Statistical Analysis Plan

Study ID: 217091

Official Title of Study: A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)

NCT ID: NCT05917288

Date of Document: 19-Nov-2024

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)
Study Number:	217091
Compound Number:	GSK1550188

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clintrials.gov	*NCT05917288*

Statistical Analysis Plan (SAP) Template v3.0 14 September 2022

TABLE OF CONTENTS

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	21 June 2023	217091 / Amendment 01 (03 January 2023)	Not Applicable	Original version
SAP amendment 1	14 Sep 2024	217091 / Amendment 01 (03 January 2023)	Section 4.3 safety analyses are modified	Clinical request
			Section 6 study population analyses and data derivation rule analyses are modified	Clinical request
SAP amendment 2	19 Nov 2024	217091 / Amendment 02 (24 January 2021)	Section 4.2 A listing of individual PK concentration was added	Individual PK concentration listing required.
			Section 4.3.3.1 Laboratory reference range shifts from baseline was modified	Analysis of laboratory reference range shifts from baseline was updated
			Section 6.1.2 allowable SLE medication usage at	Analysis for allowable SLE medication usage was updated

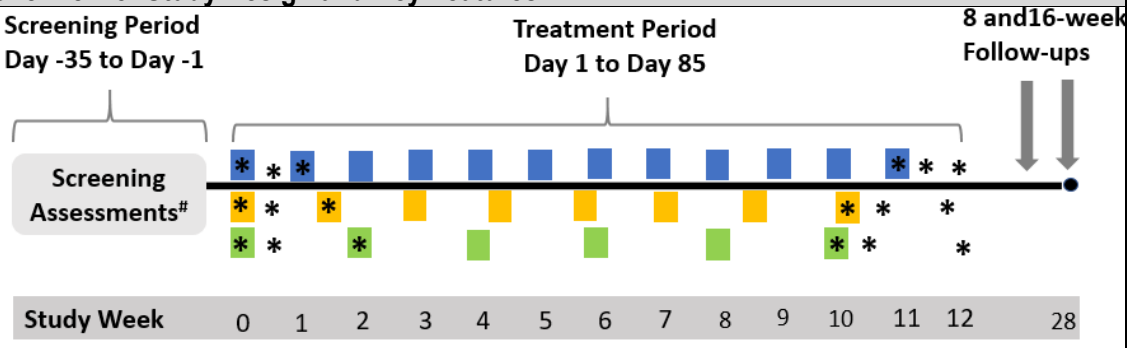
SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			baseline was added	
			Section 6.1.4 SLE medications usage was removed	Analysis for allowable SLE medication usage was updated
			Section 6.2.6 and Section 6.2.7 WHO DRUG rule was updated	Based on the study, WHO DRUG needs to be updated.
			Section 4.6 protocol version was updated	Protocol Amendment 02 is the latest version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217091. Details of the planned analyses are provided.

1.1. Study Design

Overview of Study Design and Key Features



Participants ≥50 kg body weight will receive belimumab 200 mg SC weekly
Participants ≥30 kg to <50 kg body weight will receive belimumab 200 mg SC every 10 days
Participants ≥15 kg body to <30 kg weight will receive belimumab 200 mg SC every 2 weeks

* PK sampling
# Participants will roll over from study 213560 thus the screening period of this study will have an overlap with study 213560.

Note: For those participants who don't have PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7 days (±2 days) and 14 days (±2 days) after last belimumab IV injection at Week 48 of study 213560.

Design Features	This is a single arm, multi-center open label study of belimumab plus standard of care in participants with SLE who have completed 48 weeks belimumab IV treatment in 213560 study to evaluate the PK and safety of subcutaneously administered belimumab over 12 weeks in approximately 17 paediatric participants ages 5-17 years and weighing ≥15 kg. 213560 study is an open label study to evaluate the safety, efficacy and pharmacokinetics of belimumab (10 mg/kg) IV with standard therapy in Chinese paediatric participants aged 5 to 17 years with active SLE. The participants in study 217091 will be those who have completed the 48-week treatment phase of 213560 study and who, in the investigator's judgement will benefit from continuing treatment with belimumab. The targeted aim for this study will be to recruit participants in Study 213560 who have IV PK samples collected. However, if the targeted number of participants cannot be met additional participants from the non-PK population in 213560 will also be included. The PK sample right after the last IV dose in 213560 and pre-dose PK sample of study 217091 will be collected from each patient to ensure the belimumab PK profile leading up to and following the switch to SC dosing can be accurately characterized for each participant.

Overview of Study Design and Key Features	
	Participants who have completed Week 52 assessment in study 213560, will receive the first SC dose in study 217091 no more than 4 weeks after the last IV dose (administered at week 48 visit of study 213560). The study will include: • Open-label, 12-week treatment phase. • Post-treatment follow-up assessments at 8 weeks and 16 weeks after the last dose of SC belimumab
Study intervention	Administration of belimumab 200 mg SC will be as follows: • Participants ≥50 kg body weight will receive belimumab 200 mg SC weekly. • Participants ≥30 kg to <50 kg body weight will receive belimumab 200 mg SC every 10 days. • Participants ≥15 kg to <30 kg body weight will receive belimumab 200 mg SC every 2 weeks.
Study intervention Assignment	This is an open-label study without randomization and blinding.
Interim Analysis	No formal interim analyses are planned.

2. STATISTICAL HYPOTHESES

The study is designed to descriptively evaluate the PK and safety of belimumab plus standard therapy, and as such no formal statistical hypothesis testing is planned.

2.1. Multiplicity Adjustment

There is no adjustment for multiplicity in this study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants whose parent/caregiver sign the ICF	• Study Population
Enrolled	• All participants assigned treatment.	• Study Population
Intent to Treat (ITT)	• All participants assigned treatment who received at least one dose of study treatment.	• Safety • Study Population
Pharmacokinetic (PK)	• All participants assigned treatment who received at least one dose of study treatment and for whom at least one post belimumab treatment PK sample was obtained and analyzed.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

No formal hypothesis testing is planned in the study; all analyses are descriptive.

4.1.1. General Methodology

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, the following will apply:

- Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, 25th percentile, 75th percentile and maximum.
- Categorical data will be summarized as the number and percentage of participants in each category.
- Where means or medians are displayed graphically, standard error bars or interquartile ranges (IQRs) will be presented, respectively.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, 25th percentile, and 75th percentile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. A maximum of four decimal places will be used. Percentages will be presented to one decimal place. A count of zero will have no corresponding percentage.
- When the data are summarized by week, unscheduled visits will be included.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint(s) Analyses

The primary endpoints will be described in a separate RAP written by Clinical Pharmacology Modelling & Simulation (CPMS) and analyses will be presented separately.

A by-subject listing of pharmacokinetic concentration will be produced since PK parameters will be calculated using population PK model.

4.3. Safety Analyses

The safety analyses will be based on the ITT Analysis Set, unless otherwise specified.

For estimand strategy in safety. The estimand is described by the following attributes:

Population	Chinese paediatric participants 5-17 years of age with systemic lupus erythematosus (SLE) who have previously been treated with IV belimumab
Treatment	• Repeat doses of 200mg belimumab administered subcutaneously (SC) over 12 weeks on a background of standard of care therapy
Endpoints	• Occurrence of adverse events, serious adverse events and adverse events of special interest through Week 12.
Summary Measure	• Frequency and percentage
Intercurrent events and strategies	• Discontinuation of study medication, addressed with while-on-treatment strategy. Safety data in the 12-week on-treatment period will be used in analysis.

Rationale for Estimand: This attempts to estimate on-treatment safety effects likely to be attributable to the drug.

In addition to estimand strategy in secondary endpoint, an additional analysis will be performed based on all safety data including 12-week on-treatment period and 16-week post-treatment follow-up period.

4.3.1. Extent of Exposure

The extent of exposure to study treatment through Week 12 will be assessed by examining the duration of exposure to belimumab in days and the total number of injections a subject receives.

Duration of exposure in days will be calculated as:

For 200 mg weekly, duration of exposure (days) = (Last injection date – First injection date + 7). For 200 mg every 10 days, duration of exposure (days) = (Last injection date – First injection date + 10). For 200 mg every 2 weeks, duration of exposure (days) = (Last injection date – First injection date + 14).

Only complete dates will be used when calculating duration of exposure. First and last injection dates will be used, regardless of any missed doses.

Percent compliance will be calculated as:

100* (Number of injections prescribed – Number of injections missed)/Number of injections prescribed.

The duration of exposure, the total number of injections, and the percent compliance will be summarized using descriptive statistics. The table for extent of exposure will be repeated for body weight. See Section 4.4.1 for details on the subgroup categories.

Exposure data will be listed for all subjects.

4.3.2. Adverse Events

Primary analysis

In primary analysis, AEs will be summarized for on-treatment period, unless otherwise specified. The definition of on-treatment period:

- Subjects who did not withdraw early from IP:

  Event onset date is on/after IP start date & on/before Week 12 Date.

  (IP Start Date ≤ Event Start Date ≤ Week 12 Date)

- Subjects who withdrew early from IP:

  Event onset date is on/after IP start date & on/before Early Withdrawal Date.

  (IP Start Date ≤ Event Start Date ≤ Early Withdrawal Date)

AEs with partial or missing start and/or stop dates will be assumed to be on-treatment unless there is evidence through comparison of partial dates to suggest otherwise.

The duration of the AE will be calculated as follows:

Duration of AE (days) = Date of AE resolution - AE start date + 1.

If the AE is ongoing the duration will be left blank and no imputation will be done.

Common AEs and common non-serious AEs will be defined as two or more subjects experiencing the event.

An overall summary of AEs will be presented showing the number and percent of subjects with at least one: AE, related AE, serious AE (SAE), severe AE, serious and/or severe AE, AE resulting in study agent discontinuation, and deaths during on-treatment period:

- Overview of all AEs

The number and percentage of subjects experiencing an AE and the incidence of AEs will be summarized for each of the following AE categories:

- All AEs (by SOC; by SOC and PT; by PT only)
- Serious AEs (by SOC; by SOC and PT; by PT only)
- Severe AEs (by SOC; by SOC and PT; by PT only)
- Study Agent Related AEs (by SOC; by SOC and PT; by PT only)

- AEs Resulting in Study Agent Discontinuation (by SOC; by SOC and PT; by PT only)
- Common AEs (by SOC and PT)
- Non-Serious AEs (by SOC and PT)
- Common Non-Serious AEs (by SOC and PT)
- Study Agent Related Serious AEs (by SOC and PT)
- Study Agent Related Non-Serious AEs (by SOC and PT)
- Fatal Serious AEs (by SOC and PT)
- Non-Fatal Serious AEs (by SOC and PT)
- Study Agent Related Non-Fatal Serious AEs (by SOC and PT)

A summary of AEs by SOC and severity will also be provided. For this display, the number and percentage of subjects will be summarized as mild, moderate, or severe based on the maximum severity observed across all PTs within the SOC during the specified study period for a given subject.

Summaries of AEs and drug related AEs by SOC, PT and severity will also be provided. The number and percentage of subjects will be summarized as mild, moderate, or severe based on the maximum severity observed within each PT, and within each SOC, during the specified study period.

The table for all AEs by SOC and PT will be repeated for body weight. See Section 4.4.1 for details on the subgroup categories.

A listing of all AEs will be presented, including duration and study day.

A listing for all SAEs will be produced.

Additional analysis

All subjects will be followed for safety at 16-week post-treatment follow-up period. In addition to the primary analysis for on-treatment period, overview of all AEs showing the number and percent of subjects with at least one: AE, related AE, serious AE (SAE), severe AE, serious and/or severe AE, AE resulting in study agent discontinuation, and deaths; and the following summary tables will be produced for all AEs including 12-week on-treatment period and 16-week post-treatment follow-up period:

- All AEs (by SOC and PT)
- Severe AEs (by SOC and PT)
- Serious AEs (by SOC and PT)
- Study Agent Related AEs (by SOC and PT)

Summary of AEs by SOC, PT and severity will also be provided. The number and percentage of subjects will be summarized as mild, moderate, or severe based on the maximum severity observed within each PT, and within each SOC.

The following listings will be produced:

- Listing of all AEs in 16-week post-treatment follow-up period

4.3.2.1. Adverse Events of Special Interest

In primary analysis, AESIs will be summarized for on-treatment period, unless otherwise specified.

To ensure consistency across belimumab studies, AESI will be defined per the version of the Program Safety Analysis Plan (PSAP) and MedDRA in effect at the time of data base release (DBR).

The Benlysta PSAP has been developed to include an adverse event of special interest (AESI) analysis for consistent reporting across belimumab studies. Categorizations for the AESIs are defined in the PSAP.

An overall summary of AESIs will be presented and each specific category of AESI will be presented separately by PT. The number and percentage of subjects with at least one occurrence and the number of events of the following AESIs will be provided.

The following AESI will be identified and adjudicated as detailed in the Program Safety Analysis Plan (PSAP).

Adverse Events
Adverse Events of Special Interest (AESI)

AESI will be defined per the version of the PSAP/MedDRA in effect at the time of DBR.
<u>Malignant Neoplasms</u>
• Malignancies Excluding non-melanoma skin cancer (NMSC)
• Malignancies Including NMSC
• Solid Tumour
• Hematologic
• Skin (All)
  • NMSC
  • Excluding NMSC
• Tumours of unspecified malignancy adjudicated as malignant per GSK
<u>Post-Injection Systemic Reactions (PISR)</u>
• PISR per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search
• Serious PISR per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search
• PISR per Anaphylactic Reaction CMQ broad search

Adverse Events

Adverse Events of Special Interest (AESI)

- Serious PISR per Anaphylactic Reaction CMQ broad search
- PISR per Anaphylactic Reaction CMQ algorithmic search
- Serious PISR per Anaphylactic Reaction CMQ algorithmic search

<u>All Infections of Special Interest (Opportunistic Infections (OI), Herpes Zoster (HZ), Tuberculosis (TB), And Sepsis; All and Serious, separately)</u>

- All opportunistic infections (OI) per GSK adjudication
- OI per GSK adjudication excluding Tuberculosis and Herpes Zoster
- Active Tuberculosis
  - Non-Opportunistic
  - Opportunistic
- Herpes Zoster
  - Non-Opportunistic
  - Opportunistic
    - Recurrent
    - Disseminated
- Sepsis

<u>Depression (including mood disorders and anxiety)/suicide/self-injury (All and Serious, separately)</u>

- Depression (including mood disorders and anxiety) (excluding suicide and self-injury)
- Suicide/self-injury
- Serious suicide/self-injury per GSK adjudication
  - Suicidal Behavior
    - Completed Suicide
  - Suicidal Ideation
  - Self-injurious Behavior without Suicidal Intent

Deaths

Malignant neoplasm events identified as “tumours of unspecified malignancy” will be reviewed for classification as malignant per GSK adjudication and will be presented by category and PT.

Post-injection systemic reactions and serious post- injection systemic reactions will be presented using different definitions as indicated above. These will be presented by category and PT.

Infection AESIs will be presented by Category and PT for all infections and for infections leading to study treatment discontinuation.

Depression, suicide and self-injury as defined in the PSAP will be presented by Category and PT.

Death will be presented by Category and PT.

Summaries of post-injection systemic reactions that occur on the day of an injection or within 3 days after an injection will be presented by the first six injection and over all injections, and PT for the following:

- Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the injection or within 3 days after the Belimumab injection) by PT in the first six injection.
- Serious Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the injection or within 3 days after the Belimumab injection) by PT in the first six injections.

Additional analysis

An overall summary of AESIs including 12-week on-treatment period and 16-week post-treatment follow-up period will be presented.

All AESIs including 12-week on-treatment period and 16-week post-treatment follow-up period will be presented in a listing.

4.3.3. Additional Safety Assessments

4.3.3.1. Laboratory Data

Laboratory Data including 12-week on-treatment period and 8-week post-treatment follow-up period will be included in the analysis.

Descriptive statistics for each analyte will be displayed for each week. The tables will display the mean value, standard deviation, median, 25th and 75th percentiles, minimum and maximum. No statistical tests will be performed.

A line graph will be produced for each analyte which displays the mean value by week.

Change from baseline for each analyte will also be summarized for each post-baseline week. The tables will display the mean value, standard deviation, median, 25th and 75th percentiles, minimum and maximum. No statistical tests will be performed.

A line graph will be produced for each analyte which displays the mean change from baseline value by week.

Laboratory toxicity will be graded using Adverse Event Severity Grading Tables when possible. The worst laboratory toxicity grade during treatment for each laboratory parameter within each laboratory category (hematology, liver function, chemistries, urinalysis and immunoglobulins) will be presented.

Toxicity grade shifts from baseline of ≥ 2 grades will be summarized during treatment for each laboratory parameter within each laboratory category (hematology, liver function, chemistries, urinalysis and immunoglobulins). The table will display the number and percentage of subjects with at least one ≥ 2 grade shift as well as the specific shift categories: Grade 0 to 2, Grade 0 to 3, Grade 0 to 4, Grade 1 to 3, Grade 1 to 4 and Grade 2 to 4.

For laboratory tests without toxicity grades within each laboratory category (hematology, liver function, chemistries, urinalysis and immunoglobulins), shifts relative to the normal range will be summarized for each analyte as shifts 'to low' and shifts 'to high'. For the 'to low category' the percentage of subjects with at least one low post-baseline value, including unscheduled visits, in the study period relative to baseline will be displayed using the categories: no shift to low and normal/high to low. For the 'to high category' the percentage of subjects with at least one high post-baseline value in the study period relative to baseline will be displayed using the categories: no shift to high and normal/low to high. No statistical tests will be performed.

A laboratory value that is above the testing laboratory's normal range will be considered a high abnormal laboratory value. A laboratory value that is below the testing laboratory's normal range will be considered a low abnormal value.

The number and percentage of subjects with immunoglobulin values (IgG, IgA, and IgM) below the LLN at each week will also be presented for all subjects and then repeated for subjects greater or equal to LLN at baseline. No statistical test will be performed.

All clinical laboratory data will be listed.

4.3.3.2. Vital Signs

Vital signs assessment including 12-week on-treatment period and 8-week post-treatment follow-up period will be included in the analysis.

A summary of vital signs and change from baseline of vital signs will be presented by week. A listing of all subjects' vital signs will be presented.

4.4. Other Analyses

4.4.1. Subgroup analyses

Subgroup analyses of clinical interest will be made by the following subgroups:

- Baseline Body Weight: ≥50 kg vs ≥30 kg - <50 kg vs 15 kg - <30 kg

4.5. Interim Analyses

No formal interim analyses are planned.

4.6. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 02(approval date of protocol: 24 Jan 2024).

5. SAMPLE SIZE DETERMINATION

There are no formal calculations of power for this study. The sample size justification for study 217091 is based on the precision in the estimate of the geometric mean of $C_{avg,ss}$, over all study participants. The coefficient of variation (CV) for between-subject variability in $C_{avg,ss}$ was approximated to 35.5%, equal to the variability evaluated in overseas children receiving belimumab IV in study BEL114054 [Dimelow, 2020], on the basis that bioavailability for SC dosing is similar in all subjects and does not significantly increase variability in exposure.

$C_{avg,ss}$ is expected to be log-normally distributed and the 95% confidence interval (CI) relative to the geometric mean is given by $\exp(\pm t_{97.5,\,N-1} \times sd/\sqrt{N})$, where $t_{97.5,\,N-1}$ is the 97.5th percentile of the t-distribution with N-1 degrees of freedom, sd is the standard deviation in the logarithm of $C_{avg,ss}$ equal to 0.345 for 35.5% CV, and N is the number of subjects.

For N of 14, the 95% confidence interval in $C_{avg,ss}$ relative to the geometric mean is 82% to 122%. The 95% CI therefore lies within 22% of the point estimate for C_{avg} and this level of precision is considered adequate to characterize belimumab exposure in Chinese children receiving belimumab SC.

Considering the withdrawal rate in the previous and ongoing Benlysta paediatric studies in overseas and China, the withdrawal rate in the current study is estimated to be 20%. To account for a 20% withdrawal rate, the total sample size is 17.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The ITT population will be used to summarize the study population data.

6.1.1. Participant Disposition

The number and percentage of subjects enrolled by site will be summarized.

Using the Screened population, the number of subjects in each population (Screened, Enrolled, ITT and PK) will be summarized. A summary of the reasons for the screen failures will be provided along with a listing of the subjects who were screen failures.

If there are any subjects who are enrolled but do not receive any study drug, they will be included on the subject disposition listing in the Enrolled population, but not the ITT population.

For the ITT population, the subject's completion status will be assessed to evaluate percentages of dropouts as well as the reasons for dropout. The number and percentage of subjects who completed through Week 12 and who withdrawal, including reasons for withdrawal, will be displayed. Additionally, the cumulative number and percentage of subjects who withdrew by study visit based on different body groups will be displayed. The number and percentage of subjects who complete study and who withdrew, including reasons for withdrawal, will be displayed. The number and percentage of subjects who complete study intervention and who withdrew, including reasons for withdrawal, will be displayed.

A listing of subjects that deviated from the inclusion or exclusion criteria will be provided.

A listing of subject disposition will be provided showing their completion status and whether or not they are included in each population. A listing of subjects who withdrew from the study, including reason for withdrawal will also be provided.

6.1.2. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the continuous demographic and baseline characteristics of age (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2) and vital signs (blood pressure). Counts and percentages of the following categorical demographic and baseline characteristics will be presented: sex, Hispanic or Latino origin, race, body weight group (≥50 kg, ≥30 kg - <50 kg and 15 kg - <30 kg). A summary of the number and percentage of subjects reporting each general medical history term will also be provided.

The summary of demographic and baseline characteristics, general medical history will be repeated for the following subgroups, where the subgroup categories are defined as:

- Baseline Body Weight: ≥50 kg vs ≥30 kg - <50 kg vs 15 kg - <30 kg

Demographics will be listed for all patients.

Allowable SLE medication usage– counts and percentages by class (Steroids, Anti-malarials, Nsaids, Other Immunosuppressive/Immunomodulatory Agents and Aspirin) at baseline will be summarized.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

The percentage of subjects who experience an important protocol deviation will be presented. The tables will display the number and percentage of subjects who experience any important protocol deviation and for each deviation type. A listing of subjects experiencing an important protocol deviation will be provided.

A separate summary of all inclusion/exclusion criteria deviations will also be provided.

6.1.4. Prior and Concomitant Medications

Prior medication is any medication that started before first dose of study treatment. Concomitant medications include any medication that was taken at some point during the study period (post first dose of study treatment), regardless of whether it was started prior to the first dose of study treatment or not.

Concomitant medications will be coded according to drug name as defined in the WHO Drug Dictionary, and classified according to the WHO-Drug ATC classification level 1 and ATC level 4.A summary of the number and percentage of subjects with concomitant medications by ATC level 1 term and ATC level 4 term will be displayed. A further summary of concomitant medications by ATC level 4 term and preferred term will be provided. A listing of all concomitant medication data will be displayed by subject.

The number and percentage of subjects who receive protocol-prohibited medication will be summarized.

A listing of protocol-prohibited medication will be displayed by subject.

Additionally, a summary of concomitant medications by ATC level 1 term and ATC level 4 term used 12 weeks on treatment period summary of concomitant medications by ATC level 4 term used 12 weeks on treatment period will be displayed.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Treatment period	Definition
Pre-Treatment	Event start date < IP start date
On-Treatment	IP start date ≤ Event start date ≤ Week 12 Date or Early Withdrawal Date
Post-Treatment	Event start date > Week 12 Date or Early Withdrawal Date

6.2.2. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

Assessment Date = Missing → Study Day = Missing

Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date

Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.3. Assessment Window

Different body weight will have different schedule of visits. Therefore, the data will be analysed by the analysis timepoint (Week 0, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, 8-week Follow-up and 16-week Follow-up).

Early withdrawal and unscheduled visits will be slotted to the appropriate planned visit. The assigned analysis timepoint will be based on the interval in which the Study Day for the early withdrawal or unscheduled visit falls according to intervals provided below.

Body weight ≥50 kg, Dose 200 mg QW

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
All	Day-1	na	na	Screening (Visit 1)
All	Day 1	na	na	Visit 2 (Week 0)
All	Day 4	Day 2	Day 5	Visit 3
All	Day 8	Day 6	Day 11	Visit 4
All	Day15	Day 12	Day 18	Visit 5 (Week 2)
All	Day 22	Day 19	Day 25	Visit 6
All	Day 29	Day 26	Day 32	Visit 7 (Week 4)
All	Day 36	Day 33	Day 39	Visit 8
All	Day 43	Day 40	Day 46	Visit 9 (Week 6)
All	Day 50	Day 47	Day 53	Visit 10
All	Day 57	Day 54	Day 60	Visit 11 (Week 8)
All	Day 64	Day 61	Day 67	Visit 12
All	Day 71	Day 68	Day 74	Visit 13 (Week 10)
All	Day 78	Day 75	Day 79	Visit 14
All	Day 81	Day 80	Day 82	Visit 15
All	Day 85	Day 83	Day 87	Visit 16 (Week 12)
All	Day 141	na	na	Visit 17 (8 week Follow-up)
All	Day 197	na	na	Visit 18 (16 week Follow-up)

NOTES:

- If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting.

Body weight ≥30 kg - <50 kg, Dose 200 mg Q10d

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
All	Day-1	na	na	Screening (Visit 1)
All	Day 1	na	na	Visit 2 (Week 0)
All	Day 4	Day 2	Day 7	Visit 3
All	Day 11	Day 8	Day 15	Visit 4 (Week 2)
All	Day 21	Day 16	Day 25	Visit 5
All	Day 31	Day 26	Day 35	Visit 6 (Week 4)
All	Day 41	Day 36	Day 45	Visit 7 (Week 6)
All	Day 51	Day 46	Day 55	Visit 8
All	Day 61	Day 56	Day 65	Visit 9 (Week8)
All	Day 71	Day 66	Day 72	Visit 10 (Week 10)
All	Day 74	Day 73	Day 77	Visit 11
All	Day 81	Day 78	Day 84	Visit 12 (Week 12)
All	Day 137	na	na	Visit 13 (8 week Follow-up)
All	Day 193	na	na	Visit 14 (16 week Follow-up)

NOTES:

- If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting.

Body weight ≥15 kg - <30kg, Dose 200 mg Q2W

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
All	Day-1	na	na	Screening (Visit 1)
All	Day 1	na	na	Visit 2 (Week 0)
All	Day 4	Day 2	Day 9	Visit 3
All	Day 15	Day 10	Day 21	Visit 4 (Week 2)
All	Day 29	Day 22	Day 35	Visit 5 (Week 4)
All	Day 43	Day 36	Day 49	Visit 6 (Week 6)
All	Day 57	Day 50	Day 63	Visit 7 (Week 8)
All	Day 71	Day 64	Day 72	Visit 8 (Week 10)
All	Day 74	Day 73	Day 79	Visit 9
All	Day 85	Day 80	Day 90	Visit 10 (Week 12)
All	Day 141	na	na	Visit 11 (8 week Follow-up)
All	Day 197	na	na	Visit 12 (16 week Follow-up)

NOTES:

- If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting.

6.2.4. Multiple measurements at One Analysis Time Point

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.5. Handling of Partial Dates

Element	Reporting Detail	
General	• 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., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.	
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions:	
	Missing start day	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.

Element	Reporting Detail	
		– Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	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 – 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	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	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.
	Missing start day and month	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 – 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).

Element	Reporting Detail	
	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	No imputation

6.2.6. SLE Allowable Medication Categories at Baseline

Medication Category	Rule
Anti-malarials	Set to Anti-malarial if LISTCODE = 332735 and the route of administration is not 'TOPICAL','VAGINAL', 'CONJUNCTIVAL', 'INTRANASAL','INHALATION', 'INTRA-OCULAR','INTRATRACHEAL', 'EPIDURAL', 'INTRAARTICULAR', 'OTHER'.
Steroids	Set to Steroids if LISTCODE = 30000010N, and the route of administration is "INTRADERMAL", "INTRAMUSCULAR","INTRAVENOUS", "ORAL","SUBCUTANEOUS" or "INTRA-ARTICULAR".
Immunosuppressants	Set to Immunosuppressants if TOILIST.LISTCODE = 333236, and the route of administration is not "TOPICAL". Or CMDECOD contains "MERCAPTOPURINE", and the route of administration is in 'ORAL'. Or CMDECOD contains "CYCLOPHOSPHAMIDE", and the route of administration is 'ORAL' or 'PARENTERAL'.
NSAIDs	Set to NSAIDS if LISTCODE = 30001761N.
Aspirins	Set to Aspirin if LISTCODE = 332752.
General rules	If CMATCCD contains "V90", set to null. If both "ANTIMALARIALS" and 'IMMUNOSUPPRESSANTS' definition is satisfied, define "ANTIMALARIALS" prior to 'IMMUNOSUPPRESSANTS'. If both "ASPIRIN" and 'NSAIDS' definition is satisfied, define "ASPIRIN" prior to 'NSAIDS'. If CMCAT1='IMMUNOSUPPRESSANTS' and CMDECOD='CICLOSPORIN' and CMROUTE='INTRAOCULAR' then set to null.

Adjudication is performed.

6.2.7. Prohibited Medications and Non-Drug Therapies

Participants who start prohibited medications or therapies at any time during the study will be considered a protocol violation. Belimumab will be discontinued, and participants will be withdrawn from the study.

The following medications and therapies are prohibited at any time during the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used.
- Participation in a study using an investigational agent or non-drug therapy that may interfere with the conduct of this protocol (except study 213560)
- Anti- Tumor Necrosis Factor (TNF) or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, tocilizumab, golimumab).
- All biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).
- Janus kinase (JAK) inhibitors.
- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide (oral cyclophosphamide is permitted).
- Plasmapheresis, leukapheresis.
- Any live or live attenuated vaccines. (Participants who require a live or live attenuated vaccine during the study should have belimumab discontinued prior to receiving the vaccine).

Medication Category	Rule
All Prohibited Medications	Capture any of the Prohibited Medication subcategories below.
Other investigational agents	If ATC code contains “V98”. If CMDECOD contains “ANIFROLUMAB”. If CMDECOD contains "INVESTIGATIONAL DRUG",
Participation in a study using an investigational agent or non-drug therapy that may interfere with the conduct of this protocol	Requires clinical review to decide if treatment failure.
Anti-Tumor Necrosis Factor (TNF) or anti-IL-6 therapy	If LISTCODE = 30000417N or 332753.

Medication Category	Rule
All biologics	If LISTCODE = 30000417N or 332753. If CMDECOD contains "RITUXIMAB", "ABATACEPT", "ANAKINRA", "BELIMUMAB","ADALIMUMAB", "ETANERCEPT","INFLIXIMAB", "CERTOILIZUMAB", "TOCILIZUMAB","GOLIMUMAB".
Janus kinase (JAK) inhibitors	If LISTCODE = 30001836N.
Intravenous immunoglobulin (IVIG)	If LISTCODE = 332743.
IV cyclophosphamide	If CMDECOD = "CYCLOPHOSPHAMIDE" and CMROUTE=" INTRAVENOUS".
Plasmapheresis, leukapheresis	If CMDECOD contains "PLASMAPHERESIS" or "LEUKAPHERSIS".
Any live or live attenuated vaccines	Use latest version SDG of Bacterial vaccines, live, LISTCODE = 30000934N. Use latest version SDG of Viral vaccines, live, LISTCODE = 30000962N. Include collection contains "live", and ATC code beginning with "J07".

Adjudication is performed.

6.2.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

7. REFERENCES

Dimelow R, Ji B, Struemper H. Pharmacokinetics of Belimumab in Children With Systemic Lupus Erythematosus. Clin Pharmacol Drug Dev. 2021;(6):622-633. doi: 10.1002/cpdd.889. Epub 2020 Nov 27.