# Statistical Analysis Plan

**Study ID:** 213560

**Official Title of Study:** A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Paediatric Patients with Active Systemic Lupus Erythematosus (SLE)

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# TITLE PAGE

**Protocol Title:** A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Paediatric Patients with Active Systemic Lupus Erythematosus (SLE).

**Study Number:** 213560

**Compound Number:** *GSK1550188*

**Sponsor Name:** GlaxoSmithKline Research & Development Limited

**Regulatory Agency Identifier Number(s)**

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## TABLE OF CONTENTS

**PAGE**

## LIST OF TABLES

**PAGE**



## LIST OF FIGURES

**PAGE**

# VERSION HISTORY

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 14 July 2021 | Amendment 01 (Date: 29 January 2021) | Not Applicable | Original version |
| SAP Amendment 1 | 30 Aug 2024 | Amendment 04 (Date: 22 January 2024) | • Addition of supplementary estimand and additional analysis for primary efficacy endpoints. | • Additional analysis to further explore the efficacy in supplementary estimand and additional analysis with different method of missing data imputation. |
| | | | • Change in handling of missing data imputation- and add technical details for missing data imputation. | • Change to handle missing data imputation by using multiple imputation (MI) instead of last observation carried forward (LOCF) and provide further details for missing data imputation. |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | • Addition of estimand for Safety endpoint and additional analysis based on all safety data including 52-week on-treatment period and 16-week post-treatment follow-up period. | • Addition estimand for Safety endpoint to describe the clinical interest in Safety endpoint. |
| | | | • Addition of Population Pharmacokinetic (PopPK) Analyses for Pharmacokinetic endpoints | • Added to clarify the Pharmacokinetic analysis for Pharmacokinetic endpoints |

# 1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 213560. Details of the planned analyses are provided.

## 1.1. Objectives, Estimands and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the safety and efficacy of belimumab IV in Chinese paediatric patients with SLE. | Safety<br>➢ Incidence of adverse events of special interest (AESIs) through 52 weeks:<br>• All Infections of special interest, including serious infections of special interest and opportunistic infections<br>• Infusion related systemic reactions and anaphylactic reactions<br>• Depression, suicidality<br>• Malignancies<br>Efficacy<br>➢ Incidence of patients with ≥ 4 points reduction from baseline to Week 52 in SELENA SLEDAI |
| Secondary | |
| • To evaluate safety and tolerability of belimumab IV in Chinese paediatric patients with SLE | • Incidence of AEs through 52 Weeks<br>• Incidence of SAEs through 52 Weeks |
| • To evaluate the efficacy of belimumab IV in Chinese paediatric patients with SLE | • Incidence of patients with ≥ 4 points reduction from baseline in SELENA SLEDAI by visit<br>• Change from baseline to Week 52 in Physician Global Assessment (PGA)<br>• Change from baseline to Week 52 in Parent Global Assessment (ParentGA) |

| Objectives | Endpoints |
|---|---|
| | • Change from baseline in daily prednisone equivalent dose at Week 52<br>• Time to first flare/ first severe flare over 52 weeks |
| • To evaluate the pharmacokinetics (PK) of belimumab (10 mg/kg) IV in Chinese paediatric patients with SLE | • Median belimumab concentration levels at Day 0, 7 and 14 days post first dose, and pre-infusion and post-infusion at Day 84<br>• The PK will be evaluated with respect to clearance, volume of distribution and half-life, and individual steady state exposures Cmin, Cavg, Cmax and AUC. |
| Other | Other |
| CCI [redacted] | |

AESI- adverse events of special interest, AUC- Area under the concentration curve, Cavg- average plasma concentration, IV- Intravenous, Cmin- the minimum blood plasma concentration reached by a drug prior to administration of a second dose, ParentGA - Parent Global Assessment, PGA- Physician Global Assessment, SELENA SLEDAI- Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index

**Primary estimand for efficacy**

The primary clinical question of interest is: What is the treatment effect on SELENA SLEDAI after 52 weeks of treatment with GSK1550188 in Chinese paediatric patients with SLE while considering initiation of prohibited medications and treatment discontinuation for any reason to be unfavorable outcomes. For primary efficacy evaluation, using the percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 in the placebo group in a Phase 2 paediatric study (Study BEL114055) as target value to guide the primary analysis planned for this study. The target can be described as the observed proportion of patients with clinical benefit >43.6% (the mean placebo group response rate estimate in study BEL114055).

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable / endpoint: response status at Week-52 assessment, where response is defined as:
    - with ≥ 4 points reduction from baseline at Week 52 in SELENA SLEDAI, and
    - Not using prohibited medications, and
    - Not discontinuing study intervention for any reason
- Summary measure: The percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52.
- Intercurrent event:
    - Initiation of prohibited medications– composite strategy (Non-responder)
    - Study intervention discontinuation for any reason - composite strategy (Non-responder)

Rationale for estimand: Interest lies in the treatment effect on SELENA SLEDAI after 52 weeks of treatment with GSK1550188 in Chinese paediatric patients with SLE while considering initiation of prohibited medications and treatment discontinuation for any reason to be unfavorable outcomes. Participants who receive a protocol-prohibited medication at any time during the study will be considered protocol violation. Belimumab will be discontinued and participants will be withdrawn from the study. The composite strategy is used for this intercurrent event (ICE) where response is imputed as a non-responder from the date of the earliest ICE and all timepoints thereafter through Week 52. For participants who discontinue study intervention for any reason, the participants will not remain in the study to be evaluated for efficacy. The composite strategy is used for this ICEs where response is imputed as a non-responder at all timepoints thereafter through Week 52.

## 1.2. Study Design

| Overview of Study Design and Key Features | |
|---|---|
| **Design Features** | A multicentre, open label, single arm, prospective, 52-week study to assess the safety and efficacy of belimumab IV administered in combination with background standard therapy in Chinese Paediatric Patients with Active Systemic Lupus Erythematosus (SLE). |
| **Study intervention** | All the enrolled participants will be administered Belimumab (10 mg/kg) intravenously over a minimum of 1 hour on Days 0, 14, 28 and then every 28 days through the Week 48 (Day 336) visit. |
| **Study intervention Assignment** | This is a single arm and open-label study without randomisation and blinding. |
| **Interim Analysis** | No formal interim analyses are planned. |

# 2. STATISTICAL HYPOTHESES

This is an open-label study. A descriptive approach will be used, and no formal inference is planned in this study. For primary efficacy evaluation, using the percentage of participants with ≥ 4-point reduction from baseline in SELENA SLEDAI at Week 52 in the placebo group in a Phase 2 paediatric study (Study BEL114055) as target value to guide the analysis planned for this post approval commitment (PAC) study. The target can be described as the observed proportion of patients with clinical benefit >43.6% (the mean placebo group response rate estimate in study BEL114055).

## 2.1. Multiplicity Adjustment

This is a single arm study. No formal statistical hypothesis testing is planned. Hence no adjustment for multiple comparisons is required.

# 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. | • Efficacy and safety |
| 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 analysed. | • PK |

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

### 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.

### 4.1.2. Baseline Definition

The protocol specifies “Day 0” as First Treatment, but due to CDISC standard implementation first treatment date will appear as “Day 1” in the analyses and throughout this document.

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.

If a subject has the day 1 visit but partial data of the endpoint are missing (including individual items of any component of the primary endpoint), the last available answer(s) to the corresponding question(s) from the most recent pre-dose visit will be used for the missing item or component. For example, if the data on one or more items of the 24 SELENA SLEDAI questions are missing, the last available answer(s) to the corresponding question(s) from the most recent pre-dose visit where the corresponding item(s) are non-missing will be assigned to the missing item(s) in order to obtain a total score as beseline.

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

Concomitant medications and adverse events recorded on Day 1 will be assumed to be on-treatment.

## 4.2. Primary Efficacy Endpoint(s) Analyses

### 4.2.1. Definition of estimands

The primary clinical question of interest is: What is the treatment effect on SELENA SLEDAI after 52 weeks of treatment with GSK1550188 in Chinese paediatric patients with SLE while considering initiation of prohibited medications and treatment discontinuation for any reason to be unfavorable outcomes. For primary efficacy evaluation, using the percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 in the placebo group in a Phase 2 paediatric study (Study BEL114055) as target value to guide the primary analysis planned for this study. The target can be described as the observed proportion of patients with clinical benefit >43.6% (the mean placebo group response rate estimate in study BEL114055).

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable / endpoint: response status at Week-52 assessment, where response is defined as:
    - with ≥ 4 points reduction from baseline at Week 52 in SELENA SLEDAI, and
    - Not using prohibited medications, and
    - Not discontinuing study intervention for any reason

- Summary measure: The percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52.
- Intercurrent events:
  - Initiation of prohibited medications– composite strategy (Non-responder)
  - Study intervention discontinuation for any reason - composite strategy (Non-responder)

Rationale for estimand: Interest lies in the treatment effect on SELENA SLEDAI after 52 weeks of treatment with GSK1550188 in Chinese paediatric patients with SLE while considering initiation of prohibited medications and treatment discontinuation for any reason to be unfavorable outcomes. Participants who receive a protocol-prohibited medication at any time during the study will be considered protocol violation. Belimumab will be discontinued and participants will be withdrawn from the study. The composite strategy is used for this ICE where response is imputed as a non-responder from the date of the earliest ICE and all timepoints thereafter through Week 52. For participants who discontinue study intervention for any reason, the participants will not remain in the study to be evaluated for efficacy. The composite strategy is used for this ICEs where response is imputed as a non-responder at all timepoints thereafter through Week 52.

### 4.2.2. Handling of Missing Data

Missing data will be imputed differently depending on the handling strategy for the specific intercurrent event.

- Missing data due to initiation of prohibited medications or study intervention discontinuation for any reason. For participants who receive a protocol-prohibited medication or discontinue study intervention for any reason at any time during the study, participants will be withdrawn from the study. Study withdrawal before the completion of the study will create missing outcome data. This may occur concurrently or after the ICE. The NRI (non-response imputation) is used where response is imputed as a non-responder at all timepoints thereafter through Week 52.
- Any subject not otherwise classified as a non-responder who misses the Week 52 visit will be handled as follows: the missing data will be imputed under a missing at random (MAR) assumption. Missing data will be imputed using multiple imputation (MI) model. The imputation models will include terms for baseline age group (5-11 years vs.12-17 years), baseline SELENA SLEDAI score (≤12 vs. ≥13 ) and all previous visit values. Further details of MI approach for missing data are provided in Section 6.3 Appendix 3 Missing Data Imputation Strategies.

### 4.2.3. Main analytical approach

| Endpoint / Variables |
|---|
| • Incidence of patients with ≥ 4 points reduction from baseline to Week 52 in SELENA SLEDAI |
| **Approach Specification** |
| • The efficacy analyses will be based in the "Intent-to-Treat" population, subjects with baseline SELENA SLEDAI score less than 4 are excluded from the analysis. Unless otherwise specified, endpoints/variables defined in Section 4.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.<br>• If there is any subject not classified as a non-responder but misses the Week 52 visit, the MI approach will be used to impute the missing data. In this scenario, each estimate will be generated for each imputed dataset produced by the MI procedure described in Section 4.2.2 and the corresponding results will be combined using Rubin's rules. |
| **Results Presentation** |
| • Results will be summarized using number and percentage of subjects achieving a response, standard error (SE) and 95% CI(Wald). In the event that the MI approach is used to impute missing data, the percentage of subjects (after MI) achieving a response, SE and 95% CI will be summarized. 95% CI will be constructed using their asymptotic standard errors (asymptotic Wald confidence limits).<br>• For the primary endpoint, the disposition of factors contributing to response or non-response will be presented as the number and percentage of subjects in each of the following categories at Week 52:<br>  • Responder<br>  • Non responder (if subjects have multiple ICEs, only the earliest ICE will be counted in this summary):<br>  o <4-point reduction in SELENA SLEDAI<br>  o Using prohibited medications or therapies<br>  o Study intervention discontinuation for any reason<br>  • Missing |
| **Subgroup Analyses** |
| • See Section 4.7.1 for details on subgroup analyses. The primary estimand will be used for subgroup analyses. |

### 4.2.4. Supplementary Analyses

#### 4.2.4.1. Supplemental Estimand

As a supplemental estimand for the primary objective, a hypothetical strategy will be considered for the handling of the ICE of discontinuation of study intervention for any reason. Specifically, the effects estimated will be under the hypothetical scenario where the ICE of discontinuation of study intervention for any reason did not occur. All data for the treatment response after the occurrence of this ICE or missing data will be imputed conditional on the participant's observed outcomes by MI approach. The use of this MI model assumes that missing outcomes would behave in a similar way to other participants who had data collected in the study.

All other ICE(initiation of prohibited medications) will be handled using the same strategy(composite strategy) as for the Primary Estimand Strategy.

### 4.2.5. Additional analyses

#### 4.2.5.1. Additional analyses 1

In the event that there is any subject not classified as a non-responder but misses the Week 52 visit in the primary estimand, the LOCF method (See Section 6.3.2 for details) will be used as additional analyse to impute the missing data instead of MI approach in the main analyse. The primary estimand will be used in this additional analysis.

#### 4.2.5.2. Additional analyses 2

In supplemental estimand, the missing data and all data for the treatment response after the occurrence of discontinuation from study intervention for any reason will be imputed based on MI approach. In additional analyses 2, the LOCF method (See Section 6.3.2 for details) will be used to impute the missing data and all data for treatment response after the occurrence of discontinuation from study intervention for any reason.

## 4.3. Secondary Efficacy Endpoint(s) Analyses

### 4.3.1. Secondary efficacy endpoint(s)

- Incidence of patients with ≥ 4 points reduction from baseline in SELENA SLEDAI by visit
- Change from baseline to Week 52 in Physician Global Assessment (PGA)
- Change from baseline to Week 52 in Parent Global Assessment (ParentGA)
- Change from baseline in daily prednisone equivalent dose at Week 52
- Time to first flare/ first severe flare over 52 weeks

#### 4.3.1.1. Definition of estimands

| **Endpoint(s)** |
|---|
| • Incidence of patients with ≥ 4 points reduction from baseline in SELENA SLEDAI by visit |
| **Estimand** |
| Similar estimand as the primary efficacy analysis (see Section 4.2.1 for details) will be used. |
| **Endpoint(s)** |
| • Change from baseline to Week 52 in Physician Global Assessment (PGA) |

**Estimand**

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable: Change from baseline at Week 52 in Physician Global Assessment (PGA).
- Summary measure: Mean change from baseline at Week 52 in Physician Global Assessment (PGA).
- Intercurrent events:
    - Initiation of prohibited medications - hypothetical strategy
    - Study treatment discontinuation for any reason- hypothetical strategy

The handling strategy for the ICEs will be based on a hypothetical approach; specifically, the effects estimated will be under the hypothetical scenario where the ICE did not occur.

**Endpoint(s)**

- Change from baseline to Week 52 in Parent Global Assessment (ParentGA)

**Estimand**

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable: Change from baseline at Week 52 in Parent Global Assessment (ParentGA).
- Summary measure: Mean change from baseline at Week 52 in Parent Global Assessment (ParentGA).
- Intercurrent events:
    - Initiation of prohibited medications or therapies- hypothetical strategy
    - Study treatment discontinuation for any reason- hypothetical strategy

The handling strategy for the ICEs will be based on a hypothetical approach; specifically, the effects estimated will be under the hypothetical scenario where the ICE did not occur.

**Endpoint(s)**

- Change from baseline in daily prednisone equivalent dose at Week 52

**Estimand**

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable: Change from baseline at Week 52 in daily prednisone equivalent dose.
- Summary measure: Mean change from baseline at Week 52 in in daily prednisone equivalent dose.
- Intercurrent events:
    - Initiation of prohibited medications or therapies– only the observed data before initiation of prohibited medications or therapies will be used for daily prednisone equivalent dose at each visit and no imputation will be done for missing data.
    - Study treatment discontinuation for any reason- only the observed data before initiation of prohibited medications or therapies will be used for daily prednisone equivalent dose at each visit and no imputation will be done for missing data.

Only the observed data before the ICEs will be used in the analysis.

**Endpoint(s)**

- Time to first flare/ first severe flare over 52 weeks

**Estimand**

The estimand is described by the following attributes:

- Population: Chinese paediatric patients with active SLE.
- Treatment condition: Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6.
- Variable: Time to first flare/ first severe flare over 52 weeks which is defined as the number of days from first exposure until the subject meets an event (event date – first exposure date + 1).
- Summary measure: Median of days to first flare/ first severe flare.
- Intercurrent events:
    - Initiation of prohibited medications–composite strategy (the event date is the earliest of the first flare/ first severe date and the date of initiation of prohibited medications or therapies).

- Study treatment discontinuation for any reason- hypothetical strategy (the date will be censored at last flare assessment date).
- Subject dies during Week 52-composite strategy (the event date is the date of death).

#### 4.3.1.2. Handling of Missing Data

- For incidence of patients with ≥ 4 points reduction from baseline in SELENA SLEDAI by visit, the same methodology for handling missing data as the primary efficacy endpoint in Section 4.2.2 will be used.
- For change from baseline to Week 52 in Physician Global Assessment (PGA) and Parent Global Assessment (ParentGA), missing data will be imputed as below.
  - Intermittent missing data (i.e. data between two non-missing assessments) will be imputed under a missing at random (MAR) assumption.
  - Missing data due to hypothetical strategy for intercurrent event, assuming that missing data is missing at random (MAR). Missing data will be imputed using MI model. This MI model uses all available data collected and assumes missing outcomes would behave in a similar way to participants who had data collected in the study. Further details of MI approach for missing data are provided in Section 6.3 Appendix 3 Missing Data Imputation Strategies.
  - Missing data without any intercurrent event. Assuming that missing data is missing at random (MAR). Missing data will be imputed using MI model. This MI model uses all available data collected and assumes missing outcomes would behave in a similar way to participants who had data collected in the study. Further details of MI approach for missing data are provided in Section 6.3 Appendix 3 Missing Data Imputation Strategies.
- For change from baseline in daily prednisone equivalent dose at Week 52, only the observed data will be used for analysis and no imputation will be done for missing data.
- For time to first flare/ first severe flare over 52 weeks, the censoring rules can be found in Section 4.3.1.1.

#### 4.3.1.3. Main analytical approach

| **Endpoint / Variables** |
|---|
| • Incidence of patients with ≥ 4 points reduction from baseline in SELENA SLEDAI by visit |
| **Approach Specification** |
| • This endpoint will be analyzed using the same methodology as the primary efficacy endpoint in Section 4.2.3. |

| **Results Presentation** |
|---|
| • Similar results as the primary efficacy analysis (see Section 4.2.3 for details) will be presented. The number and percentage of subjects with ≥ 4 points reduction from baseline in SELENA SLEDAI will be summarized by visit. Plots of the proportion of subjects (after MI) achieving a response and their corresponding errors will be generated by time. |
| **Additional Analysis** |
| • The LOCF method (See Section 6.3.2 for details) will be used as additional analyse to impute the missing data instead of MI approach in the main analyse. The primary estimand will be used in this additional analysis.<br>• The observed SELENA SLEDAI response at each visit will be summarized. No imputation will be done for missing data.<br>• The change from baseline and percent change from baseline in SELENA SLEDAI score will be summarized by visit. Similar primary estimand as PGA and ParentGA (see Section 4.3.1.1 for details) will be used. The mean change from baseline and mean percent change from baseline in SELENA SLEDAI score at each visit will be presented graphically using a line graph by visit. For missing data imputation and intercurrent events with hypothetical strategy, each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure described in Section 4.3.1.2 and the corresponding results will be combined using Rubin's rules. |
| **Endpoint / Variables** |
| • Change from baseline to Week 52 in Physician Global Assessment (PGA) |
| **Approach Specification** |
| • The efficacy analyses will be based in the "Intent-to-Treat" population, unless otherwise specified. This endpoint will be summarized using descriptive statistics and graphically presented (where appropriate).<br>• For missing data imputation and intercurrent events with hypothetical strategy, each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure described in Section 4.3.1.2 and the corresponding results will be combined using Rubin's rules. |
| **Results Presentation** |
| • The change from baseline at week 52 in PGA will be summarized. Descriptive statistics with N, Min, Median, Max, Mean, SE, SD, 95% CI, 25th and 75th percentiles will be presented. The change from baseline in PGA will also be summarized by visit. The mean change from baseline in PGA at each visit will be presented graphically using a line graph by visit. |
| **Additional Analysis** |
| • The LOCF method (See Section 6.3.2 for details) will be used as additional analyse to impute the missing data and all data after the occurrence of initiation of prohibited medications and study treatment discontinuation for any reason. |

| |
|---|
| • The observed change from baseline in PGA at each visit will be summarized. No imputation will be done for missing data.<br>• The percent change from baseline in PGA will be summarized by visit. Similar primary estimand as change from baseline in PGA will be used. The mean percent change from baseline in PGA at each visit will be presented graphically using a line graph by visit. For missing data imputation and intercurrent events with hypothetical strategy, each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure described in Section 4.3.1.2 and the corresponding results will be combined using Rubin's rules.<br>• The number and percentage of subjects with no worsening (increase of <0.30 points from baseline) in PGA will be summarized by visit. Similar estimand and methodology as the primary efficacy endpoint (see Section 4.2.1 for details) will be used.<br>• To evaluate the response over time, the number and percentage of subjects with a<br>• ≥0.3 point improvement in PGA will be summarized by visit and presented graphically. Similar estimand and methodology as the primary efficacy endpoint (see Section 4.2.1 for details) will be used. |
| **Endpoint / Variables** |
| • Change from baseline to Week 52 in Parent Global Assessment (ParentGA) |
| **Approach Specification** |
| • The efficacy analyses will be based in the "Intent-to-Treat" population, unless otherwise specified. This endpoint will be summarized using descriptive statistics and graphically presented (where appropriate).<br>• For missing data imputation and intercurrent events with hypothetical strategy, each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure described in Section 4.3.1.2 and the corresponding results will be combined using Rubin's rules. |
| **Results Presentation** |
| • The change from baseline at week 52 in ParentGA will be summarized. Descriptive statistics with N, Min, Median, Max, Mean, SE, SD, 95% CI, 25th and 75th percentiles will be presented. The change from baseline in ParentGA will also be summarized by visit. The mean change from baseline in ParentGA at each visit will be presented graphically using a line graph by visit. |
| **Additional Analysis** |
| • The LOCF method (See Section 6.3.2 for details) will be used as additional analyse to impute the missing data and all data after the occurrence of initiation of prohibited medications and study treatment discontinuation for any reason.<br>• The observed change from baseline in ParentGA at each visit will be summarized. No imputation will be done for missing data.<br>• The percent change from baseline in ParentGA will be summarized by visit. The mean percent change from baseline in ParentGA at each visit will be presented |

graphically using a line graph by visit. For missing data imputation and intercurrent events with hypothetical strategy, each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure described in Section 4.3.1.2 and the corresponding results will be combined using Rubin's rules.

**Endpoint / Variables**

- Change from baseline in daily prednisone equivalent dose at Week 52

**Approach Specification**

- For analyses, all corticosteroids are converted to a prednisone equivalent average daily dose (mg/day), therefore analyses refer to average daily prednisone equivalent dose instead of average daily steroid dose. The definition and derivation of this can be found in Section 6.2.7.
- The analyses will be based in the "Intent-to-Treat" population, unless otherwise specified. The absolute change from baseline in average daily prednisone equivalent dose (mg/day) at each post-baseline visit up to and including Week 52 will be summarized. This summary will be based on the observed data only. No imputation will be done for missing data.

**Results Presentation**

- The change from baseline at week 52 in daily prednisone equivalent dose will be summarized. Descriptive statistics with N, Min, Median, Max, Mean, SE, SD, 95% CI, 25th and 75th percentiles will be presented. The change from baseline in daily prednisone equivalent dose will also be summarized by visit. The absolute change from baseline in daily prednisone dose at each visit will be presented graphically using a line graph.

**Additional Analysis**

- The number and percentage of subjects with any decrease in daily prednisone equivalent dose will be summarized by visit and presented graphically. A responder is defined as having any reduction in prednisone compared to baseline. Similar estimand and methodology as the primary efficacy analysis (see Section 4.2.1 for details) will be used.
- The number and percentage of subjects with any increase in daily prednisone equivalent dose will be summarized by visit. Hypothetical strategy will be used for study intervention discontinuation for any reason and initiation of prohibited medications or therapies. Each estimate will be generated for each imputed dataset produced by the multiple imputation (MI) procedure and the corresponding results will be combined using Rubin's rules.

**Endpoint / Variables**

- Time to first flare/ first severe flare over 52 weeks

| Approach Specification |
|---|
| • Time to first flare(defined as mild, moderate, or severe) over 52 weeks and time to first severe flare over 52 weeks will be analysed separately.<br>• The derivations rule of flares and severe flares can be found in Section 6.2.10.<br>• The analyses will be based in the "Intent-to-Treat" population, unless otherwise specified. Descriptive statistics will be used to summarise time to first flare/ first severe flare over 52 weeks. For subjects who experience a flare/ severe flare, the study day of the flare/severe flare will be summarized. |
| **Results Presentation** |
| • Descriptive statistics with the number and percentage of subjects with a flare /severe flare, the median and 25th and 75th percentiles of days to first severe flare to summarise time to first flare/ first severe flare over 52 weeks. Statistics will be missing when the number of events is too low to estimate the value. For subjects who experience a flare/ severe flare, the study day of the flare/severe flare will be summarized and the table will display the N, median, $25^{th}$ and $75^{th}$ percentiles , minimum, and maximum. A Kaplan-Meier plot for time to first flare/ first severe flare will also be produced. |

## 4.4. Safety Analyses

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

| Endpoint | Statistical Analysis Methods |
|---|---|
| Safety | Endpoints:<br>➢ Incidence of adverse events of special interest (AESIs) through 52 weeks:<br>o All infections of special interest, including serious infections of special interest and opportunistic infections<br>o Infusion-related systemic reactions and anaphylactic reactions<br>o Depression, suicidality<br>o Malignancies<br>➢ Incidence of AEs through 52 Weeks<br>➢ Incidence of SAEs through 52 weeks<br>Analysis:<br>Descriptive statistics will be used to summarise AEs, SAEs and AESIs. The frequency of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term. |

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

| | |
|---|---|
| **Population** | Chinese paediatric patients with active SLE. |
| **Treatment** | • Belimumab will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 in combination with standard therapy. Further details on standard therapy can be found in protocol Section 6. |
| **Endpoints** | • Incidence of adverse events, serious adverse events and adverse events of special interest through Week 52. |
| **Summary Measure** | • Frequency and percentage |
| **Intercurrent events and strategies** | • Discontinuation of study medication, addressed with while-on-treatment strategy. Safety data in the 52-week on-treatment period will be used in analysis. The definition of on-treatment period can be found in Section 6.2.2. |

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

In addition to the primary estimand strategy in safety, additional analysis will be performed in some key endpoints based on all safety data including 52-week on-treatment period and 16-week post-treatment follow-up period. The definition of on-treatment period and post-Treatment period can be found in Section 6.2.2.

### 4.4.1. Extent of Exposure

Summaries of extent of exposure will be presented for the ITT population.

The extent of exposure to study treatment through Week 52 will be assessed by examining the duration of exposure to belimumab in days and the total number of infusions a subject receives.

The duration of exposure, the total number of infusions (including partial and complete), and the percent compliance will be summarized using descriptive statistics. The total number of infusions will also be summarized using counts and percentages using the following categories: 1 – 5 doses, 6 – 10 doses and 11 – 14 doses.

Duration of exposure in days for each subject will be calculated as: Last infusion date– first infusion date + 28.

Study intervention Compliance (%) = (Number of infusions prescribed- Number of infusions missed / Number of infusions prescribed])*100.

Exposure data will be listed for all subjects.

### 4.4.2. Adverse Events

**Primary analysis**

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

The definition of on-treatment period can be found in Section 6.2.2.

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.

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:

- 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 (≥ 5%) Adverse Events(by SOC and PT)
- Non-Serious Adverse Events (by SOC and PT)
- Common (>= 5%) Non-Serious Adverse Events (by SOC and PT)
- Study Agent Related Serious Adverse Events (by SOC and PT)
- Fatal Serious Adverse Events (by SOC and PT)
- Non-Fatal Serious Adverse Events (by SOC and PT)
- Study Agent Related Non-Fatal Serious Adverse Events (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.

A 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, during

the specified study period.

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 (except for participant who transfers into study 217091) will be followed for safety at 16 weeks post last dose of belimumab. In addition to the primary analysis for on-treatment period, the following summary tables will be produced for all AEs including 52-week on-treatment period and 16-week post-treatment follow-up period:

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

The following listings will be produced:

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

#### 4.4.2.1. Adverse Events of Special Interest

**Primary analysis**

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 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.

Malignant Neoplasms

- 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

Post-Infusion Systemic Reactions (PISR)

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

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

- 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

| **Adverse Events** |
| --- |
| **Adverse Events of Special Interest (AESI)** |
| o Opportunistic<br>o Recurrent<br>o Disseminated<br>• Sepsis<br><u>Depression (including mood disorders and anxiety)/suicide/self-injury (All and Serious, separately)</u><br>• Depression (including mood disorders and anxiety) (excluding suicide and self-injury)<br>• Suicide/self-injury<br>• Serous suicide/self-injury per GSK adjudication<br>o Suicidal Behavior<br>o Completed Suicide<br>o Suicidal Ideation<br>o Self-injurious Behavior without Suicidal Intent<br><u>Deaths</u> |

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-infusion systemic reactions and serious post- infusion 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.

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

- Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the Belimumabinfusion) by PT in the first six infusion.

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

All AESI will be presented in a listing.

**Additional analysis**

All subjects (except for participant who transfers into study 217091) will be followed for safety at 16 weeks post last dose of belimumab. In addition to the primary analysis for on-treatment period, an overall summary of AESIs will be produced including 52-week on-treatment period and 16-week post-treatment follow-up period.

## 4.4.3. Additional Safety Assessments

### 4.4.3.1. Laboratory Data

For laboratory analyses, only analytes with a numeric normal range will be analyzed. Summaries and analyses will be performed based on the observed data. No imputation will be done for missing data.

Listings will be generated for all laboratory results.

- Descriptive statistics for each analyte will be displayed for each visit. No statistical tests will be performed. Line graphs will be produced for each analyte which displays the mean value by visit.
- Laboratory toxicity will be graded using Adverse Event Severity Grading Tables when possible. The worst laboratory toxicity grade during the study period, including unscheduled visits, for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries and urinalysis) will be presented.
- Toxicity grade shifts from baseline of $\geq 2$ grades during the study period, including unscheduled visits, will be summarized for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries, urinalysis, and immunoglobulins). The table will display the number and percentage of subjects with at least one $\geq 2$ 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, electrolytes, other chemistries, urinalysis and immunoglobulin), shifts relative to the normal range will be summarized for each analyte as shifts ‘to low’ and shifts ‘to high’. For example, for the ‘to low’ category the percentage of subjects with at least one low post-baseline value relative to the baseline will be displayed using the categories: remained low and normal/high to low. For the ‘to normal/high’ category the percentage of subjects with at least one high post-baseline value relative to baseline will be displayed using the categories: remained normal/high and low to normal/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.

#### 4.4.3.2. Vital Signs

A summary of vital signs and change from baseline of vital signs will be presented by visit.

## 4.5. Pharmacokinetic Analyses

### 4.5.1. Pharmacokinetic endpoint(s)

- Median belimumab concentration levels at Day 0, 7 and 14 days post first dose, and pre-infusion and post-infusion at Day 84
- The PK will be evaluated with respect to clearance, volume of distribution and half-life, and individual steady-state exposures (e.g., Cmin, Cavg, Cmax and AUC).

### 4.5.2. Main analytical approach

The PK analyses will be based on the PK Population, unless otherwise specified.

#### 4.5.2.1. Drug Concentration Measures

Pharmacokinetic concentration data will be summarized descriptively, listed and plotted. Standard summary statistics will be calculated (i.e. mean, geometric mean and SD, 95% confidence intervals for mean/geometric means, CV%, median, minimum, and maximum) for Pharmacokinetic concentration data. It will be summarized at each sampling visit / time point. Individual subject concentration data will be listed. Median and geometric mean belimumab concentrations will be graphically presented.

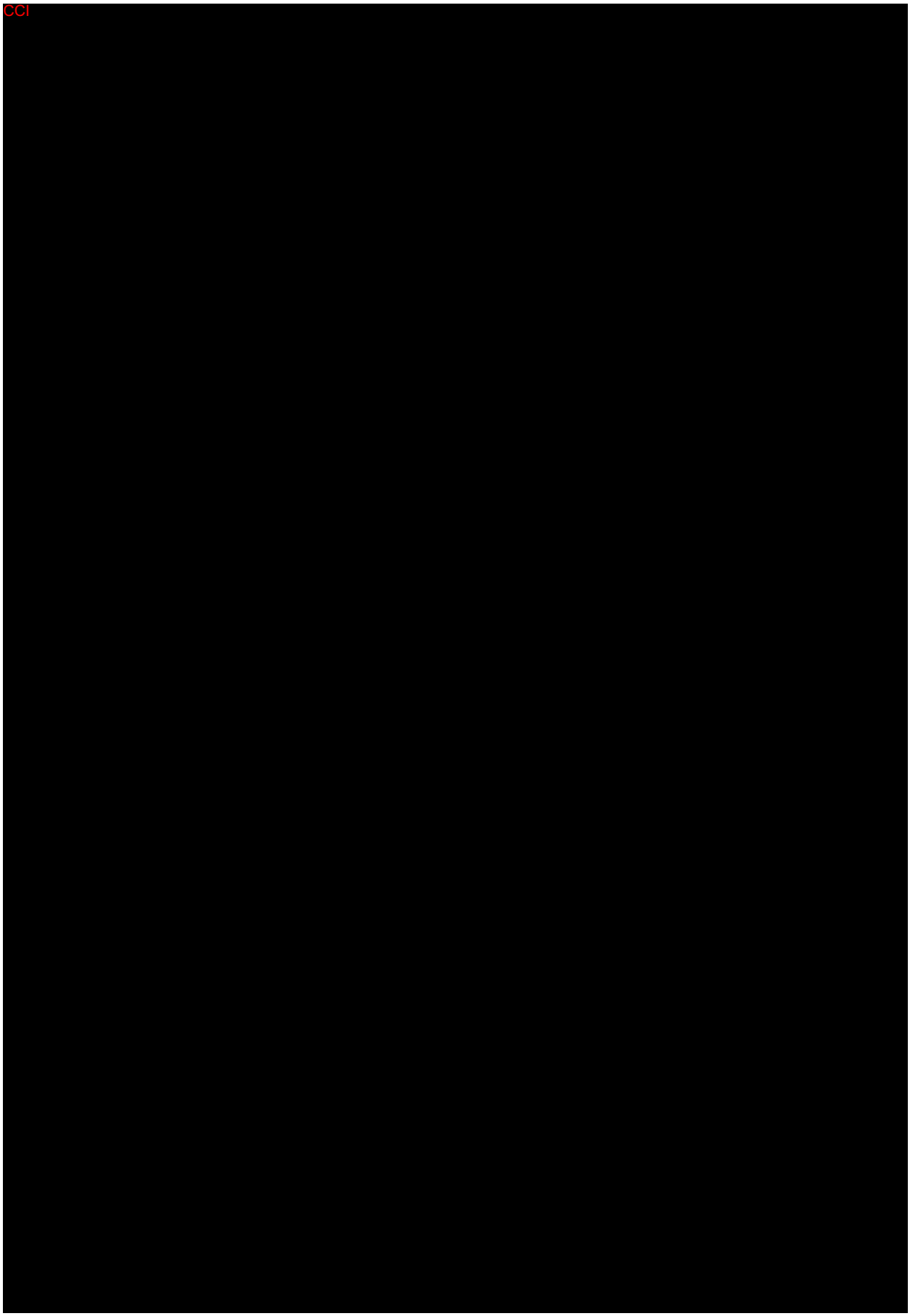
#### 4.5.2.2. Population Pharmacokinetic (PopPK) Analyses

Pharmacokinetic parameters data will be summarized and listed by population pharmacokinetic (PopPK) methods. Standard summary statistics will be calculated (i.e. arithmetic mean, standard deviation of the untransformed data, 95% confidence intervals for the arithmetic mean, median, minimum and maximum, geometric mean, standard deviation of the log-transformed data, 95% confidence intervals for geometric means, between subject coefficient of variation (%CVb)) for Pharmacokinetic parameters data. A by-subject listing of pharmacokinetic parameters will be produced. Since PK parameters will be calculated using population PK model, these outputs will be displayed in population PK modelling report.

## 4.6. Other Endpoint(s) Analyses

CCI [redacted]

CCI




## 4.8. Interim Analyses

No formal interim analyses are planned.

## 4.9. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 04 (Dated: [22-JAN-2024]).

# 5. SAMPLE SIZE DETERMINATION

Focusing on serious infections, the incidence rate of the serious AE "Infections and Infestations" (SOC) was 7.5% (4/53 participants) in the 10 mg/kg-IV group of the global paediatric study (Study BEL114055).

Under the assumption that the incidence rate of the serious infections is 7.5%, it is calculated that a study with 65 participants will have more than 99.0% probability to observe at least one serious infection. Under this sample size, for any other adverse

events, there are more than 90% probability to observe at least one event once the incidence rate is larger than 4%. Additionally, using the Exact method in PASS 2019 for the confidence interval (CI) around a single proportion: a sample size of 65 would have produced a 95% CI of [2.4%, 16.8%] when the incidence rate of the serious infections is 7.5%.

For the efficacy purpose, as one of the key efficacy endpoints, the estimated percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 is 54.7% in BEL114055. Using the Exact method in PASS 2019 for the confidence interval (CI) around a single proportion: a sample size of 65 would produce a 95% CI of [41.9%, 67.1%] when the estimate is 54.7%. Under the assumption that the percentage of participants with ≥4 points reduction from baseline in SELENA SLEDAI at week 52 is 54.7%, it is calculated by simulation that a study with 65 participants will have more than 95.0% probability to observe a percentage lager than 43.6%.

## 5.1. PK Sample Size Determination

The FDA recommends that for paediatric studies, the 95% confidence interval of the average CL and V estimates are within 60% to 140% of the geometric mean, with at least 80% power [Wang, 2012]. The same principles are applied here, but for this study a more stringent criterion will be applied requiring the precision of the CL and V to be determined within 80% to 120% of the geometric mean with at least 80% power. It is recommended to collect PK blood samples from 25 Chinese paediatric patients, which is considered the minimum number to meet this more stringent condition and therefore enable a quantitative comparison with the PK in a Western paediatric population.

The sampling of the PK from each subject will be sparse, but when the data is integrated with the population PK model previously developed for paediatrics, the belimumab clearance (CL) and volume of distribution (V) may be estimated for each subject as if the PK had been frequently sampled in these subjects. To show that PK samples from N=25 evaluable Chinese paediatric patients should be sufficient to accurately determine the PK in a Chinese paediatric population, one needs to consider the precision of the average CL and V estimates derived from the N=25 individual values.

The power to estimate the CL is calculated by integrating over all possible values of the estimated standard deviations, weighted by the probability density and for each value assigning one to the integrand if the 95% confidence interval is within the 80% to 120% range or zero otherwise:

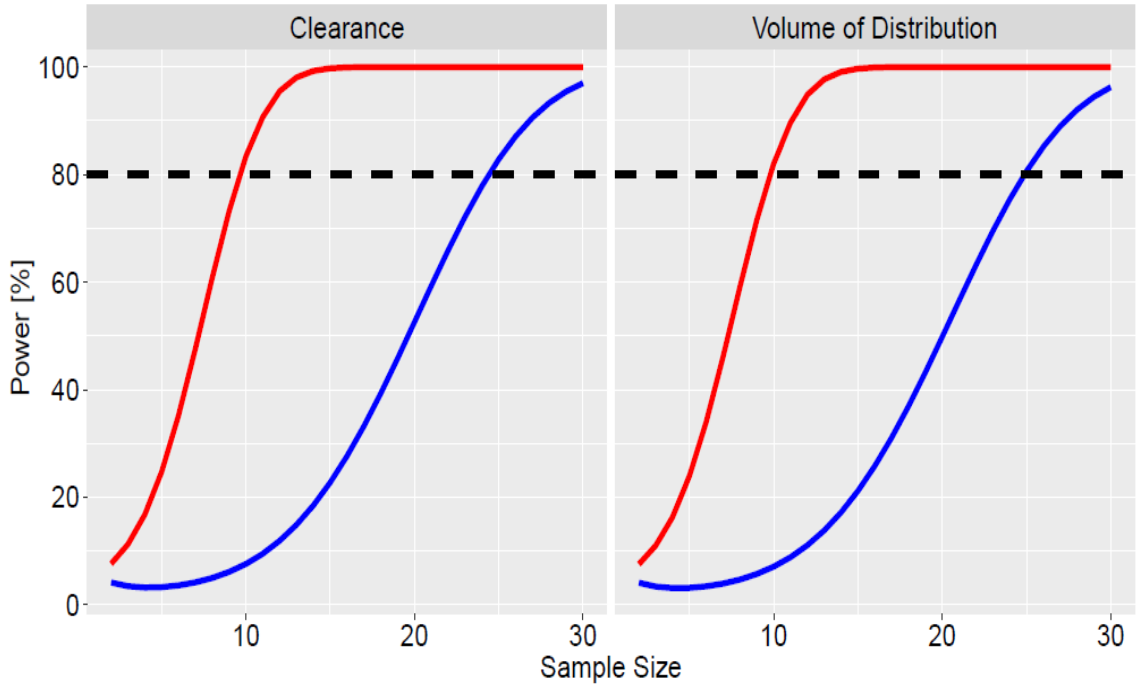
$$Power = \int_0^\infty ds \times f(s; N-1) \times \lambda$$

where $\lambda = \begin{cases} 1 & \text{if } 80\% < CI_{95\%} < 120\% \\ 0 & \text{othewise} \end{cases}$

The results from this power calculation show N=25 paediatric subjects with evaluable PK results in at least 80% power to estimate the CL and V with 95% confidence intervals within 80% to 120% of their geometric mean values (blue line, Figure 1). In this regard

the precision of the CL and V estimates in a Chinese paediatric population can be considered sufficient for this study design to compare against the corresponding parameters derived in a Western paediatric population. Additionally, there is 100% power the same sample size will estimate CL and V with 95% confidence intervals within the wider window of 60%-140% of their geometric means (red line, Figure 1).

**Figure 1 The power to estimate CL and V versus sample size**




**The power to estimate the 95% confidence interval within 80% to 120% of the geometric mean is shown (blue solid line). The power calculation was also repeated for the less stringent criteria requiring the 95% confidence interval to be within 60% to 140% of the geometric mean (red solid line).**

# 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

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 study withdrawal will be summarized. Additionally, the cumulative number and percentage of subjects who withdrew from the study by visit will be displayed.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention. Additionally, the cumulative number and percentage of subjects who discontinued study intervention by study visit will be displayed.

The summary of study visit impacted by COVID-19 will be provided.

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.

A listing of subject disposition will be provided showing completion status and whether or not they are included in each population. A listing of subjects who withdrew from the study, including reason and date of 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 at screening (years), height (cm), weight (kg), BMI (kg/m2) and vital signs (temperature, heart rate and blood pressure).

Counts and percentages of the following categorical demographic and baseline characteristics will be presented: sex, age group at screening (<13 years and ≥13 years), cardiovascular history (family history [yes/no/ unknown]), tobacco use (never smoked, current smoker, former smoker). 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 will be repeated for the age subgroups, as defined in Section 4.7.1.

Demographic and baseline characteristics will be listed for all subjects.

A summary of baseline disease activity will be provided, including counts and percentages for the following variables:

- SLE disease duration category (≤0.5, >0.5-<1.5, 1.5-<3, ≥3)
- SLE disease duration category (<2, ≥2)
- SELENA SLEDAI category (≤12, ≥13)
- SELENA SLEDAI category (≤7, ≥8)
- SELENA SLEDAI category (≤5, ≥6)
- PGA category (0-1, >1 – 2.5, >2.5)
- ParentGA category (0-2.5, >2.5 – 5, >5 – 7.5, >7.5)
- Proteinuria category (≤0.5, >0.5-<1, 1-<3, ≥3)

Descriptive statistics (N, Min, Median, Max, Mean, SD, 25th and 75th percentiles) for the continuous scores will be presented for the following variables:

- SELENA SLEDAI
- PGA
- ParentGA
- Proteinuria levels

The summary of baseline disease activity will be repeated for the age subgroups, as detailed in Section 4.7.1.

The following indicators of disease activity will also be summarized at baseline:

- SLE disease duration (years)
- SELENA SLEDAI category by organ domain and item (count and percentage with each item present)
- CCI [redacted]
- CCI [redacted]
- [redacted]
- CCI [redacted].
- Allowable SLE medication usage– counts and percentages by class (Steroids, Anti-malarials, and Other Immunosuppressive/Immunomodulatory Agents) and drug as well as summary statistics for average daily prednisone dose (mg/day) at baseline.

- Steroid, Anti-malarial and Immunosuppressant Use at Baseline – counts and percentages by class (Steroid Only, Immunosuppressant Only, Anti-malarial Only, Steroid and Immunosuppressant Only, Steroid and Anti-malarial Only, Immunosuppressant and Anti-malarial Only, Steroid and Immunosuppressant and Anti-malarial)

### 6.1.3. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

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

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

All violations will be discussed and adjudicated as important or not important. Full details describing important deviations are given in the Protocol Deviation Management Plan (PDMP)

In addition to the overall summary of important protocol deviations, separate summaries will be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarized.

### 6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded according to drug name as defined in the GSK Drug Dictionary, and classified according to the GSK-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.

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. Unless otherwise stated, all concomitant medications summaries will use the "while on treatment" approach, i.e., any concomitant medications which are taken post intervention period will be excluded. Medications which are taken post intervention period will be considered post-treatment.

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

### 6.1.5. Study Intervention Compliance

A summary of overall compliance based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics.

Study intervention Compliance (%) = (Number of infusions prescribed- Number of infusions missed / Number of infusions prescribed])*100.

## 6.2. Appendix 2 Data Derivations Rule

### 6.2.1. Analysis age

**Screening Age**

For screening age, three variables are required in the dataset: age in years, age in months, and age in years and months (e.g. "12 yrs 9 mo").

Age in years will be used for the demography summary. Age in months is required to derive age in years and months, which will be displayed in the listing.

Screening age (years) will be calculated as:

INTCK ('YEAR', Date of birth, Screening Date, 'C').

Screening age in months will be calculated as follows:

INTCK ('MONTH', Date of birth, Screening Date, 'C').

For age in months and years, the year component will be equivalent to age in years. The number of additional months will be calculated as follows:

Age in months – (Age in years * 12)

**Baseline Age**

Baseline age (years) will be calculated as:

*INTCK ('YEAR', Date of birth, Treatment Start Date, 'C').*

The baseline age(years) will be used in subgroup analyses.

### 6.2.2. Study Period

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

**Pre-Treatment** is defined as time prior to the first dose of study intervention.

**On-Treatment** is defined as time from first dose to Week 52 Visit Date/Early withdrawal Date/IP Discontinuation Date + 28 days (i.e., Study Treatment Start Date ≤ Event Start Date ≤ Week 52 Visit Date/Early withdrawal Date/IP Discontinuation Date + 28 days.

- For Subjects who did not withdraw early from IP:

  Event onset date is on/after IP start date & on/before Week 52 Date.

  (IP Start Date ≤ Event Start Date ≤ Week 52 Date)

- For Subjects who withdrew early from IP:

  Event onset date is on/after IP start date & on/before the earliest of Early Withdrawal Date/IP Discontinuation Date + 28 days.

  (IP Start Date ≤ Event Start Date ≤ the earliest of Early withdrawal Date/IP Discontinuation Date + 28 days)

**Post-Treatment** is defined as any time post on-treatment window, i.e. > Week 52 Visit Date/Early withdrawal Date/IP Discontinuation Date + 28 days.

### 6.2.3. 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 efficacy reference date is the study intervention start date and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

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

### 6.2.4. Assessment Window

Data will be analysed as per the planned visit assignment.

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

For data summaries by visit, the planned (nominal) visit description will be used. Unscheduled, Safety FU and Early withdrawal visit data will be slotted into a target visit based on visit window defined in the table below using the visit Study Day. If there are multiple assessments within the same visit window, a scheduled visit assessment will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the value closest to the target day for that window will be used.

If the Early withdrawal visit is slotted into the same visit as the visit prior to Early withdrawal, slot the Early withdrawal visit to the next scheduled visit. For example, if the subject's last visit prior to the Early withdrawal visit was Week 12 and the Early withdrawal visit mapped as another Week 12, map the Early withdrawal visit to Week 16.

| Analysis Visit | Analysis Visit Number | Target Study Day | Analysis Window | |
|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint |
| Screening | 10 | up to -35 days | na | na |
| Week 0 | 20 | 1 | na | na |
| Week 1 | 30 | 8 | 2 | 11 |
| Week 2 | 40 | 15 | 12 | 21 |
| Week 4 | 50 | 29 | 22 | 42 |
| Week 8 | 60 | 57 | 43 | 70 |
| Week 12 | 70 | 85 | 71 | 98 |
| Week 16 | 80 | 113 | 99 | 126 |
| Week 20 | 90 | 141 | 127 | 154 |
| Week 24 | 100 | 169 | 155 | 182 |
| Week 28 | 110 | 197 | 183 | 210 |
| Week 32 | 120 | 225 | 211 | 238 |
| Week 36 | 130 | 253 | 239 | 266 |
| Week 40 | 140 | 281 | 267 | 294 |
| Week 44 | 150 | 309 | 295 | 322 |
| Week 48 | 160 | 337 | 323 | 350 |
| Week 52 | 170 | 365 | 351 | 378 |
| 16 Week post last dose Follow-Up | 180 | 449 | 379 | na |

### 6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to baseline assessments.

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.

### 6.2.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>
<ul>
<li>Partial dates will be displayed as captured in participant listing displays.</li>
<li>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.</li>
<li>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.</li>
</ul>
</td></tr>
<tr><td>Adverse Events</td><td>
<ul>
<li>Partial dates for AE recorded in the CRF will be imputed using the following conventions:</li>
</ul>
<table>
<tr><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.<br><br>Else if study intervention start date is not missing:<br><br>o If month and year of start date = month and year of study intervention start date, then<br><br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.<br><br>▪ Else set start date = study intervention start date.<br><br>Else set start date = 1st of month.</td></tr>
<tr><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.<br><br>Else if study intervention start date is not missing:<br><br>If year of start date = year of study intervention start date, then<br><br>If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br><br>Else set start date = study intervention start date.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Else set start date = January 1.</td></tr>
<tr><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>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
<ul><li>Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</li></ul>
<table>
<tr><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.<br><br>Else if study intervention start date is not missing:<br><br>o If month and year of start date = month and year of study intervention start date, then<br><br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.<br>▪ Else set start date = study intervention start date.<br>Else set start date = 1st of month.</td></tr>
<tr><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.<br><br>Else if study intervention start date is not missing:<br><br>o If year of start date = year of study intervention start date, then<br><br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br><br>▪ Else set start date = study. intervention start date.<br><br>Else set start date = January 1.</td></tr>
</table>
</td></tr>
</table>

| Element | Reporting Detail | |
|---|---|---|
| | 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 | ▪ No imputation |

### 6.2.7. Average Daily Prednisone Equivalent

Average daily prednisone equivalent dose will be expressed in milligrams per day (mg/day). To determine average daily prednisone equivalent, all steroid dosages are converted to a prednisone equivalent in milligrams at each visit. See Table 1 for conversion factors and detail of how values should be converted.

The average daily prednisone equivalent dose takes into account all steroids taken IV, intramuscularly (IM), subcutaneously (SC), intradermally and orally for both SLE and non-SLE reasons. The total systemic steroid dose is defined as the average daily dose of all steroids taken IV, IM, SC, intradermally and orally for all reasons.

A concomitant medication is identified as a steroid if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02.'

- The following routes are considered to provide systemic exposure: oral, subcutaneous, intramuscular, intradermal and intravenous steroids. Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).
- At data base release and in-stream, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor and dosing frequency exist for all terms with a systemic route of administration.
- Similarly, all routes of administration for preferred terms with an ATC code beginning with 'H02'will be reviewed to ensure all systemic routes have been identified in the list above.
- In order to be converted, the frequency and dose of the steroid must be present with the unit dose in milligrams (mg).
- Reported dose for systemic steroid is converted to prednisone equivalent dose using conversion factor for each particular medication (refer to online calculator http://www.globalrph.com/corticocalc.htm).

Daily Prednisone Equivalent Dose (mg) = Collected Dose (mg) x Conversion Factor x

Frequency Factor

**Table 1 Prednisone Conversion Factors (mg)**

| Preferred term | Conversion factor for converting to a prednisone-equivalent dose |
|---|---|
| BETAMETHASONE | 8.333 |
| BETAMETHASONE DIPROPIONATE | 8.333 |
| BETAMETHASONE SODIUM PHOSPHATE | 8.333 |
| BETAMETHASONE VAL | 8.333 |
| BETROSPAM | 8.333 |
| CELESTONA BIFAS | 8.333 |
| CORTISONE | 0.2 |
| CORTISONE ACETATE | 0.2 |
| CRONOLEVEL | 8.333 |
| DEFLAZACORT | 0.8333 |
| DEPO-MEDROL MED LIDOKAIN | 1.25 |
| DEXAMETHASONE | 6.667 |
| DEXAMETHASONE ACETATE | 6.667 |
| DEXAMETHASONE SODIUM PHOSPHATE | 6.667 |
| FLUOCORTOLONE | 3 |
| HYDROCORTISONE | 0.25 |
| HYDROCORTISONE ACETATE 0.25 | 0.25 |
| HYDROCORTISONE SODIUM SUCCINATE | 0.25 |
| MEPREDNISONE | 1.25 |
| METHYLPREDNISOLONE | 1.25 |
| METHYLPREDNISOLONE ACEP | 1.25 |
| METHYLPREDNISOLONE ACETATE | 1.25 |
| METHYLPREDNISOLONE SODIUM SUCCINATE | 1.25 |
| PARAMETHASONE | 2.5 |
| PREDNISOLONE | 1 |
| PREDNISOLONE SODIUM PHOSPHATE | 1 |
| PREDNISOLONE SODIUM SUCCINATE | 1 |
| PREDNISONE | 1 |

| Preferred term | Conversion factor for converting to a prednisone-equivalent dose |
|---|---|
| PREDNISONE ACETATE | 1 |
| TRIAMCINOLONE | 1.25 |
| TRIAMCINOLONE ACETATE | 1.25 |
| TRIAMCINOLONE ACETONIDE | 1.25 |
| BUDESONIDE | 0.333 |

**Table 2 Frequency Factors**

| Frequency Factor | Factor |
|---|---|
| BID | 2 |
| BIW | 2/7 |
| OAM | 1/30 |
| Once | 1 |
| PRN | null |
| Q2H | 12 |
| Q2W | 1/14 |
| Q3H | 8 |
| Q3MO | 1/84 |
| Q3w | 1/21 |
| Q4H | 6 |
| Q4W | 1/28 |
| Q6H | 4 |
| Q8H | 3 |
| Q12H | 2 |
| QAM | 1 |
| QD | 1 |
| QH | 24 |
| QHS | 1 |
| QID | 4 |
| QM | 1 |
| QOD | ½ |
| QPM | 1 |
| QW | 1/7 |
| QWK | 1/7 |
| TID | 3 |
| TIW | 3/7 |
| UNK | Null |
| 2 TIMES PER WEEK | 2/7 |

| Frequency Factor | Factor |
|---|---|
| 3 TIMES PER WEEK | 3/7 |
| 4 TIMES PER WEEK | 4/7 |
| 5 TIMES PER WEEK | 5/7 |
| 5 TIMES PER DAY | 5 |
| EVERY 2 WEEKS | 1/14 |
| EVERY 3 WEEKS | 1/21 |
| EVERY 4 WEEKS | 1/28 |
| EVERY WEEK | 1/7 |

#### 6.2.7.1. Baseline Prednisone Dose

At baseline, the average daily prednisone equivalent dose is the sum of all prednisone doses over 7 consecutive days up to, but not including Day 1, divided by 7.

#### 6.2.7.2. Average Daily Prednisone Dose Between Visits

The average daily prednisone dose between visits will be calculated for each scheduled post-baseline visit by summing all prednisone doses since the previous visit (previous visit date +1) up to and including the current visit and then dividing by the number of days in this period (Date of current visit – Date of previous scheduled visit). Days on which a subject does not have prednisone use recorded will be considered as 0 mg for the day in the calculation of average daily prednisone dose.

For subjects who withdraw from the study prior to a scheduled visit, the average dose from the previous scheduled visit will be used in order to have complete data between visits.

#### 6.2.7.3. Average Daily Prednisone Dose at the Visit

While on treatment, the average daily prednisone dose at the visit is the sum of all prednisone doses over 7 consecutive days up to and including the day of interest, divided by 7, unless otherwise specified. Days on which a subject does not have prednisone use recorded will be considered as 0 mg for the day in the calculation of average daily prednisone dose.

The average daily prednisone equivalent dose will be calculated for each scheduled visit.

For subjects who withdraw from the study prior to a scheduled visit, the average dose will be calculated at the date of withdrawal.

### 6.2.8. SLE Allowable Medication Categories

| Medication Category | Rule |
|---|---|
| Anti-malarials | Set to "ANTIMALARIALS" if the preferred term begins with "QUINACRINE", "QUININE", "HYDROXYCHLOROQUINE","MEPACRINE", or "CHLOROQUINE" AND the route of administration is not 'TOPICAL','VAGINAL', 'CONJUNCTIVAL', 'INTRANASAL', 'INHALATION', 'INTRA-OCULAR', 'INTRATRACHEAL', 'EPIDURAL', 'INTRAARTICULAR', or 'OTHER'. |
| Steroids | Set to 'STEROIDS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02' AND Route of administration is "INTRADERMAL", "INTRAMUSCULAR", "INTRAVENOUS", "ORAL", "SUBCUTANEOUS", or "INTRA-ARTICULAR". |
| Immunosuppressants | Set to 'IMMUNOSUPPRESSANTS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04A' or the preferred term begins with "CYCLOPHOSPHAMIDE" (oral and parenteral routes) or "MERCAPTOPURINE" (oral route) **AND route of administration is not "TOPICAL"**. Chinese patent medicines will be identified by clinical physicians and should be excluded from this category. For example, the preferred term begins with "TRIPTERYGIUM", etc. Specially, if ADECOD="CICLOSPORIN" and CMROUTE="INTRAOCULAR", it will be excluded from this category. |
| NSAIDs | Set to NSAIDs if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'M01A'. Chinese patent medicines will be identified by clinical physicians and should be excluded from this category. For example, the preferred term begins with " FORSYTHIA", " MORUS", "SCROPHULARIA","DRYNARIA", "ACONITUM", etc. |
| Aspirin | Set to "ASPIRIN" if CMDECOD contains "ACETYLSALICYLIC ACID" or "ACETYLSALICYLATE LYSINE". Chinese patent medicines will be identified by clinical physicians and should be excluded from this category. For example, the preferred term begins with "TRIPTERYGIUM", "PAEONIA", etc. |

### 6.2.9. Prohibited Medications and Non-Drug Therapies

Participants who start prohibited medications or therapies at any time during the study will be considered 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.
- Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, tocilizumab, golimumab).
- All biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).
- 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** |
|---|---|
| Prohibited | Set to "PROHIBITED" if any of the following conditions are met, if CMDECOD equals "INVESTIGATIONAL DRUG","ADALIMUMAB", "BELIMUMAB", "ETANERCEPT", "INFLIXIMAB", "CERTILIZUMAB", "TOCILIZUMAB", "GOLIMUMAB", "RITUXIMAB", "ABATACEPT","ANAKINRA","IMMUNOGLOBULIN"(IV route), "CYCLOPHOSPHAMIDE" (IV route), "PLASMAPHERESIS" or "LEUKAPHERSIS". |

### 6.2.10. SLE Flare Index

- SFI reports the first mild /moderate or severe flare occurrence since the last visit assessment.
- The SLEDAI criteria will be assessed programmatically to determine if the SELENA SLEDAI criteria for a flare has been met and used for the assessment of flare, irrespective of what was recorded on the SFI form.

- Although there are boxes on the form for the investigator to classify the most recent flare to mild/moderate or severe, the classification will be re-derived from the subcategory scores. Flares originally marked severe will be downgraded to "Not Severe" if the only reason marked is a change in SELENA SLEDAI score to > 12. In this case, if any of the mild/moderate reasons are checked or if the SELENA SLEDAI score has a change from previous visit of at least 3, then the flare will be considered Mild/Moderate.
- Flares that are marked mild/moderate where the only reason checked is SELENA SLEDAI increase of at least 3 points but not more than 12 points will be re-derived using the SELENA SLEDAI score. If it's found that the change is not actually ≥ 3, and no other reasons are checked, then the flare will not be counted.

## 6.3. Appendix 3 Missing Data Imputation

### 6.3.1. Multiple imputation under MAR assumption

1. Set all data at each visit after the intercurrent event to missing.
2. For all missing data(including intermittent missing data), generate 1000 multiply imputed datasets using a monotone regression imputation including terms for baseline value (this covariate will not be included in the model for endpoints related to SELENA SLEDAI), baseline age group (5-11 years vs.12-17 years) ,baseline SELENA SLEDAI score (≤12 vs. ≥13) , and all previous visit values, i.e. a model of the form:

$$y_i = \alpha_{1i} + \alpha_{2i}base + \alpha_{3i}age + \alpha_{4i}score + \beta_{i-1}y_{i-1} + \cdots + \beta_1 y_1$$

   where $y_i$ is the result at visit *i, i=1, 2, 3,…,14.*
3. Derive the endpoint based on the imputed data and estimand as detailed in Section 4.2.1, Sections 4.2.3, 4.2.4 and Section 4.3.1.1.
4. Perform statistical analysis as detailed in Section 4.2.3 and Section 4.3.1.3.

### 6.3.2. LOCF

The last observation carried forward (LOCF) principle is applied whereby missing values will be replaced with the last previous non-missing value. If the first on-treatment assessment is missing, then the missing data will be imputed with the baseline value.

If a subject has a visit but partial data of the endpoint are missing (including individual items of any component of the primary endpoint), LOCF will be used for the missing item or component.

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# 7. REFERENCES

Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. Jr Clin Pharmacol. 2012;52(10):1601-6.