned as tertiary objective	Emerging variant of concern
SAP Amendment 2	14 Mar 2024	Clinical Study Protocol amendment 1 (26 September 2023)	[redacted]	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Added protocol deviation elimination codes	Added for clarity as we are not using GSK codes
			CCI [redacted]	
			Added summary of proportion of samples above LLOQ	Summary was not included in previous version. It is standard to include this summary to help understand the amount of imputed data

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 219075. Details of the planned analysis to support Independent Data Monitoring Committee (IDMC), internal Data Review Committee (iDRC) and Safety Review Team (SRT), interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives and endpoints for Part A

Primary Objectives	Primary Endpoints (population summary)
To compare the immunogenicity of CV0701 and CV0601 booster vaccines with CCI CCI vaccine at Day 29	• Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (GMT) • Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (GMT)
To evaluate the safety and reactogenicity of CV0701 and CV0601 booster vaccines	• Occurrence of solicited administration site and systemic AEs within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants) • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) of study intervention administration (percentage of participants) • Occurrence of MAAEs, SAEs and AESIs from Day 1 through the end of the study (approximately 180 days after the study intervention administration), each summarized separately (percentage of participants)
Secondary Objective	**Secondary Endpoints (population summary)**
To compare the immunogenicity of CV0701 and CV0601 booster vaccines with CCI CCI vaccine	• Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 91 and Day 181 (GMT) • Serum neutralization titers against pseudovirus bearing specific CCI spike at Day 91 and Day 181 (GMT) • Serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, 91 and Day 181 (GMT) • Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (percentage of participants) • Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI CCI spike protein at Day 29 (percentage of participants) • Seroresponse* from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29 (percentage of participants) • Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, Day 91, and Day 181 (GMI) • Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI

	CCI spike protein at Day 29, Day 91, and Day 181 (GMI) • Fold increase from baseline of serum neutralization titers against pseudovirus bearing specific CCI spike protein at Day 29, Day 91, and Day 181 (GMI)
e ti r bi c iv s	e ti r E d in s
CCI [redacted]	

AE: adverse event; AESI: adverse events of special interest; GMF: geometric mean frequency; GMI: geometric mean increase; GMC: geometric mean concentration; GMT: geometric mean titer; IgG Ab: immunoglobulin G antibody; MAAE: medically attended adverse event; mRNA: messenger ribonucleic acid; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

* CCI [redacted]
CCI [redacted]

Objectives and endpoints for Part B

Primary Safety Objective	Primary Safety Endpoints (population summary)
• To evaluate the safety and reactogenicity of three CV0801 booster vaccine manufacturing specifications	• Solicited events: • Occurrence of solicited administration site and systemic AEs within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants) • Unsolicited events: • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) of study intervention administration (percentage of participants) • SAEs, AESIs and MAAEs: • Occurrence of MAAEs, SAEs and AESIs from Day 1 through the end of the study (approximately 180 days after the study intervention administration), each summarized separately (percentage of participants)
Primary Immunogenicity Objective	**Primary Immunogenicity Endpoint (population summary)**
• To evaluate the immunogenicity of three CV0801 booster vaccine manufacturing specifications	• Serum neutralization titers against pseudovirus bearing specific CCI [redacted] spike protein at Day 29 (GMT)

AE: adverse event; AESI: adverse events of special interest; GMT: geometric mean titer; MAAE: medically attended adverse event; SAE: serious adverse event

Complementary information on estimands can be found in Section 3.

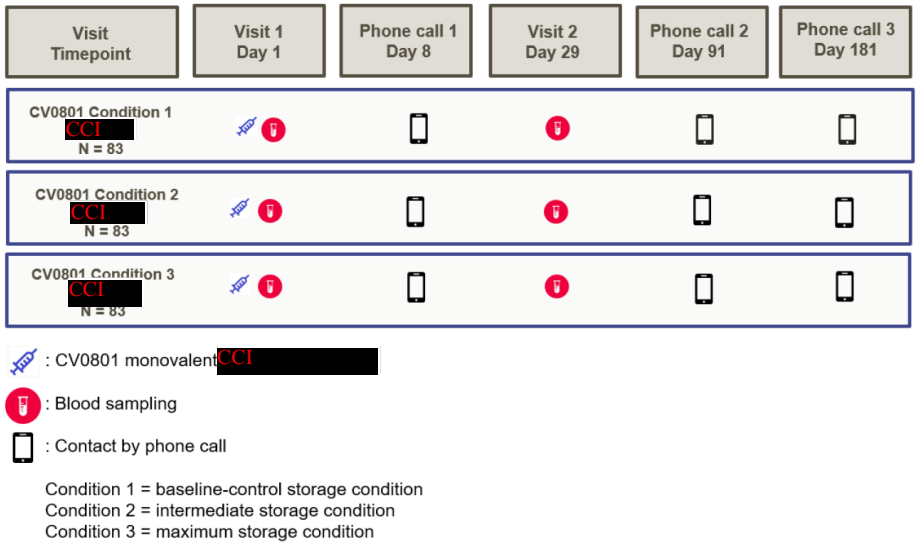
1.2. Study Design

Overview of Study Design and Key Features

Part A

Overview of Study Design and Key Features

Part B



Design Features	• Multi-country, multi-center. • Intended duration of the study per participant: Approximately 6 months. • Aspects of data collection: blood samples, safety events. • Method of data collection: – Standardized electronic Case Report Form (eCRF) – Solicited AEs that occur during the 7-day follow-up period after study intervention will be collected using an electronic Diary (eDiary). Unsolicited AEs will be collected using eCRF. • Safety monitoring: the continual review of safety data will be performed by an unblinded IDMC and a blinded SRT. An unblinded iDRC will review safety (and immunogenicity) data from the Day 29 interim analysis to make recommendations for a future Phase 3 study: Part A - on dose selection and PartB – on storage condition. Refer to Section 8.4 of the protocol for more information on safety monitoring strategy applicable to this study and Section 8.5 of the protocol for IDMC, SRT and iDRC composition and role.
Study intervention	• Part A: The study interventions administered in part A of the study include the CV0701 bivalent vaccine, CV0601 monovalent vaccine and comparator vaccine CCI CCI • Part B: The study intervention administered in part B of the study is the CV0801 monovalent vaccine under 3 different storage conditions baseline control (condition 1), intermediate (condition 2) and maximum storage (condition 3) condition. • All study interventions are administered as single-dose intramuscularly (IM).
Study intervention Assignment	• Part A: Participants will be randomly assigned (1:1:1:1:1) to the study groups using a central randomization system. The randomization will be based on permutation blocking scheme using country, previous known COVID-19 (yes, no), and age (< 65 years, ≥65 years) as stratification factors. • Part B: Participants will be randomly assigned (1:1:1) to the study groups using a central randomization system. The randomization will be based on permutation blocking scheme using country, previous known COVID-19 (yes, no), and age (< 65 years, ≥65 years) as stratification factors.
Interim Analysis	• For Part A and Part B separately, interim analysis will be performed based on safety and immunogenicity data (neutralization titers matched to the variant encoded on the study vaccines) for all participants up to Day 29. • Additional analyses e.g., safety analyses, will be conducted to support IDMC and SRT decisions.

2. STATISTICAL HYPOTHESES

There is no hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% confidence interval (CI). To provide preliminary evidence of non-inferiority, p-values for the null hypothesis that the group GMT ratio (investigational group over the control group for Part A; Conditions 2 and 3 groups over Condition 1 group for Part B) is below 0.67 will be provided for the immunogenicity primary endpoints (see Section 4.2.2).

2.1. Multiplicity Adjustment

As this study is descriptive, no adjustment for type 1 error will be done.

3. ANALYSIS SETS

Table 1 Analysis set definition and analyses evaluated

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post-screening procedure) NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.	• Study Population
Exposed Set (ES)	• Participants who received study intervention • Participants will be analysed according to the study intervention administered.	• Safety, immunogenicity if applicable, demography
eDiary Set	• All participants in the Safety analysis set for whom eDiary data are available (complete or partial).	• Solicited AEs
Per-Protocol Set (PPS)	• All participants from the ES who were eligible, complied with vaccination as per protocol (e.g., vaccine not expired, with appropriate temperature storage), and had a pre-dose and Day 29 anti-neutralizing titer against either the CCI [redacted] CCI [redacted] strains. Immunogenicity data at a post-vaccination visit will be censored in case of noncompliance for the blood sample visit. Likewise, immunogenicity data after the following intercurrent event will be censored: COVID-19, immunosuppressive or immunodeficient conditions, COVID-19 vaccination and prohibited medication/vaccination after study intervention.	• Immunogenicity , demography

4. STATISTICAL ANALYSES

4.1. General Considerations

All statistical analyses will be performed using SAS® software Version 9.4 or later. Part A and Part B will be analyzed independently, the considerations outlined in this SAP apply separately to each part unless stated otherwise.

Missing data will not be imputed unless mentioned otherwise (refer to Section 6.2.2).

4.1.1. General Methodology

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

Continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, quartiles, minimum, and maximum). Categorical data will be summarized using the participant count and percentage for each category.

A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of participants with non-missing values of corresponding parameter in that study group within the analysis population of interest, unless otherwise specified.

Confidence intervals (CIs) will use 95% confidence levels.

For calculations regarding antibody levels/titers descriptive statistics will also be provided i.e. number of evaluable samples, geometric mean titer (GMT) and geometric mean increase (GMI) (and the associated geometric standard deviations), median, quartiles, minimum, and maximum and 95% CI. Geometric means are calculated by obtaining the mean of the log10 titers and then back transforming to the original scale. Geometric standard deviations (SDs) are calculated as 10^(standard deviation of log10 titers). CIs are calculated using t-distribution of log transformed values then back transformed to the original scale. Antibody values reported as below the LLOQ or a quantifiable threshold will be replaced, respectively, by half the LLOQ or by half the threshold while values above a quantifiable threshold will be assigned the value of the threshold. For neutralization assays CCI [redacted], the value of the LLOQ is 10. The percentage of participants with titer above the LLOQ will also be provided per variant per time-point.

CCI [redacted]

CCI [redacted]

A listing (TLF) is to be generated on the enrolled set for any required item even where no data is available or reported. In such cases, the listing will state: “No Data Reported”.

4.1.2. Baseline Definition

Baseline will be defined as the last non-missing evaluation prior to study intervention administration, unless otherwise specified.

4.2. Primary Endpoint(s) Analyses

4.2.1. Safety and reactogenicity endpoints

For Part A and Part B separately, reactogenicity descriptive summary statistics will be provided for the eDiary Set by vaccine group; other safety endpoints, descriptive summary statistics will be provided for the ES.

4.2.1.1. Solicited AEs

All solicited events must be recorded into the eDiary by the participant during the first 7 days following administration of the dose of study intervention (Day 1 to Day 7 included), irrespective of occurrence or intensity. Solicited events ongoing after Day 7 will be recorded in the eCRF and followed-up until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, the participant is lost to follow up, or study is completed. If the collection of solicited Aes was not possible for any reasons via the eDiary and solicited Aes were reported to the investigator by the participant, then it would be possible for them to be reported directly to the site staff and submitted (e.g., via the eCRF).

The following administration site events will be solicited:

a. Pain
b. Redness
c. Swelling
d. Lymphadenopathy, defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the injection arm

The following systemic events will be solicited:

e. Fever
f. Chills
g. Headache
h. Fatigue

i. Myalgia

j. Arthralgia

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

Grading or actual temperature/redness and swelling will be captured in the eDiary as per a modified grading of symptoms based on the FDA toxicity grading guidance for industry [FDA, 2007] with Grades 3 and 4 combined and swelling evaluated using the actual measurement only (refer to Section 6.2.2.2). When solicited AE data entered by the participant are missing or incorrect, data collected by study investigator/staff will be used in the summaries if available.

The percentage of participants reporting each individual solicited administration site event (any grade, Grade 1, Grade 2, Grade 3, any grade ongoing at day 7 and medically attended events) and solicited systemic event (any grade, Grade 1, Grade 2, Grade 3, any grade ongoing at day 7 and medically attended events) within the 7-day follow up period (i.e., Day 1-Day 7 post-dosing) will be tabulated for each group.

The duration of solicited AEs of any grade (see Section 6.2.1.10) will be summarized. The start date is the first day during the 7-day solicitation period with the symptom at grade > 0 while the stop date is the last day with the symptom at grade > 0 in or beyond the solicited period. In addition, the duration for specific grade(s) for each symptom defined as the number of days in the reporting period with grade above or equal to specific grade will be summarized.

Prolonged solicited Aes that continue beyond Day 7 or Day 28 will be identified using a flag in listing of Aes.

The percentage of eDiary days completed in the solicited period will be summarized by group. A day is considered completed in the eDiary if it was entered by the participant or the investigator. The percentage of completed days will be calculated as follows:

$$SumSymp/(7*NumSymp*ExpSubj)$$

SumSymp is the sum of the total number of days completed for a specific symptom across all symptoms and exposed subjects. NumSymp is the number of symptoms and ExpSubj is the number of exposed subjects.

4.2.1.2. Unsolicited AEs with onset within the 28 days follow-up period (day 1-28)

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate PT.

A study intervention causally related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". Investigators will not be required to assess the causality of solicited Aes if the onset is during the solicitation period.

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/. The investigator will use clinical judgment to determine the relationship.

The percentage of participants with any unsolicited Aes within the 28-day follow up period (i.e., Day 1-Day 28) with its exact 95% confidence interval (CI) will be tabulated by group and by MedDRA PT and System Organ Class (SOC). Similar tabulation will be done for Grade 3 unsolicited Aes, for any causally related unsolicited Aes, for Grade 3 causally related unsolicited Aes, for unsolicited Aes resulting in a medically attended visit and for SAE.

A data listing for all unsolicited AEs will be provided by age group (< 65 years, ≥ 65 years), dose group and participant number.

4.2.1.3. MAAEs, SAEs and AESIs with onset after vaccination (day1 up to study end)

The study will capture the following specific over the full study period: MAAE, SAE and AESIs defined as either :

- Potential immune-mediated disorders (pIMDs),
- Any laboratory-confirmed moderate to severe case of COVID-19,
- Myocarditis and pericarditis and,
- Anaphylaxis or severe hypersensitivity within 24 hours after study intervention administration.

All suspected cases of COVID-19, myocarditis, and pericarditis in study participants will be diagnosed and clinically evaluated, which may require unscheduled study site visits and additional testing based on the investigator's judgment.

The number and percentage of participants with any event for each MAAE, SAE, AESI In addition, summary will be provided by relationship to study intervention, maximum grade/severity and outcome. The worst-case approach will be applied at participant level for the maximum grade/severity, i.e., a participant will only be counted once as the worst case from all the events experienced by the participant.

The percentage of participants with at least 1 report of SAE (any, related, fatal and fatal related), with at least 1 report of MAAE and with at least 1 report of AESI, respectively,

classified by the MedDRA SOC and PT and reported from Dose 1 up to study end will be tabulated with exact 95% CI.

In the AESI/SAE summaries, a participant with 2 or more Aes within the same SOC or PT level but different relationship will be counted only once in the level using the related incident.

4.2.2. Co-primary and Secondary Immunogenicity Endpoints

All immunogenicity endpoints will be analyzed separately for Part A and Part B. Prior to the final study analysis, all primary endpoint immunogenicity analyses will be based on the ES (e.g. interim analysis, analyses to support IDMC and iDRC). At the final analyses immunogenicity will be based presented for both ES and PPS.

In part A, for each variant CCI) and at the specified time points the comparison of CV0701 and CV0601 booster vaccines with CCI CCI will be performed. In part B, each of Conditions 2 and 3 will be compared with Condition 1 at Day 29 with respect to CCI . In both Part A and Part B, the comparisons will be obtained as follows:

The group GMT ratio, associated 2-sided 95% CI and p-value for the null hypothesis that group GMT ratio is below 0.67 will be based on group contrast from an ANCOVA model on log10-transformed anti-neutralizing titer. The model will include the vaccine group, country, previous known COVID-19 infection (yes, defined by self-reporting or positive N protein at pre-vaccination, no), age (< 65 years, ≥ 65 years), and log10-transformed pre-dose titer as fixed effects. The adjusted GMT and GMI in each group will be obtained from the same model with 95% CI. Missing data will not be replaced. For this model, a titer below LLOQ or a quantifiable threshold will be assigned, respectively, half the LLOQ or threshold while a titer above a quantifiable threshold will be assigned the threshold.

For each vaccine group the seroresponse rate will be provided together with 95% CI derived using the method of Clopper and Pearson [Clopper, 1934]. The 2-sided 95% CI on group difference in seroresponse rate between an investigational study intervention and (minus) the control group will be computed based on the method of Miettinen and Nurminen [Miettinen, 1985].

Table 2 GMI and Seroresponse definition

Abbreviation/term	Definition
GMI	The geometric mean of the ratios of the post-dose titer over the pre-dose titer.
Seroresponse rate	The percentage of dosed participants who have either a pre-dose titer < LLOQ and a post-dose titer ≥4*LLOQ or a pre-dose titer ≥LLOQ and at least a 4-fold increase in post-dose titer.

The following SAS code will be used for computation of GMT ratio where ‘log’ and ‘logbase’ are the $\log_{10}$ transformed values at post-dose and pre-dose respectively, ‘trt’ is

the vaccine group, while country, 'priorcovid' and 'agegroup' are the stratification factors at randomization:

```
PROC GLM DATA=is ALPHA=0.05;
    CLASS trt country priorcovid agegroup;
    BY visit istest variant;
    MODEL log = trt country priorcovid agegroup logbase;
    LSMEANS trt / CL;
RUN;
```

The seroresponse rate will be computed using the following SAS code where 'seroresp' is the seroresponse status post-dose:

```
PROC FREQ DATA=immuno;
        BY istest variant;
        TABLE trt*seroresp / RISKDIFF (CL=MN) ALPHA=0.05;
RUN;
```

4.3. Secondary Endpoint(s) Analyses (Part A)

Prior to the final study analysis, all secondary endpoint analyses will be based on the ES (e.g. interim analysis, analyses to support IDMC and iDRC). At the final analyses immunogenicity will be based presented for both ES and PPS.

For each variant CCI [redacted], a secondary comparison of the immunogenicity of CV0701 and CV0601 booster vaccines with CCI [redacted] vaccine will be performed as follows:

- Serum neutralization at Day 91 and Day 181 (GMT)
- Seroresponse from baseline of serum neutralization titers at Day 29 (percentage of participants)
- Fold increase from baseline of serum neutralization titers at Day 29, Day 91, and Day 181 (GMI)

4.3.1. Main analytical approach

The analyses of secondary endpoints at the specified time points will be performed as described in Section 4.2.2.

4.4. Tertiary/Exploratory Endpoint(s) Analyses (Part A)

CCI [redacted]

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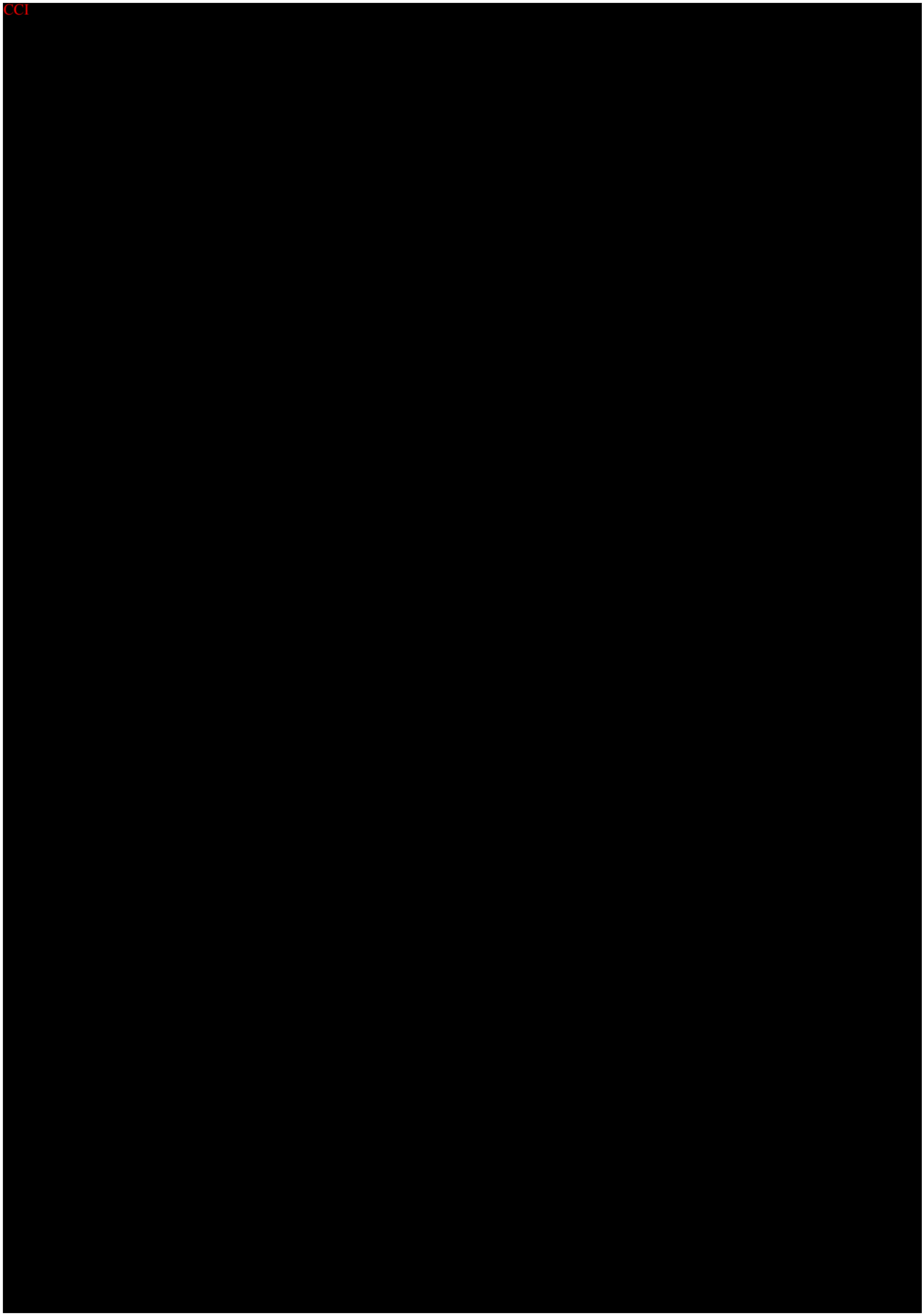

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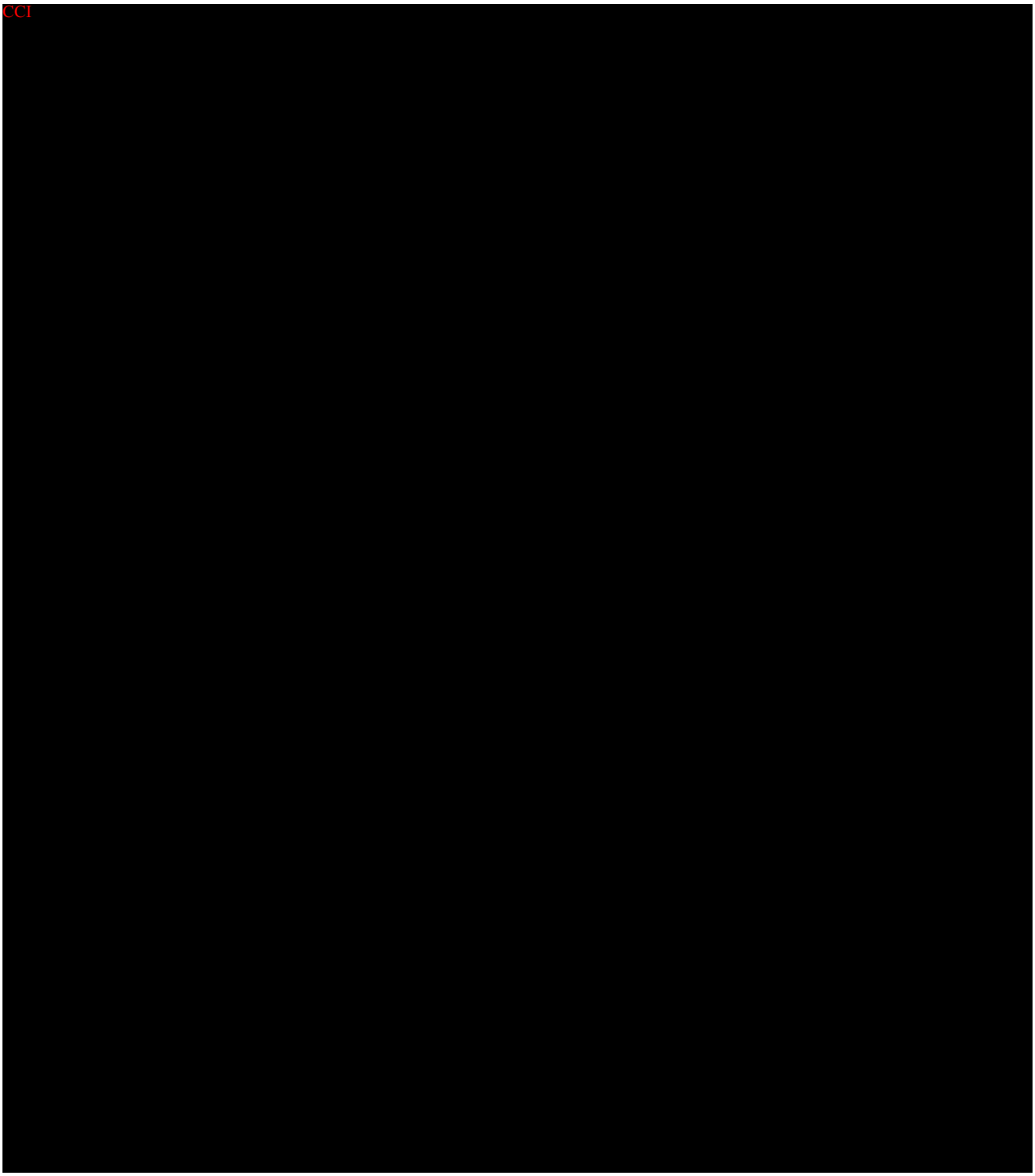

4.5. Safety Analyses

Refer to Section 4.2.1.

4.5.1. Independent Data Monitoring Committee (IDMC) and Safety Review Team (SRT) and Internal Data Review Committee (iDRC)

An unblinded IDMC will review all available safety (and/or immunogenicity) data at scheduled timepoints. The IDMC will meet at the following timepoints:

- After 20% of participants have completed solicited reporting period (Day 7).
- Interim analysis, which will be based on Day 29 data from all participants.
- Every 3 months until the end of the study.
- Ad hoc meetings, as needed, to review safety data.

The SRT will contribute to the continual assessment of incoming new safety (and efficacy) information. The SRT will remain blinded to study group allocation.

An unblinded iDRC will review safety, reactogenicity, and immunogenicity data from the Day 29 interim analysis to make recommendations on dose selection for a future Phase 3 study.

The Tables Figures and Listings to be generated to support IDMC and SRT reviews will be detailed in a dedicated output programming specification (OPS).

4.6. Other Analyses

A table summarizing solicited as well as unsolicited Aes excluding SAE will be provided by group – the number and percentage of participants with AE will be provided with exact 95% CI. Unsolicited Aes will also be tabulated by MedDRA PT and SOC.

4.6.1. Subgroup analyses

For primary immunogenicity and seroresponse endpoints subgroup analysis will be performed by age (< 65 years, ≥ 65 years), prior infection, number of prior COVID-19 vaccinations and country if there are at least 15 participants with data per vaccine group in each subgroup. For immunogenicity endpoints subgroup analysis will focus on between group summaries only based on the PPS.

4.7. Interim Analyses

For each study part, an interim analysis will be performed based on safety and immunogenicity data (neutralization titers matched to the variant encoded on the study vaccines) for all participants up to Day 29. To maintain the study blinding, the unblinded analysis will be available to the IDMC, iDRC core members and study statisticians in charge of the analysis. In addition, aggregate summaries will be used for regulatory interaction before LSLV. However, all efforts will be made to ensure that participants, investigators and monitoring staff will continue to remain blinded. Sequence of interim and other planned analyses is as follows:

- Interim analysis: up to Day 29 safety and immunogenicity data (neutralization titers matched to the variant encoded on the candidate vaccines) for all participants (Part A and B separately).

- Final analysis: up to Day 181 safety and immunogenicity data for all participants (Part A and B separately).

The interim analysis as well as safety and immunogenicity analyses to support IDMC, iDRC and SRT will be based on the ES.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 26 September 2023).

5. SAMPLE SIZE DETERMINATION

Part A

Approximately 415 participants will be enrolled in the study and randomized in a 1:1:1:1:1 ratio to receive 1 of the 3 CV0701 formulations, CV0601, or the comparator vaccine (i.e., 83 participants will be enrolled in each of the 5 groups).

Part A will provide preliminary evidence of CCI [redacted]

Part B

In Part B, a total of 249 participants will be enrolled and randomized in a 1:1:1 ratio to receive an injection of 1 of the 3 vaccine storage conditions; baseline-control, intermediate or maximum storage conditions (83 participants in each of the 3 groups).

Part B study will provide preliminary evidence of CCI [redacted]

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the exposed set.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for exclusion from analysis will be summarized for the enrolled set and ES.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, sex, ethnicity, height/weight, body mass index (BMI) (kg/m^2) on Day 1, race, country, N-protein status, prior COVID-19 infection status (defined by self-reporting or positive N protein at pre-vaccination) and number of prior COVID-19 vaccinations will be summarized with descriptive statistics (see Section 4.1.1). In addition, the following age categories will be summarized: 18-64 and 65-84 based on the Enrolled Set, ES and PPS at day 29.

6.1.3. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study. Important PDs include, but are not limited to, the following:

All participant data is excluded from the PPS:

- Study intervention not administered at all
- Invalid/missing informed consent
- Fraudulent data
- Participants got dosed but not as per protocol
- Study intervention storage temperature deviation which is not accepted by quality
- Expired study intervention administered
- Ineligible participant
- no pre-dose and Day 29 anti-neutralizing titer against either the CCI [redacted] CCI [redacted]

Participant data collected on the day or after the event is excluded from the PPS:

- SARS-CoV-2 infection
- Administration of concomitant vaccine(s) forbidden in the protocol
- Administration of any medication forbidden by the protocol, namely administration during the study period of investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention, of long-acting immune-modifying drugs or of immunoglobulins and/or any blood products or plasma derivatives with the exception of monoclonal antibodies specifically directed against the spike protein of SARS-CoV-2 virus, for treatment of COVID-19 disease

Participant lab data collected on the day of the event is excluded from the PPS:

- Participants did not comply with blood sample schedule (see schedule of activities in protocol, Section 1.3)
- Immunogenicity results not available post-dose
- Serological results available but results unreliable (e.g., wrong blood sample management)

The following exclusion codes (as per PPD processes) will be used in this study:

Code	Description
3	Exclude from the PPS only
6	Exclude from the PPS at this visit
7	Exclude from the PPS from this visit onwards
99	Include in all analysis (minor PD)

Note regarding scheduled visits for neutralization samples (D1 D29 D91 D181): For out of window neutralization samples code 6 will be used for all scheduled visits. For missing neutralization samples code 3 will be used for D1 or D29 visits and code 6 will be used for D91 and D181 visits. For other lab related blood sample deviations, code 99 will be used which will not lead to any exclusion from the PPS.

The number of participants with important protocol deviations will be summarized by study group across time points separately (ie Day 29, 91 and Day 181. Important protocol deviations will be listed with date of occurrence, deviation description, and analysis set, including time point for PPS) from which participant is excluded. Important protocol deviation summary will be based on the Enrolled Set.

The important PDs will be reported in the Clinical Study Report (CSR). The important PDs leading to elimination from the PPS will be summarized by study group for the ES and the important PDs leading to elimination from the ES will be summarized accross groups (ie pooled groups) for the Enrolled Set.

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Table 3 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1 (Day 1)→Phone call / CCI (Day 8)	7 days	7±1
Visit 1 (Day 1)→Visit 2 (Day 29)	28 days	28±3
Visit 1 (Day 1)→Visit 3 (Day 91)	90 days	90±7
Visit 1 (Day 1)→Visit 4 (Day 181)	180 days	180±7

If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.
Interval is computed as the difference between 2 dates.

6.1.4. Prior and Concomitant Medications

Concomitant medications are defined as any medications and vaccines (other than study intervention) taken after the study intervention administration. Any medication or vaccine (other than study intervention) started prior to the study intervention administration and continued after the study intervention administration will be considered a concomitant medication.

Concomitant medications/vaccinations will be coded using both the GSK Drug and WHO Drug dictionaries and will be listed and summarized descriptively (any medication, any antipyretic, and any antipyretic taken prophylactically, respectively) by study group using the ES.

The antipyretic classification is derived from the following ATC code

ATC Code
A03D, A03DA, A03DB, A03DC, A03EA
M01, M01A, M01AA, M01AC, M01AE, M01AG, M01AB, M01AH, M01AX, M03B, M03BA, M03BB, M03BB, M03BC, M03BX
N02BG, N02AC, N02AG, N02AX, N02B, N02BA, N02BB, N02BE
R05, R05D, R05X

The percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 28-day follow up period (i.e., Day 1-Day 28 post-dose) will be summarized by group.

6.2. Appendix 2: Data Derivations Rule

6.2.1. Data derivation

This section includes complementary derivation rules.

6.2.1.1. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.2.1.2. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.2.1.3. Body Mass Index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

6.2.1.4. 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

6.2.1.5. 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, with the exclusion of CCI data, the following derivation rules apply:

Table 4 Numerical serology results

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
All other cases	missing

6.2.1.6. Geometric Mean Titres (GMTs) and Concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable titres or concentrations will be converted as described in Section 6.2.1.5 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.1.7. Onset Day

The onset day for an event (e.g., AE, concomitant medication/vaccination) is the number of days between the study dose administration and the start date of the event. This is 1 for an event occurring on the same day as a study dose when the timing of vaccination is prior to the onset time of the AE.

6.2.1.8. Study Day

Study day will be calculated as follows:

- Study day prior to dosing will be calculated as: date of assessment – date of the study intervention administration
- Study day on or after the date of the dosing will be calculated as: date of assessment – date of the study intervention administration + 1.

6.2.1.9. Solicited and Unsolicited AEs

For clinicaltrials.gov and EudraCT posting purposes, the number and percentage of participants reporting any solicited and unsolicited adverse events excluding SAE will be summarized according to MedDRA PTs together with the number of events. A solicited AE starting within the solicited period (day 1-7) will be counted as one

event. Unsolicited AE, excluding prolonged solicited AE, with the same PT and start date will be counted as one event. Solicited AEs will be mapped to MedDRA as follows:

Table 5 Mapping of solicited events to MedDRA

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Lymphadenopathy	10025197	Lymphadenopathy
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia
Chills	10008531	Chills

6.2.1.10. 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 1 day, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

For any grade, duration of solicited AE is defined as Stop date – Start date + 1, with Start date defined as the first day with the symptom at Grade ≥ 0 within the 7-day solicitation period and Stop date defined as the last day with the symptom (i.e., Grade > 0) in or beyond the solicited period. For solicited AE continuing beyond Day 7, stop date will be the last day with the symptom . .

6.2.1.11. Counting Rules for Occurrences of Solicited Events starting during the solicitation period

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only 1 occurrence regardless of the number of days on which it occurs.

6.2.1.12. AESIs

GSK MedDRA queries will be used to identify AESI:

- pIMD: refer to Table 9 from the protocol
- Severe hypersensitivity (including anaphylaxis): Grade 3 unsolicited AEs under MedDRA SMQ hypersensitivity, narrow search (includes anaphylaxis), with an onset within 24 hours after dosing

Myocarditis/pericarditis. In addition to identification based on the medical and scientific judgement of the investigator, the following non-exhaustive list of PTs will be used: autoimmune myocarditis; eosinophilic myocarditis; giant cell myocarditis; hypersensitivity myocarditis; immune-mediated myocarditis; myocarditis; autoimmune pericarditis, pericarditis; pericarditis adhesive; pericarditis constrictive; pleuropericarditis.

These pIMD, myocarditis and pericarditis queries may be revised based on MedDRA dictionary version.

AESI summaries will include AEs identified by either the investigator or the MedDRA queries.

6.2.2. Handling of Partial Dates

6.2.2.1. Dates

When partially completed dates (i.e., dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.
- For stop date, the maximum between the start and imputed stop date by above rule will be used instead.

The following exceptions apply:

- Adverse events start dates on the same day as the vaccination but with missing time:
  - Onset day will be day 1.
- Adverse events start dates with missing day:
  - If the event starts in the same month as the study dose administration then the imputed start date will match the study dose given during that month.
- Adverse events start dates with missing day and month:
  - If the event starts in the same year as the study doses the imputed start date will match the study dose given during that year.

- Adverse events stop dates with missing day: the last day of the month or the last contact date will be used, which ever come first.
- Adverse events stop dates with missing day and month: the last day of December or the last contact date will be used, which ever come first.
- Adverse events stop dates with missing day, month, and year: the last contact date will be used.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

6.2.2.2. Daily Recording of Solicited Events

For studies **using electronic diaries** for the collection of solicited events, a solicited event will be considered present only when a daily recording of Grade 1 or more is present. To determine the grading, the following rule will be used:

Table 6 Local solicited AE grading

Administration Site (Local) reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Mild: Any pain neither interfering with nor preventing normal everyday activities.	Moderate: Painful when limb is moved and interferes with everyday activities.	Significant pain at rest. Prevents normal everyday activities.
Redness *	25 – 50 mm	51 – 100 mm	>100 mm
Swelling	25 – 50 mm	51 – 100 mm	> 100 mm
Lymphadenopathy**	Present but does not interfere with activity	Interferes with normal activity	Prevents normal activity

* For redness and swelling, in addition to grading the measured administration site reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the administration arm.

Table 7 Systemic solicited AE grading

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	>38.9 >102.0
Headache	Headache that is easily tolerated	Headache that interferes with normal activity	Headache that prevents normal activity
Fatigue	Fatigue that is easily tolerated	Fatigue that interferes with normal activity	Fatigue that prevents normal activity
Myalgia	Myalgia present but does not interfere with activity	Myalgia that interferes with normal activity	Myalgia that prevents normal activity
Arthralgia	Arthralgia present but does not interfere with activity	Arthralgia that interferes with normal activity	Arthralgia that prevents normal activity
Chills	Chills present but do not interfere with activity	Chills that interfere with normal activity	Severe: chills that prevent normal activity

* Axillary temperature.

6.2.2.3. Unsolicited Adverse Events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

For the summary of unsolicited adverse events, ongoing solicited events reported as unsolicited AEs will not be counted.

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

6.2.3. Display of Decimals

6.2.3.1. Percentages

Percentages and their corresponding confidence limits will be displayed with 1 decimal except for 100%, in which case no decimal will be displayed.

6.2.3.2. Differences in Percentages

Differences in percentages and their corresponding confidence limits will be displayed with 2 decimals.

6.2.3.3. Demographic/Baseline Characteristics Statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-dose body temperature) will be presented with 1 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 maxima and minima of transformed height/weight variables will be displayed without decimals.

The maximum and minimum of transformed body temperatures will be displayed with 1 decimal.

6.2.3.4. Serological Summary Statistics

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

6.2.4. Trademarks

Trademarks of the GlaxoSmithKline /Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
Not applicable	SAS
Not applicable	CCI [redacted]

7. REFERENCES

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