Statistical Analysis Plan Amendment 1

Study ID: 200908

Official Title of Study: Reporting and Analysis Plan for study 200908, a MultiCenter, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE)

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Title	:	Reporting and Analysis Plan for study 200908, a Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE)
Compound Number	:	GSK1550188
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Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200908.
- This RAP is intended to describe the planned pharmacokinetics, safety, pharmacodynamics and efficacy analyses required for the study. Note that there is also a separate analysis plan for the Population Pharmacokinetics analyses.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report (CSR) for the Protocol, as shown in Table 1.

Table 1 Protocol Revision Chronology

Document	DNG number	Date	Rationale
Original Protocol (00)	2018N373284_00	29-Apr-2019	Original
Amendment 1	2018N373284_01	24-Jul-2019	To adjust and clarify the number of planned participants to ensure compliance with regulatory commitments.
Amendment 1/GER-1	2018N373284_02	22-Nov-2019	This is a country-specific protocol amendment for Germany to further clarify the exclusion criterion #12.
Amendment 2	2018N373284_03	24-Apr-2020	To adjust the protocol in response to the COVID-19 pandemic. The purpose is to provide flexibility to protocol specified visits and assessments in accordance with guidance from regulatory agencies, while maintaining trial and data integrity.
Amendment 3	TMF-13827130	14-Jul-2021	To add an optional access extension phase post Week 52 exclusively for eligible participants who complete Part B of the study (e.g., participants from countries where the IV formulation is not approved for pediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges).
Amendment 4	TMF-15202454	14-Dec-2022	To accurately reflect the end of study definition as the last subject last visit occurring during the optional access extension phase vs. Part A and Part B of the study.

As described in Table 1, amendment 3 incorporates an optional access extension phase. The data collected during this phase will be limited to key safety information (SAEs, pregnancies and medical device incidents) and will be reported in a synoptic CSR after the conclusion of the extension phase, therefore this data is not covered in the RAP. There will be no formal statistical analyses performed in the optional access extension phase.

2. SUMMARY OF KEY PROTOCOL INFORMATION

This is the first version of the RAP, and is in keeping with additional detail to that provided in Protocol amendment 4.

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes to the originally planned statistical analysis specified in Protocol amendment 4.

2.2. Study Objectives and Endpoints

The protocol defined objectives and endpoints (Protocol Section 3) are shown in Table 2.

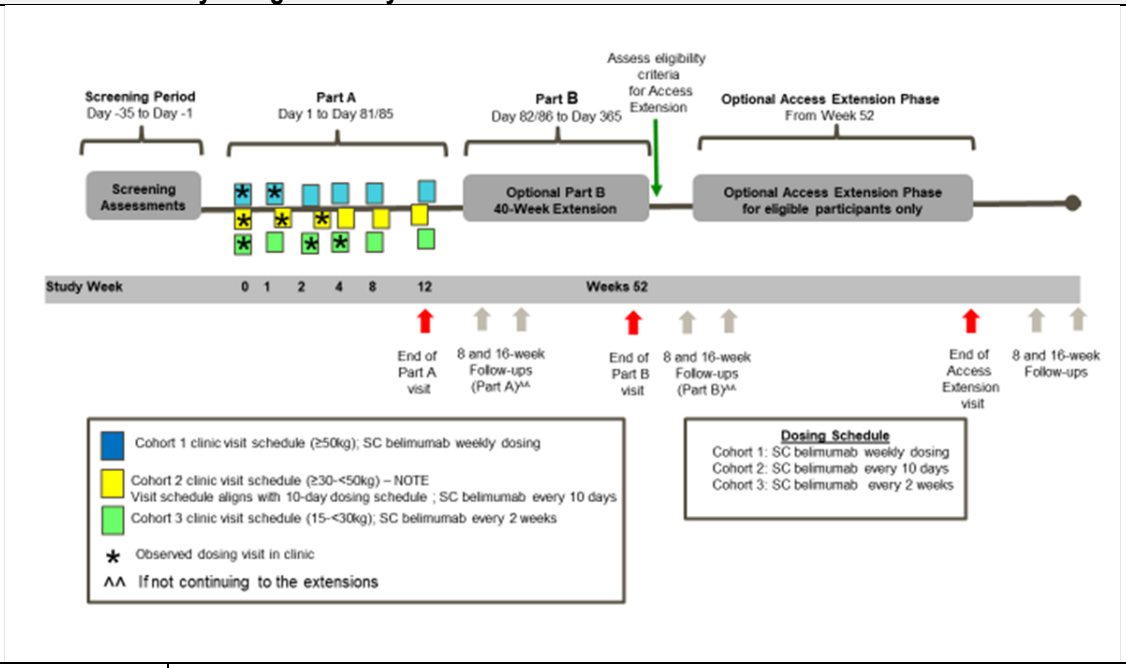
Table 2 Protocol defined objectives and endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To characterize the pharmacokinetic (PK) profile of belimumab 200 mg SC in pediatric systemic lupus erythematous (SLE) participants	• Observed belimumab concentrations at Week 12 • Steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates)[1]
Secondary Objectives: Safety	**Secondary Endpoints: Safety**
• To evaluate the safety and tolerability of belimumab 200 mg SC in pediatric SLE participants	• Incidence of adverse events, serious adverse events and adverse events of special interest through Week 52
Secondary Objectives: Biomarkers	**Secondary Endpoints: Biomarkers**
• To characterize the pharmacodynamic (PD) profile of belimumab 200 mg SC in pediatric SLE participants	• Change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52
Exploratory Objectives: Efficacy	**Exploratory Endpoints: Efficacy**
• To characterize the impact of belimumab 200 mg SC on disease activity in pediatric SLE participants	• Percentage of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52

[1] Note that these endpoints will be described in a separate RAP written by Clinical Pharmacology Modelling & Simulation (CPMS) and analyses will be presented separately.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a single arm, multi-center, open-label study to evaluate the pharmacokinetic (PK), safety, and pharmacodynamic (PD) of subcutaneous (SC) belimumab plus background standard therapy in approximately 28 pediatric participants 5 to 17 years of age and weighing ≥ 15 kg with active SLE. • The study will include three main parts: 12 weeks of Part A open-label treatment phase, 40 weeks of Part B extension phase among participants who complete Part A, and up to 16 weeks of follow-up phase. • Note that there is also an optional access extension phase, which provides a mechanism for continued access to belimumab SC from Week 52 and is exclusively for eligible participants who complete Part B of the study (see Protocol Section 6.7.1). The data from the optional access extension phase will be limited and will be reported in a separate CSR. • Participants will be allocated to treatment cohorts based on their body weight at baseline. There will be three cohorts: ○ Cohort 1 consists of participants with baseline body weight ≥ 50 kg. ○ Cohort 2 consists of participants with baseline body weight ≥ 30 and < 50 kg. ○ Cohort 3 consists of participants with baseline body weight < 30 kg.
Dosing	• In Part A, the dosing frequency of belimumab 200 mg SC will be every week for Cohort 1, every 10 days for Cohort 2, and every 2 weeks for Cohort 3. • In Part B, dosing of SC belimumab may continue at the same frequency as in Part A or may require a change in frequency according to changes in participant body weight. • In the access extension phase, dosing of SC belimumab may continue at the same frequency as in Part A/B or may require a change in frequency according to changes in participant body weight.
Schedule of Activities	• Refer to Protocol Section 1.3 Schedule of Activities
Treatment Assignment	• This is a single arm study. All participants will be assigned to belimumab 200 mg SC.

Overview of Study Design and Key Features	
Interim Analysis	• No formal interim analyses are planned. In-stream review of the safety and PK data will be performed, see Section 3.1.

2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of the study is to characterize the PK profile of belimumab 200 mg SC, and to descriptively evaluate the safety and PD of belimumab 200 mg SC in pediatric SLE participants.

No formal statistical hypothesis testing is planned. All analyses will be descriptive.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned. In-stream review of the safety and PK data will be performed by the study Medical Monitor, members of the GSK Safety Review Team (SRT) and the GSK Pharmacokinetics Review Team (PRT).

3.1.1. GSK Safety Review Team (SRT)

The study Medical Monitor and members of the GSK SRT will perform in-stream review of all safety data for the duration of the study and communicate recommendations as appropriate.

3.1.2. GSK Pharmacokinetics Review Team (PRT)

The GSK PRT will include the study Medical Monitor, Clinical Science Lead, Statistician, Safety Scientist/Physician and Pharmacokineticist. Additional GSK scientists/physicians may also be invited to assist the PRT with data reviews.

The PRT will review all available PK data after the first 6 participants in Cohort 1 (≥50 kg) or Cohort 2 (≥30 kg to <50 kg) have completed Week 12. For Cohort 3 (<30 kg), preliminary PK data will be reviewed by the PRT based on a data cut triggered by the first Cohort 3 participant having completed Week 12.

The primary objective of the PRT meetings will be to either confirm the initial dose or to recommend an adjustment in dosing frequency if a substantial difference in exposure is observed compared to exposure in adult SLE participants receiving 200 mg SC belimumab every week.

When necessary, additional interim reviews may be performed. Recommendations will be made regarding dose confirmation or adjustment. The recommendations of the PRT will be summarized and distributed to study team members and investigators.

3.2. Final Analyses

There will be two Database Locks (DBL) for this study.

The first DBL corresponds to all data collected in Part A and Part B of the study (including Follow Up assessments). The results will be reported in the primary CSR.

The second DBL corresponds to the access extension phase of the study. This data will predominantly be collected on paper Case Report Forms (CRFs) and is therefore not discussed within this document. The results will be reported in a synoptic CSR at the end of the access extension phase. No formal statistical analyses will be performed in the optional access extension phase.

Data for the access extension phase that is collected within the eCRF is limited to the following:

Data	Reported
Subject continuation in the access extension phase (Yes/No)	Primary CSR & Synoptic CSR
Pregnancy status during the access extension phase	Synoptic CSR
Phase conclusion for the access extension phase (Date of completion/withdrawal and reason for withdrawal if applicable)	Synoptic CSR

For subjects who do not enter the access extension phase, all data will be retained in the Primary datasets and reported in the Primary CSR.

For subjects who do enter the access extension phase, all data will be retained in the Primary datasets and reported in the Primary CSR up to and including the End of Study conclusion date recorded on the eCRF. This date represents the end of each subjects Part A and B data (including Follow Up assessments if applicable). All data collected after that date will be reported in the Synoptic CSR. Any data collected after this date in the eCRF for disposition or on log forms (AEs or concomitant medications) will be removed from the Primary datasets to avoid double reporting.

The first DBL will be performed after completion of the following sequential steps:

1. The last subject's completion of Part B (including all 16 week follow-up visits)
2. All required database cleaning activities have been completed
3. All criteria for reporting the study have been met, including:
    - Review of Protocol Deviations
    - Categorization of Adverse Events of Special Interest (AESI)
    - Review of dropouts
4. DBL declared by Data Management

The second DBL will be performed after completion of the following sequential steps:

1. The last subject's completion of the last visit in the optional access extension phase
2. All required database cleaning activities have been completed
3. DBL declared by Data Management

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants whose parent/caregiver sign the Informed Consent Form (ICF)	• Screen failures • Study Population
Enrolled	• All participants assigned treatment by the Interactive Web Response System (IWRS).	• Study Population
Intent-To-Treat (ITT)	• All participants assigned treatment who received at least one dose of study treatment.	• Study Population • Safety • Efficacy • Pharmacodynamic and Biomarker
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

Listings will be presented using the Enrolled population unless otherwise specified.

4.1. Protocol Deviations

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

- Data will be reviewed prior to database lock to ensure all deviations are captured and categorized in the protocol deviations dataset. All deviations will be discussed and categorized as important or not important.
- This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Subgroup Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TFL
A	Belimumab SC	Belimumab 200mg	1

Table 3 Treatment Descriptors, Colors, Line Style and Symbols for Reporting

Treatment Descriptor	Color	SAS Color	Line Style	Symbol
Belimumab 200mg	Blue	CX0000FF	Solid	Triangle (filled)

5.2. On Study Definition

On study is defined as Day 1 until the date of study completion or study withdrawal (including LTFU and death), excluding the access extension phase (see Section 3.2).

5.3. Study Day

Study day is calculated as the number of days from Belimumab study treatment start date to the study day of interest (see Section 13.4.1). Note that study day cannot be zero. It will be missing if either date is missing.

5.4. Baseline Definitions

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.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy			
SELENA-SLEDAI	X	X	Day 1
Safety and Biomarker			

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Laboratory assessments (including hematology, urinalysis, chemistry, Anti-dsDNA/ANA and complement C3/C4)	X	X	Day 1
Biomarkers (including BLyS Protein, B-Cells, and immunogenicity)		X	Day 1

Note that the SELENA-SLEDAI total score is calculated by summing 24 individual items. The total score used as Baseline will be calculated from all available items at Day 1, but if individual items are missing, the Screening assessment for those items will be used.

Concomitant medications are considered to be present at baseline if the start date is prior to Day 1 and the end date is on or after Day 1. Medications with a start date on Day 1 are considered as being on-treatment (concomitant). For further details, see Section 13.2.1.

Adverse events (AE) are considered pre-treatment if the start date is prior to Day 1, or if the start date is on Day 1 but the AE start time shows that the event starts pre-dose. Treatment emergent AEs are defined in Section 13.2.2.

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

5.5. Change from Baseline and Percentage Change from Baseline

Change from baseline for the visit of interest will be calculated as

$$Visit\ value - baseline\ value.$$

If either value is missing, the change from baseline will be missing.

Percentage change from baseline for a visit of interest will be calculated as

$$\frac{Visit\ value - baseline\ value}{baseline\ value} \times 100.$$

Subjects with a baseline value of zero will not have a value calculated due to division by zero. If the baseline value is zero or missing, then the percentage change will set to missing.

5.6. Multicentre Studies

In this multicentre global study, enrolment will be presented by country and investigative site.

5.7. Examination of Covariates, Other Strata and Subgroups

Subgroups of clinical interest may be considered for post-hoc analyses, such as baseline weight cohorts.

5.8. Presentation of data

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum and maximum).

Categorical variables will be summarized using counts and percentages.

Subjects are recruited into the study in different weight cohorts, with different planned visit dates during Part A (as per Protocol Section 1.3). The majority of the SAC outputs will present all of the data together, regardless of cohort. Table 4 shows the visits for Part A that are combined across the cohorts when outputs are presented by visit.

Table 4 Part A presentation of results by visit

	Target Study Day[1]	
Visit label on outputs	**Cohorts 1 and 3**	**Cohort 2**
Week 1 (Day 8/11)	Day 8	Day 11
Week 2 (Day 15/21)	Day 15	Day 21
Week 4 (Day 29/31)	Day 29	Day 31
Week 8 (Day 57/61)	Day 57	Day 61
Week 12 (Day 85/81)	Day 85	Day 81

[1] Target Study Day, relative to Baseline/Treatment Start Date as Day 1.

5.9. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.1	Appendix 1: Assessment Windows
13.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
13.3	Appendix 3: Data Display Standards & Handling Conventions
13.4	Appendix 4: Derived and Transformed Data
13.5	Appendix 5: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

The study population tables and figures will be based on the ITT population and the listings will be based on the enrolled population, unless otherwise specified.

Study population analyses including analyses of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications and exposure will be based on GSK Core Data Standards. See 'RAP mock outputs 200908' document for mock displays.

6.1. Disposition of Subjects

The number and percentage of subjects enrolled by country and site will be summarized using the Enrolled population [T1.01]. A summary of subject status in the study by country and site will also be produced using the Screened population [T1.21].

The number of subjects in each population (Screened, Enrolled, Intent-to-Treat, and Pharmacokinetic) will be summarized [T1.02].

A summary of the screening status and reasons for screen failure will be provided for the Screened population [T1.03]. A listing of the subjects who were screen or run-in failures will also be provided for the Screened population who were not ultimately enrolled in the study [L1.01].

The number and percentage of subjects who completed and who withdrew from the study, including reasons for withdrawal, will be displayed for Week 12 (Part A) [T1.04] and Week 52 (Part B) [T1.05]. The number and percentage of subjects continuing into the optional access extension phase will be also summarized [T1.05].

The cumulative number and percentage of subjects withdrawing from the study by visit will be summarized [T1.06].

A listing of subject disposition will be provided showing the subjects completion status at Week 12 and Week 52 and whether they are included in each population [L1.02]. 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.

A listing of subjects who withdraw from the study will be provided [L1.03]. This will include the primary reason, date and study day of withdrawal (based on the Part A or Part B phase conclusion page of the eCRF) and also the last contact date (based on the study conclusion page of the eCRF).

A listing will also be provided for subjects who discontinue study treatment [L1.13]. This will include the primary reason, date of last dose and study day.

A Kaplan Meier (KM) plot of time to study withdrawal will be generated [F1.01]. This will be based on the withdrawal date recorded on the Part A or Part B phase conclusion page of the eCRF.

At baseline, each subject is allocated to a treatment cohort according to their body weight, which dictates the dosing schedule for the subject (Protocol Section 4.1). During Part A, subjects should remain in the same dosing group. During Part B, the dosing group may remain the same or may require a change, according to the subjects' body weight (Protocol Section 6.6). A shift table that summarizes the differences between dosing group at baseline compared to the last observed dosing group (based on the last treatment date) will be provided [T1.12]. Subjects who withdraw from the study during Part A will be assumed to have remained in their original dosing group.

6.2. Demographic and Baseline Characteristics

The following Demographic and Baseline disease activity indicators will be summarized:

PARAMETER	SUMMARY TYPE
Demographic and Baseline Characteristics [T1.08, T1.09]	
Country [T1.08]	Categorical: Argentina, Germany, Japan, Mexico, Netherlands, Spain, United States
Sex [T1.08]	Categorical: Female, Male
Age at screening (years) [T1.08]	Continuous
Age group at screening (years) [T1.08]	Categorical: <=18, 19-64, >=65
Ethnicity: Hispanic or Latino origin [T1.08]	Categorical: Hispanic or Latino origin, Not Hispanic or Latino origin
High Level Race [T1.08]	Categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Race Detail [T1.08]	Categorical: American Indian or Alaska Native, Asian (Central/South Asian, East Asian, Japanese, South East Asian), Black or African American, Native Hawaiian or Other Pacific Islander, White (Arabic/North African, White/Caucasian/European), Mixed Asian, Mixed White, Mixed Race
Weight (kg) [T1.08]	Continuous
Body Weight Cohort at Baseline [T1.08]	Categorical: Cohort 1 (≥50kg), Cohort 2 (≥30kg to <50kg), Cohort 3 (<30 kg)
Age Ranges at Screening [T1.09], using the Enrolled population	Categorical: Children (2-11 years), Adolescents (12-17 years)
Medical History [T1.10, T1.11]	
Current Medical Conditions [T1.10]	Categorical by Classification: presented if Current medical history is present
Family History of Systemic Lupus Erythematosus [T1.11]	Categorical for Biological Mother, Father, Sister and Brother: Yes, No, Unknown, Not applicable
Baseline Disease Activity [T1.13, 1.14]	
Proteinuria Level (mg/mg) [T1.13]	Continuous Categorical: <=0.5, >0.5 - <1, 1 - <2, >=2
SELENA SLEDAI score [T1.14]	Continuous Categorical: <=7, >=8 Categorical: <=9, >=10

PARAMETER	SUMMARY TYPE
SELENA SLEDAI Organ and Item involvement [T1.14]	Categorical: presented if Yes
Baseline autoantibody levels and other Biomarkers [T1.15]	
Anti-dsDNA [IU/mL]	Categorical: - negative (<30 IU/mL) - positive (>=30 IU/mL) Continuous (for positive subjects)
Anti-nuclear Antibody (ANA) [Titer]	Categorical: - negative (Index <80) - positive (Index >=80) Continuous (for positive subjects)
Anti-dsDNA and/or ANA positive	Categorical: Yes, No - Yes if Anti-dsDNA positive (>=30 IU/mL) and/or ANA positive (Index >=80) - No if Anti-dsDNA negative and ANA negative
Anti-dsDNA Positive and Low Complement	Categorical: Yes, No - Yes if Anti-dsDNA positive (>=30 IU/mL) and Low Complement (C3<90 mg/dL and/or C4<13 mg/dL) - No otherwise
C Reactive Protein (CRP) (mg/L)	Categorical: - negative (<4 mg/L) - positive (>=4 mg/L) Continuous (for positive subjects)
Complement and BLyS Levels at Baseline [T1.16]	
Complement: C3 [mg/dL]	Continuous Categorical: - high (>161 mg/dL) - normal (90 - 161 mg/dL) - low (<90 mg/dL)
Complement: C4 [mg/dL]	Continuous Categorical: - high (>38 mg/dL) - normal (13 - 38 mg/dL) - low (<13 mg/dL)
Baseline BLyS (free) protein [ng/mL]	Categorical: - below limit of quantification [LOQ] (<0.05 ng/mL), - above LOQ Continuous (for subjects above LOQ)
Allowable SLE Medication Usage at Baseline [T1.17, T1.18]	
Average daily prednisone dose (mg/day) [T1.17] Note that Steroids are converted to prednisone equivalent dose, see Section 13.4.4	Categorical: - 0 mg/day - >0 to <=7.5 mg/day - >7.5 mg/day Continuous

PARAMETER	SUMMARY TYPE
Allowable SLE medications by class and drug [T1.17]	Categorical (see Section 13.4.5): - Steroids - Antimalarials - Immunosuppressants - Aspirin - NSAIDs
Steroid, Anti-malarial and Immunosuppressant Use at Baseline [T1.18]	Categorical: - Steroid Only - Immunosuppressant Only - Antimalarial Only - Steroid and Immunosuppressant Only - Steroid and Antimalarial Only - Immunosuppressant and Antimalarial Only - Steroid and Immunosuppressant and Antimalarial

Note that other baseline summaries (e.g. vital signs, B cells) are provided in later tables.

Demographic and baseline characteristics, including body weight and cohort, will be listed [L1.06]. Age at screening will be presented in years and months.

A listing of race and race detail will be provided [L1.07].

A listing will be provided for past and current medical conditions [L1.08]. Conditions that are not assessed, or reported as no medical condition, will be indicated in this listing.

The summaries of demographic and baseline characteristics, and allowable SLE medication may be repeated for the following subgroups in post-hoc analyses:

- Baseline Weight Cohorts: Cohort 1 (≥50 kg), Cohort 2 (≥30 kg - <50 kg) and Cohort 3 (<30 kg)

6.3. Concomitant Medications

Prior and concomitant medications will be coded according to drug name as defined in the GSK Drug Dictionary (version in use at time of reporting), and classified according to ATC classification level 1 and level 4.

Concomitant medications are defined as medications that start on or before the first dose date of study drug and end on or after the first dose date of study drug, or medications that start on or after the first dose date of study drug (see Section 13.2.1 for further details). Note that medications with partial or missing start and/or stop dates will be assumed to be concomitant unless there is evidence through comparison of partial dates to suggest otherwise, for example if the day is missing, then the month and year will be compared to the month and year of the first dose date of study drug and if the month and year are the same or later, then the medication will be considered concomitant (see Section 13.5.2.1 for further details).

A summary of concomitant medications by ATC level 1 and level 4 term will be provided [T1.19].

A listing of all prior and concomitant medication data will be displayed by subject [L1.09]. An additional listing will be provided by subject for all concomitant belimumab medication [L1.12].

6.4. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized [T1.07] and listed [L1.05]. The table will display the number and percentage of subjects who experienced any important protocol deviation and for each deviation type.

A separate listing of all inclusion/exclusion criteria deviations will also be provided [L1.04]. This will be based on data recorded on the inclusion/exclusion page of the eCRF. It will include any re-screened subjects who are enrolled into the study.

6.5. Study Drug Administration

Study drug exposure through Week 52 will be summarized [T1.20]. Duration of exposure (days) (see Section 13.4.2) and the total number of injections will be summarized using continuous summary statistics. The total number of injections will also be categorized as 1 – 12, 13 – 24, 25 – 36, 37 – 51 or >51.

A listing of all injections will be presented by subject, including injection number, dosing cohort, and some additional details if the injection has been given [L1.11].

6.6. CRF Listing

A spreadsheet will be created that identifies which subjects in the study should have Case Report Forms (CRFs) included in the submission for each Country [L6]. The following Countries and criteria for CRF inclusion will be implemented:

- United States: Death, Study Withdrawals Due to AEs (Serious and Non-Serious), i.e. the default criteria
- Canada: Death, Study Withdrawals Due to AEs, Serious Adverse Events, i.e. the default criteria
- China: Does not require CRFs, therefore no criteria will be applied and the column will be left blank
- Japan: Does not require CRFs, therefore no criteria will be applied and the column will be left blank
- European Union: Does not require CRFs, therefore no criteria will be applied and the column will be left blank

7. EFFICACY ANALYSES

Efficacy will be evaluated by the exploratory endpoint (≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52) and the other efficacy endpoints of interest (including other SELENA SLEDAI summaries, proteinuria and prednisone summaries).

The efficacy tables and figures will be based on the ITT population and the listings will be based on the enrolled population, unless otherwise specified. See 'RAP mock outputs 200908' document for mock displays.

Efficacy outputs will report all observed On Study data (see Section 5.2). Efficacy data will be summarised using a treatment policy approach, including all data regardless of any Intercurrent Events (ICE).

7.1. Exploratory Efficacy Analyses

7.1.1. Summary Measure

The percentage of subjects with ≥ 4-point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52.

7.1.2. Population of Interest

The exploratory efficacy analyses will be based on the ITT population.

7.1.3. Subgroup, Supportive and Sensitivity Analyses

Summaries will be presented by baseline weight cohort and overall. There are no planned supportive or sensitivity analyses for the exploratory efficacy endpoints. Post-hoc analyses may be considered for other subgroups.

7.1.4. Statistical Methodology Specification

The number and percentage of subjects with ≥ 4-point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52 will be provided using the observed data. Each of the three cohorts will be summarized separately and overall [T2.01]. No statistical tests will be performed.

Summary statistics will be provided for SELENA SLEDAI percentage change from baseline by visit for each of the three cohorts and overall [T2.02] and change from baseline by visit for each of the three cohorts and overall [T2.03] using the observed data. No statistical tests will be performed.

A line graph will be produced to show the percentage (±SE) of subjects who have at least a 4-point reduction from baseline in SELENA SLEDAI by visit using the observed data for all subjects [F2.01], as well as by cohort [F2.04].

A listing of SELENA SLEDAI analysis results for each subject will be provided by visit. The listing will include SELENA SLEDAI total score, change and percentage change from baseline in total score [L2.01].

7.2. Other Efficacy Analyses

7.2.1. Proteinuria

Proteinuria shifts from baseline will be summarized by visit [T2.04].

Baseline proteinuria data will be summarized as the number and percentage of subjects who are normal (≤0.5 mg/mg) or high (>0.5 mg/mg). For each post-baseline visit the data will be summarized by normal or high baseline status. Among subjects normal at baseline, the shifts presented will be 'No Change' or 'Normal to High'. Among subjects high at baseline, the shifts presented will be 'No Change' or 'High to Normal'.

As well as presenting the data for each visit, the proteinuria shifts will be summarized based on shifts at any time post-baseline. Among subjects with normal proteinuria at baseline, the number and percentage of subjects with at least one high post-baseline value will be presented as 'Normal to High'; subjects who never experience a high proteinuria value post-baseline will be presented as 'No Change'. Among subjects with high baseline proteinuria, subjects with at least one normal post-baseline value will be presented as 'High to Normal'; subjects who never experience a normal post-baseline value will be presented as 'No Change'.

No statistical tests will be performed.

7.2.2. Prednisone

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 13.4.4.

Prednisone data presented by visit will use the visit date recorded on the vital signs panel of the eCRF. These dates will then be used to assess the prednisone dose at that visit, using the derivations specified in Section 7.2.2.2 and Section 7.2.2.3.

A listing of daily prednisone dose will be provided for each subject by visit [L2.02]. The listing will present the average daily prednisone dose at the visit and the change from baseline in average daily prednisone dose in the 7 days prior to the visit (Section 7.2.2.3), as well as the average daily prednisone dose between visits and the change from baseline in average daily prednisone dose from the previous visit (Section 7.2.2.2).

7.2.2.1. Baseline Prednisone Dose

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

7.2.2.2. 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, the early withdrawal visit will only be presented if it slots into a scheduled visit (see Section 13.1.1).

7.2.2.3. Average Daily Prednisone Dose at the Visit

While on study, 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. 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, the early withdrawal visit will only be presented if it slots into a scheduled visit (see Section 13.1.1).

7.2.2.4. Any Decrease from Baseline in Prednisone among Subjects using Prednisone at Baseline (Observed)

The number and percentage of subjects having any decrease compared to baseline among subjects using prednisone at baseline will be presented by visit [T2.05]. These summaries will be based on the average daily prednisone dose at the visit, as calculated in Section 7.2.2.3. No statistical tests will be performed.

A line graph will be produced by visit for the percentage of subjects (±SE) having any decrease in prednisone compared to baseline among subjects using prednisone at baseline [F2.02].

7.2.2.5. Any Increase from Baseline in Prednisone (Observed)

The number and percentage of subjects having any increase compared to baseline will be presented by visit [T2.06]. These summaries will be based on the average daily prednisone dose at the visit, as calculated in Section 7.2.2.3. No statistical tests will be performed.

A line graph will be produced by visit for the percentage of subjects (±SE) having any increase in prednisone compared to baseline [F2.03].

8. SAFETY ANALYSES

Safety will be evaluated by the secondary endpoints (adverse events, serious adverse events and adverse events of special interest) and the other safety endpoints of interest (including laboratory summaries and vital signs).

The safety tables and figures will be based on the ITT population and the listings will be based on the enrolled population, unless otherwise specified. See 'RAP mock outputs 200908' document for mock displays.

Safety outputs will report all On Study data (see Section 5.2). Safety data will be summarised using a treatment policy approach, including all data regardless of any Intercurrent Events (ICE).

8.1. Secondary Endpoint - Adverse Events

8.1.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious adverse events (SAEs) and AEs of special interest (AESIs) will be based on GSK Core Data Standards. All subjects will be followed for safety up to 16 weeks post-treatment.

All AEs will be classified using the current standard GSK Medical Dictionary for Regulatory Activities (i.e. MedDRA version in use at the time of reporting), and grouped by System Organ Class (SOC) and/or Preferred Term (PT). The MedDRA version is detailed on every table that uses MedDRA. The investigator will evaluate all AEs with respect to seriousness, severity and causality. The severity of an AE is to be determined using the Assessment of Intensity provided in Appendix 2 of the protocol, if a grade is provided for the AE of interest.

For the following summaries, only treatment-emergent AEs will be summarized, unless otherwise stated. Treatment-emergent AEs are defined in Section 13.2.2 based on start date/time of AE versus first dose date/time of study treatment. AEs with missing start and/or stop dates will be assumed to be treatment-emergent.

The duration of the AE will be calculated as follows:

$$\textit{Duration of AE (days)} = \textit{Date of AE resolution} - \textit{AE start date} + 1.$$

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

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 percentage of subjects with at least one: AE, related AE, SAE, severe AE, SAE and/or severe AE, AE resulting in study agent discontinuation and death [T3.01].

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

- All AEs (by SOC and PT; by PT only) [T3.02, T3.03]
- All SAEs (by SOC and PT) [T3.04]
- AEs resulting in study agent discontinuation (by PT only) [T3.05]
- Common non-serious AEs (number of subjects and occurrences) (by SOC and PT) [T3.06]
- SAEs (number of subjects and occurrences) (by SOC and PT) [T3.07]
- Study drug related Non-Serious AEs (by PT only) [T3.08]
- Study drug related fatal and non-fatal SAEs (by PT only) [T3.09]
- AEs by severity (by SOC and PT) [T3.10]
- Study drug related AEs by severity (by SOC and PT) [T3.11]

The tabular summary for each category of AE listed above will include the number of subjects with any event (incidence), the number of subjects with any event in each SOC (where applicable), plus the number of subjects with any event in each PT.

For the tables by severity, 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 for a given subject. Additionally, 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.

By default, AEs will be sorted by MedDRA SOCs, in descending order from the SOC with the highest total incidence to the SOC with the lowest total incidence – firstly based on the number of subjects and then based on the number of occurrences. If the total incidence for any two or more SOCs is equal (based on number of subjects and occurrences), the SOCs will be presented in alphabetical order. Only SOCs with observed AE PTs will be presented. The sort order for MedDRA PTs within each SOC will be repeated, i.e. PTs will be presented in descending order of incidence (number of subjects, then number of occurrences) and then alphabetically if the incidence is equal.

The table displaying all AEs by SOC and PT may be repeated for subgroups for post-hoc analyses.

A listing of all AEs will be presented by subject [L3.01].

A listing that displays which subjects reported each AE will also be produced. AEs will be sorted by SOC and PT [L3.02].

A listing of all AEs resulting in study agent discontinuation will be presented by subject [L3.05].

The hierarchical relationship between MedDRA SOCs, PTs and verbatim text will be displayed in a listing for all AEs [L3.09].

8.1.2. Additional Adverse Event Summaries to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic

A listing will be produced to show COVID-19 assessments and symptoms for all subjects with a suspected, probable or confirmed COVID-19 infection throughout the study [L3.08]. This listing will be based on information collected on the COVID-19 Coronavirus Infection Assessment CRF page.

No additional summaries/listings will be produced due to the timing of recruitment in relation to the COVID-19 pandemic. The first subject was screened for the study in November 2019 and COVID-19 pandemic environment onset dates for each Country are presented in Section 13.4.6. Therefore, nearly all on-treatment data was collected during the COVID-19 pandemic and summaries split by pre COVID-19 or during COVID-19 would not be informative.

8.1.3. Serious Adverse Events

In addition to the tabular summaries of SAEs described in Section 8.1, listings will be provided by subject for all SAEs [L3.03] and all deaths [L3.04]. The cause of death will be categorized by GSK.

A listing will be provided by subject to display the reason(s) why each SAE was considered Serious [L3.06].

8.1.4. AE outputs required for Mexico

The number and percentage of subjects experiencing SAEs will be presented by Country and Preferred Term [T3.43], both overall and by gender.

The number and percentage of subjects experiencing AEs will be presented by Preferred Term [T3.44], both overall and by Seriousness (Serious/Non-Serious).

A listing of all non-serious AEs for subjects in Mexico will be presented for the Enrolled population [T3.45].

A listing of all SAEs for subjects in Mexico will also be presented for the Enrolled population [T3.46].

8.1.5. Adverse Events of Special Interest (AESI) Analyses

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

The Benlysta PSAP has been developed to include an AESI analysis for consistent reporting across belimumab studies. Categorizations for the AESIs will be defined in the PSAP.

The milestone defined in the PSAP for categorizations will be the first DBL, for the primary analysis (Section 3.2).

Events will only be reported once even if the event does not resolve by the Week 52 visit.

An overall summary of AESIs will be presented and each specific category of AESI will be presented separately by PT [T3.12]. The number and percentage of subjects with at least one occurrence and the number of events will be provided.

The following AESI will be identified and categorized 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 DBL.

Malignant Neoplasms

- Malignancies Excluding non-melanoma skin cancer (NMSC)
- Malignancies Including NMSC
  - Solid Tumour
  - Hematologic
  - Skin (All)
    - NMSC
    - Excluding NMSC
  - Tumours of unspecified malignancy categorized as malignant per GSK

Post-Injection Systemic Reactions (PISR)

- PISR per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search
- PISR per Anaphylactic Reaction CMQ broad search
- PISR per Anaphylactic Reaction CMQ algorithmic search
- Serious Anaphylaxis per Sampson Criteria per GSK categorization
- Serious Acute PISR/Hypersensitivity Per GSK categorization
  - Serious Acute PISR Excluding Hypersensitivity per GSK categorization
  - Serious Acute Hypersensitivity Reactions per GSK categorization
- Serious Delayed Acute Hypersensitivity Reactions per GSK categorization
- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK categorization

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 categorization
- OI per GSK categorization excluding Tuberculosis and Herpes Zoster
- Active Tuberculosis
  - Non-Opportunistic
  - Opportunistic
- Herpes Zoster
  - Non-Opportunistic
  - Opportunistic
    - Recurrent
    - Disseminated
- Sepsis

Adverse Events
Adverse Events of Special Interest (AESI)
Depression (including mood disorders and anxiety)/suicide/self-injury (All and Serious, separately) • Depression (including mood disorders and anxiety) (excluding suicide and self-injury) • Suicide/self-injury • Serous suicide/self-injury per GSK categorization – 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 categorization and will be presented by category and PT.

Post-injection systemic reactions and serious post-injection systemic reactions will be presented using nine different definitions as indicated above.

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

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

All AESI will be presented in a listing by AESI subcategory and subject [L3.07].

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional AESI, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

8.1.5.1. Injection/Anaphylaxis/Hypersensitivity Reactions by Infusion

Summaries of injection, hypersensitivity, and anaphylactic reactions that occur in relation to the first six injections will be presented by each injection and PT for the following:

- Post-Injection Systemic Reactions per Anaphylactic Reactions CMQ Broad Search by PT, in First Six Injections [T3.13]
- Serious Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ Broad search by PT, in First Six Injections [T3.14]

- Serious Acute Post-Injection Systemic Reactions/Hypersensitivity per GSK Categorization by PT, in First Six Injections [T3.15]
- Serious Delayed Acute Hypersensitivity Reactions per GSK Categorization by PT, in First Six Injections [T3.16]
- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Categorization by PT, in First Six Injections [T3.17]

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis and liver function tests will be based on GSK Core Data Standards.

For laboratory analyses, analytes will be summarized and analyses will be performed based on the observed data, no imputation will be done for missing data. Baseline is defined as described in Section 5.4.

Laboratory toxicity will be graded using the Adverse Event and Laboratory Value Severity Grading Table (see Protocol Appendix 2, Section 10.2.1). The Table is based upon publicly available Tables from the National Institute of Allergy and Infectious Disease Division of Microbiology and Infectious Diseases (www.niaid.nih.gov) and Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (U.S. Department of Health and Human Services, 2010). Toxicity grades provided by the laboratory will be used. Any laboratory parameters where toxicity grades are expected but not provided by the laboratory will be programmed according to the Protocol.

If a numeric laboratory value, has a non-detectable level reported in the database, then typically the numeric value is missing, and a character value starting with '<x' or '>x' is present. A numeric value will be derived using the number of decimal places in the observed character values i.e.

- 2 Decimal Places = '<x' becomes x-0.01
- 1 Decimal Place = '>x' becomes x+0.1
- 0 Decimal places = '<x' becomes x-1

Laboratory parameters are shown in Table 5, split by output category (hematology, liver function, electrolytes, other chemistries, urinalysis and immunoglobulins) and indicating which type of outputs are applicable for each parameter.

Table 5 Laboratory Parameters

Laboratory Parameter	Lab Results by Visit (Section 8.2.1)	Toxicity Grade (Section 8.2.2 and Section 8.2.3)	Reference Range Shifts (Section 8.2.4)
Hematology			
Basophils (10^9/L)	Yes		Yes
Basophils/Leukocytes (%)	Yes		Yes
Eosinophils (10^9/L)	Yes		Yes
Eosinophils/Leukocytes (%)	Yes		Yes
Ery. Mean Corpuscular Hemoglobin (pg)	Yes		Yes
Ery. Mean Corpuscular Volume (fL)	Yes		Yes
Erythrocytes (10^12/L)	Yes		Yes
Hematocrit (%)	Yes		Yes
Hemoglobin (g/L)	Yes	Yes	
Leukocytes (10^9/L)	Yes	Yes	
Lymphocytes (10^9/L)	Yes	Yes	
Lymphocytes/Leukocytes (%)	Yes		Yes
Monocytes (10^9/L)	Yes		Yes
Monocytes/Leukocytes (%)	Yes		Yes
Neutrophils (10^9/L)	Yes	Yes	
Neutrophils, Segmented (10^9/L)	Yes		Yes
Neutrophils, Segmented/Leukocytes (%)	Yes		Yes
Neutrophils/Leukocytes (%)	Yes		Yes
Platelets (10^9/L)	Yes	Yes	
% Reticulocytes (%)	Yes		Yes
Liver Function			
Alanine Aminotransferase (U/L)	Yes	Yes	
Alkaline Phosphatase (U/L)	Yes	Yes	
Aspartate Aminotransferase (U/L)	Yes	Yes	
Bilirubin (umol/L)	Yes	Yes	
Direct Bilirubin (umol/L)	Yes		Yes
Gamma Glutamyl Transferase (U/L)	Yes	Yes	
Electrolytes			
Calcium (mmol/L)	Yes		Yes
Calcium Corrected for albumin (mmol/L)	Yes		
Calcium corrected for albumin - Hypercalcemia (mmol/L)		Yes	
Calcium corrected for albumin - Hypocalcemia (mmol/L)		Yes	
Carbon Dioxide (mmol/L)	Yes		Yes
Magnesium (mmol/L)	Yes	Yes	
Phosphate (mmol/L)	Yes	Yes	
Potassium (mmol/L)	Yes		
Potassium - Hyperkalemia (mmol/L)		Yes	
Potassium - Hypokalemia (mmol/L)		Yes	
Sodium (mmol/L)	Yes		
Sodium - Hypernatremia (mmol/L)		Yes	
Sodium - Hyponatremia (mmol/L)		Yes	
Other Chemistries			

Laboratory Parameter	Lab Results by Visit (Section 8.2.1)	Toxicity Grade (Section 8.2.2 and Section 8.2.3)	Reference Range Shifts (Section 8.2.4)
Albumin (g/L)	Yes	Yes	
Creatinine (umol/L)	Yes	Yes	
GFR from Creatinine Adjusted for BSA (mL/sec/1.73m2)	Yes		Yes
Glucose (mmol/L)	Yes		
Glucose - Hyperglycemia (mmol/L)		Yes	
Glucose - Hypoglycemia (mmol/L)		Yes	
Protein (g/L)	Yes		Yes
Urate (umol/L)	Yes	Yes	
Urea (mmol/L)	Yes		Yes
Urea Nitrogen/Creatinine	Yes		Yes
Urinalysis			
Erythrocytes		Yes	
Protein (Dipstick)		Yes	
Protein/Creatinine (mg/mg)		Yes	
Leukocytes			Yes
pH			Yes
Immunoglobulins			
Immunoglobulin G (g/L)		Yes	

Listings will be generated for all laboratory results for hematology [L3.12], liver function [L3.13], electrolytes [L3.14], other chemistries [L3.15], urinalysis [L3.16] and immunoglobulins [L3.17].

Listings will also be generated for all Grade 3 or Grade 4 laboratory toxicity results for hematology [L3.18], liver function [L3.19], electrolytes [L3.20], other chemistries [L3.21], urinalysis [L3.22] and immunoglobulins [L3.23]. If a subject has a lab parameter where a Grade 3 or 4 result is obtained at any visit, all of the data for that subject and that lab parameter will be presented at all visits.

8.2.1. Laboratory Assessments by Visit

Descriptive summary statistics for each laboratory parameter will be displayed for each visit, for hematology [T3.18], liver function [T3.19], electrolytes [T3.20] and other chemistries [T3.21]. No statistical tests will be performed.

A line graph will be produced for each lab parameter which displays the mean value (±SE) by visit for hematology [F3.01], liver function [F3.02], electrolytes [F3.03] and other chemistries [F3.04].

8.2.2. Worst Laboratory Toxicity Grade Post-baseline

The worst laboratory toxicity grade post-baseline (including unscheduled visits and follow up assessments) will be presented for each laboratory parameter within

hematology [T3.22], liver function [T3.23], electrolytes [T3.24], other chemistries [T3.25], urinalysis [T3.26] and immunoglobulins [T3.27].

8.2.3. Laboratory Toxicity ≥ 2 Grade Worsening Post-Baseline

Toxicity grade worsening of ≥ 2 grades from baseline will be summarized post-baseline (including unscheduled visits and follow up assessments) for each laboratory parameter with toxicity grades within hematology [T3.28], liver function [T3.29], electrolytes [T3.30], other chemistries [T3.31], urinalysis [T3.32] and immunoglobulins [T3.33]).

The tables 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.

8.2.4. Laboratory Reference Range Shifts from Baseline by Visit

For laboratory tests without toxicity grades, shifts relative to the normal range will be summarized for each lab parameter within hematology [T3.34], liver function [T3.35], electrolytes [T3.36], other chemistries [T3.37] and urinalysis [T3.38]. No statistical tests will be performed.

For the 'shift to low' category, the percentage of subjects with at least one low post-baseline value will be displayed using the categories: 'remained low' and 'shift normal/high to low'.

For the 'shift to normal/high' category, the percentage of subjects with at least one normal/high post-baseline value will be displayed using the categories: 'remained normal/high' and 'shift low to normal/high'.

8.2.5. Immunoglobulin Levels Below LLN by Visit

The number and percentage of subjects with immunoglobulin values (IgG, IgA, and IgM) below the LLN at each visit will be presented for all subjects [T3.39]. No statistical tests will be performed.

8.2.6. Liver Events

A listing will be produced for liver monitoring/stopping events reported [L3.25]. The alcohol intake at onset of the liver event will be presented [L3.26].

8.2.7. Immunogenicity

For the immunogenicity assessment for belimumab, two types of antibody assays will be performed, i.e. a binding assay and neutralizing assay. For the binding assay, there will be 3-testing steps. A screening assessment is performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay is then carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titer value will also be obtained to quantify the degree of binding in a titration assay step. Subjects will be viewed as positive for the binding assay

if the confirmation assay was positive. Subjects, who tested positive for the binding assay, will be tested for the neutralizing assay, which again produces a result of positive or negative.

For incidence of subjects with positive binding antibody during the study period, a table will be produced summarizing results for the binding antibody assay by visit. The table will include the number and proportion of subjects in each results category for each visit in the study period (including early withdrawal visit). Binding confirmatory assay results will be categorized as negative, persistent positive (defined as a positive immunogenic response for at least two consecutive assessments during the study period or a single result at the final assessment in the study period) or transient positive (defined as a single positive immunogenic response that does not occur at the final assessment in the study period).

Results will be summarized by visit and any time post baseline [T3.40].

A listing of immunogenicity results will be presented for any subject who had a positive result at any time [L3.24].

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs will be based on GSK Core Data Standards, unless otherwise specified.

8.3.1. Vital Signs

Summary statistics of observed vital signs will be presented by visit [T3.41]. Summary statistics of change from baseline in vital signs will also be presented by visit [T3.42].

A listing of vital signs will be presented by subject [L3.10].

8.3.2. Device Malfunction

A listing of device malfunction will be provided by subject and date of malfunction [L1.10].

8.3.3. Possible Suicidality-Related Adverse Event

A listing of possible suicidality-related adverse event data will be presented [L3.11].

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

The PK analyses will be based on the PK population. See ‘RAP mock outputs 200908’ document for mock displays.

PK outputs will report all On Study data (see Section 5.2). On-treatment PK data will be summarised using a treatment policy approach, including all data regardless of any Intercurrent Events (ICE). Week 8 Follow Up data will only be summarised if the subject has stopped their study treatment and hasn't taken any concomitant Belimumab during the follow-up period.

Descriptive statistics for observed belimumab concentrations will be displayed for each scheduled visit where pre-dosing PK samples are available for analysis. Each of the three cohorts will be summarized separately and overall [T5.01], and the following statistics will be displayed: number of subjects, mean value, standard deviation, 95% confidence interval, geometric mean, geometric standard deviation, geometric 95% confidence interval, geometric coefficient of variation (%), median, 25th and 75th percentiles, minimum, and maximum. No statistical tests will be performed.

The geometric mean, standard deviation and confidence interval are calculated at each visit using all of the non-zero PK concentration values. These non-zero concentration values are log transformed and the arithmetic mean, standard deviation and confidence interval are calculated. The geometric mean, geometric standard deviation and geometric confidence intervals are the exponentials of these values.

The geometric Coefficient of Variation is calculated as follows:

$$CV(\%) = \sqrt{exponential(logSD^2) - 1} * 100$$

where logSD is the standard deviation of the log-transformed concentrations.

A graph will be produced which displays the median pre-injection belimumab concentrations (+/- interquartile range) by visit through Week 52 for all subjects [F5.01], as well as by cohort [F5.02].

Additionally, a line graph will be produced which displays the geometric mean pre-injection belimumab concentrations (with 95% Confidence Interval) by visit through Week 52 for all subjects [F5.03], as well as by cohort [F5.04].

A listing of belimumab PK concentration-time data will be presented by subject [L5.01].

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of belimumab administered subcutaneously in pediatric participants with systemic lupus erythematosus.

A brief summary of the planned analysis is presented below. A complete analysis plan for the popPK analyses will be reported separately.

10.1. Statistical Analyses / Methods

All analyses will be carried out on the Modelling and Analysis Platform (MAP), a validated and version-controlled system. To support the analysis a PopPK dataset will be generated from the source data. Details of the dataset specification will be provided in the separate popPK reporting and analysis plan. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Belimumab SC concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model for SC dosing to pediatric patients with SLE.

The influence of subject level baseline characteristics on the pharmacokinetics of belimumab SC in this patient population will be investigated, including the allometric effects of body size.

Individual estimated PK parameters (clearance, volume of distribution at steady state and terminal phase half-life) and belimumab exposure parameters at steady state (minimum, average and maximum concentration and the area under the curve over a 7-day dosing period) will be summarized descriptively and compared with the corresponding PK parameters from the pediatric IV study [BEL114055].

The population PK model will be used to assess the dependence of belimumab exposure on body weight to inform SC dose selection in low body weight pediatrics, who may require less-frequent administration compared to the weekly SC dosing frequency approved for adults.

11. PHARMACODYNAMIC AND BIOMARKER ANALYSES

Autoantibodies, Serum Immunoglobulin Isotypes, Serum Complement, Peripheral Lymphocytes including B lymphocytes and Proteins will be collected according to the Schedule of Activities (Protocol Section 1.3).

All biomarker analyses will be performed on the ITT Population. See 'RAP mock outputs 200908' document for mock displays.

Biomarker outputs will report all On Study data (see Section 5.2). Biomarker data will be summarised using a treatment policy approach, including all data regardless of any Intercurrent Events (ICE).

The specific biomarkers analysed are listed in Table 6.

Table 6 Biomarkers for Analysis

		Parameter Code (LBTESTCD)
Serum Immunoglobulin Isotypes	Immunoglobulin A (g/L)	IGA
	Immunoglobulin G (g/L)	IGG
	Immunoglobulin M (g/L)	IGM
	Anti-dsDNA Antibody (IU/mL)	ADSDNAAB

Autoantibodies and C Reactive Protein	Antinuclear Antibodies (titer)	ANA
	C Reactive Protein (mg/L)	CRP
Serum Complement	Complement C3 (mg/dL)	C3
	Complement C4 (mg/dL)	C4
Peripheral Lymphocytes (B cells)	CD19+ Total B cells (cells/mL)	CD19
	B cells CD20+ (cells/mL)	CDX111
	Memory B cells CD20+ CD27+ (cells/mL)	CDX732
	Naive B cells CD20+ CD27- (cells/mL)	CDX731
	Plasmablasts CD27b CD38b (cells/mL)	CDX734

Note that, Plasmablasts CD27b CD38b was previously referred to as SLE subset plasmablasts.
Note that BLyS (free) Protein is only collected at Baseline and will be summarized in the study population outputs.

A listing of all biomarker results including both autoantibodies (ANA, Anti-dsDNA, CRP, BLyS (free) protein) and serum complement (C3, C4) will be presented [L4.01]. Additionally, a listing of B cell results will be presented [L4.02].

11.1. Secondary Endpoint - Pharmacodynamic and Biomarker Analyses

11.1.1. Endpoint / Variables

The change from baseline and percentage change from baseline will be evaluated by visit for each of the biomarkers listed in Table 6.

11.1.2. Population of Interest

The biomarker analyses will be based on the ITT population.

11.1.3. Strategy for Intercurrent (Post-Randomization) Events

The analyses will be performed on the observed data. No imputation will be carried out for missing data.

11.1.4. Change from Baseline

Change from baseline will be summarized by visit for the following:

- Immunoglobulin levels for all subjects [T4.02]
- B-cells for all subjects [T4.11]
- Autoantibody levels among subjects who were positive at baseline (ANA Index ≥80 titer; anti-dsDNA ≥ 30 IU/mL; CRP ≥ 4 mg/L) [T4.05]. Note that positive baseline assessments are assessed at a parameter level, e.g. the anti-dsDNA summary will include all subjects who were positive at baseline for anti-dsDNA.
- Complement levels among subjects with low values at baseline (C3<90 mg/dL; C4 < 13 mg/dL) [T4.08]. Note that low baseline assessments are assessed at a

parameter level, e.g. the C3 summary will include all subjects who were low at baseline for C3.

No statistical tests will be performed.

A figure of median change from baseline (+/- Interquartile Range) will be produced by visit for complement levels for subjects with low complement at baseline [F4.04].

11.1.5. Percentage Change from Baseline

Percentage change from baseline will be summarized by visit for the following:

- Immunoglobulin levels for all subjects [T4.01]
- B-cells for all subjects [T4.10]
- Autoantibody levels among subjects who were positive at baseline (ANA Index ≥80 titer; anti-dsDNA ≥ 30 IU/mL; CRP ≥ 4 mg/L) [T4.04]. Note that positive baseline assessments are assessed at a parameter level, e.g. the anti-dsDNA summary will include all subjects who were positive at baseline for anti-dsDNA.
- Complement levels among subjects with low values at baseline (C3<90 mg/dL; C4 < 13 mg/dL) [T4.07] . Note that low baseline assessments are assessed at a parameter level, e.g. the C3 summary will include all subjects who were low at baseline for C3.

The B cell subsets that will be summarized are CD19+ Total B cells, B cells CD20+, Memory CD20+ CD27+ , Naïve CD20+ CD27– and Plasmablasts CD27b CD38b.

No statistical tests will be performed.

Figures of median percentage change from baseline (+/- Interquartile Range) will be produced by visit for:

- Immunoglobulin levels for all subjects [F4.01]
- B-cells for all subjects [F4.05]
- Autoantibody levels among subjects who were positive at baseline (as described above) [F4.02].
- Complement levels among subjects with low values at baseline (as described above) [F4.03].

11.2. Other Pharmacodynamic and Biomarker Analyses

Shift tables will be used to summarize the shifts from baseline in immunoglobulins [T4.03], autoantibodies [T4.06] and complement [T4.09] by visit.

11.2.1. Endpoint / Variables

Changes in biomarker category (Positive vs Negative; Low vs Normal/High) will be the endpoint.

11.2.2. Population of Interest

The biomarker analyses will be based on the ITT population.

11.2.3. Strategy for Intercurrent (Post-Randomization) Events

The analyses will be performed on the observed data. No imputation will be carried out for missing data.

11.2.4. Statistical Analysis

For Immunoglobulins (IgG, IgA, and IgM), baseline data will be summarized as the number and percentage of subjects who were low (<LLN) or normal/high (>=LLN). For post-baseline visits, the data will be summarized by the baseline status. Among subjects who were low at baseline, the shifts presented will be 'low to normal/high' or 'no change'. Among subjects who were normal/high at baseline, the shifts presented will be 'normal/high to low' or 'no change'.

For ANA titer, anti-dsDNA and C-Reactive Protein (CRP), baseline data will be summarized as the number and percentage of subjects who were positive (ANA Index ≥80 titer; Anti-dsDNA >=30 IU/mL; CRP >=4 mg/L) or negative (ANA Index <80 titer; Anti-dsDNA <30 IU/mL; CRP <4 mg/L) at baseline. Among subjects who were positive at baseline, the shifts presented will be 'positive to negative' or 'no change'. Among subjects who were negative at baseline, the shifts presented will be 'negative to positive' or 'no change'.

For serum complement C3 and C4, baseline data will be summarized as the number and percentage of subjects who were low (C3 <90 mg/dL; C4 <13 mg/dL) or normal/high (C3 ≥90 mg/dL; C4 ≥13 mg/dL) at baseline. Among subjects who were low at baseline, the shifts presented will be 'low to normal/high' or 'no change'. Among subjects who were normal/high at baseline, the shifts presented will be 'normal/high to low' or 'no change'. Note that the baseline categories presented above are for paediatric subjects. If a subject turns 18 during the study, any visits following their 18th birthday will be flagged using adult Normal Ranges. No statistical tests will be performed.

12. REFERENCES

GlaxoSmithKline Document Number 2017N343626_00 Clinical Study Report (CSR) for BEL114055, A Multi-center, Randomized Parallel Group, Placebo-Controlled Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE) – Double-Blind Endpoint Analysis (Part A). 2018.

GlaxoSmithKline Document Number TMF-15202454 Protocol for Study 200908, A Multi-center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE). 2022.

Reporting and Analysis Plan for GSK1550188 Study BEL114055, A Multi-center, Randomized Parallel Group, Placebo-Controlled Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE) – Double-Blind Endpoint Analysis (Part A). 2018.

U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

13. APPENDICES

13.1. Appendix 1: Assessment Windows

13.1.1. Definitions of Assessment Windows for Analyses

The data is analysed as per the planned visit assignment.

Exit/withdrawal and unscheduled visits will be slotted to the appropriate planned visit. The assigned visit is based on the interval in which the Study Day for the exit/withdrawal or unscheduled visit falls according to intervals (inclusive) provided below. For completeness, the table also includes visits which are not slotted; these visits will have 'N/A' for 'not available' listed for the Interval Start and End Day.

Analysis Set / Domain	Parameter (if applicable)	Target[1]	Analysis Window		Analysis Timepoint Number	Analysis Timepoint
			Beginning Timepoint	Ending Timepoint		
All	NA	Day -35	N/A	N/A	10	Screening
Cohort 1 and Cohort 3						
All	All	Day 1	N/A	N/A	20	Week 0 (Day 1)
		Day 8	2	11	30	Week 1 (Day 8/11)
		Day 15	12	21	40	Week 2 (Day 15/21)
		Day 29	22	42	50	Week 4 (Day 29/31)
		Day 57	43	70	60	Week 8 (Day 57/61)
		Day 85	71	98	70	Week 12 (Day 85/81)
		Day 113	99	126	80	Week 16
		Day 141	127	154	90	Week 20
		Day 169	155	189	100	Week 24
		Day 211	190	231	110	Week 30
		Day 253	232	280	120	Week 36
		Day 309	281	336	130	Week 44
		Day 365	337	378	140	Week 52
		Day 421	N/A	N/A	175	8 Week Follow-up[2]
		Day 477	N/A	N/A	185	16 Week Follow-up[3]
Cohort 2						
All	All	Day 1	N/A	N/A	20	Week 0 (Day 1)
		Day 11	2	15	30	Week 1 (Day 8/11)
		Day 21	16	25	40	Week 2 (Day 15/21)
		Day 31	26	45	50	Week 4 (Day 29/31)
		Day 61	46	70	60	Week 8 (Day 57/61)
		Day 81	71	96	70	Week 12 (Day 85/81)
		Day 113	97	126	80	Week 16
		Day 141	127	154	90	Week 20
		Day 169	155	189	100	Week 24

Analysis Set / Domain	Parameter (if applicable)	Target[1]	Analysis Window		Analysis Timepoint Number	Analysis Timepoint
			Beginning Timepoint	Ending Timepoint		
		Day 211	190	231	110	Week 30
		Day 253	232	280	120	Week 36
		Day 309	281	336	130	Week 44
		Day 365	337	378	140	Week 52
		Day 421	N/A	N/A	175	8 Week Follow-up[2]
		Day 477	N/A	N/A	185	16 Week Follow-up[3]

Note:
[1] Study Day with Baseline/Treatment Start Date as Day 1.
[2] The 8-week follow-up occurs 8 weeks after Week 52, or 8 weeks after early withdrawal or 8 weeks after last dose for subjects who withdraw from Part A and do not enter Part B.
[3] The 16-week follow-up occurs 16 weeks after Week 52, or 16 weeks after early withdrawal or 16 weeks after last dose for subjects who withdraw from Part A and do not enter Part B.

13.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

13.2.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before the first exposure date to study drug
Concomitant	Any medication that is not a prior. Note that medications with partial or missing start and/or stop dates will be assumed to be concomitant unless there is evidence through comparison of partial dates to suggest otherwise.

13.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE onset date is on or after treatment start date, having been absent pre-treatment, or the AE worsens relative to the pre-treatment state.

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.
- Worsening of an event is captured in the eCRF by modifying the severity of the original event; therefore, worsening is accounted for in how the AE is recorded and no programming is required to identify worsening events.

13.3. Appendix 3: Data Display Standards & Handling Conventions

13.3.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used (version 9.4 or higher).	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: gsk1550188
Study location	: gsk1550188\mid200908
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1).	
Generation of RTF Files	
• RTF files will be generated for all tables.	

13.3.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.4. Appendix 4: Derived and Transformed Data

13.4.1. General

Multiple Measurements at One Analysis Time Point
• For continuous data, if there are two values within a time window (as per Section 13.1.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. All data will be presented in the listings. • For categorical data, if there are two values within a time window (as per Section 13.1.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the value prior to the target day will be taken. All data will be presented in the listings. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Study Day = Ref Date – First Dose Date + 1

Study Completion
• A participant is considered to have completed the primary study if he/she has completed all phases during Parts A and B of the study, including the Week 52 Visit, as defined in the Schedule of Activities (SoA) Section 1.3 of the protocol. • A participant is considered to have completed Part A of the study if he/she has completed all 12 weeks of the treatment phase, including the Week 12 Visit, as defined in the SoA (see Section 1.3 of the protocol). • Participants who withdraw from study treatment prior to the end of Part A and participants who complete Part A but do not wish to continue into Part B are required to complete 8 and 16 week follow-up visits. • Participants who withdraw from treatment prior to Week 12, should complete an early withdrawal (EW) visit, in addition to the 8 and 16 week follow-up visit and assessments. The EW visit requires identical assessments and procedures to the Week 12 (Day 85/81) visit. • Participants who withdraw from treatment prior to Week 52, should complete an EW visit, in addition to the 8 and 16 week follow-up visit and assessments. The EW visit requires identical assessments and procedures to the Week 52 visit.

13.4.2. Study Population

Age Derivation
If the day of date of birth is unavailable, age on any specified day (e.g. screening, 1st dose etc.) will be derived as: If the specified day is on or after the 15th of the birth month then: • Year of specific timepoint – DOB year If the specified day is before the 15th of the birth month then: • (Year of specific timepoint – DOB year) - 1 Age at screening will be defined as the screening date, and derived as above.

Age Derivation
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + X, where X is 7, 10, or 14 for the three weight cohorts respectively.** • Only complete dates will be used when calculating duration of exposure. First and last injection dates will be used, regardless of any missing doses. • Participants who were enrolled but did not report a treatment start date will be categorised as having zero days of exposure.

13.4.3. SELENA SLEDAI

SELENA SLEDAI assessment

The SELENA SLEDAI assessment consists of 24 individual weighted items in which signs and symptoms, laboratory tests, and physician's assessment for each of 8 organ systems are given a weighted score and summed if present (marked 'Yes') at the time of the visit or in the preceding 10 days.

The SELENA SLEDAI total score is calculated by adding the weighted scores together for all items that are present. If any item is missing, the SELENA SLEDAI total score will be missing.

The maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No').

Organ System	Descriptor	Weight
CNS	Seizure	8
	Psychosis	8
	Organic Brain Syndrome	8
	Visual Disturbance	8
	Cranial Nerve Disorder	8
	Lupus Headache	8
	CVA[1]	8
Vascular	Vasculitis	8
Musculoskeletal	Arthritis	4
	Myositis	4
Renal	Urinary Casts	4
	Hematuria	4
	Proteinuria	4
	Pyuria	4
Mucocutaneous	Rash	2
	Alopecia	2
	Mucosal Ulcers	2

SELENA SLEDAI assessment		
Cardiovascular and Respiratory	Pleurisy Pericarditis	2 2
Immunologic	Low Complement Increased DNA Binding	2 2
Constitutional	Fever[1]	1
Hematologic	Thrombocytopenia Leukopenia	1 1

[1] In the analysis of SELENA SLEDAI by organ systems and items (baseline, improvements, and worsening), CVA will be moved from the CNS to the Vascular organ system and the Constitutional organ system will be eliminated and its one component, fever, will be moved to the hematologic organ system.

13.4.4. Prednisone Equivalent Conversion

- A concomitant medication is identified as a steroid if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02.' Mineralocorticords are included in the group of ATC codes beginning with 'H02' but do not have sufficient anti-inflammatory properties to be considered as a prednisone equivalent. For this reason, the conversion factor has been set to 0.
- The following routes are considered to provide systemic exposure: oral, buccal, parenteral, subcutaneous, intramuscular, intradermal, and intravenous. Although not systemic, intra-articular steroids are also identified for treatment failure rules. Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).
- At database lock, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor exists 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 below.
- In order to be converted, the frequency and dose of the steroid must be present with the unit dose in milligrams (mg) or grams (g). Doses recorded in grams will be converted to milligrams by multiplying the dose in grams by 1000 prior to applying the conversion factor.
- 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).

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

Prednisone Conversion Factors (mg)	
Preferred term	**Conversion factor for converting to a prednisone-equivalent dose**
BETAMETHASONE	8.3333`
BETAMETHASONE DIPROPIONATE	8.3333`
BETAMETHASONE SODIUM PHOSPHATE	8.3333`
BETROSPAM	8.3333`
BUDESONIDE	0.3333`
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.3333`
DEFLAZACORT	0.8333`
DEXAMETHASONE	6.6666`
DEXAMETHASONE ACETATE	6.6666`
DEXAMETHASONE SODIUM PHOSPHATE	6.6666`
FLUDROCORTISONE	0
FLUOCORTOLONE	3
HYDROCORTISONE	0.25
HYDROCORTISONE ACETATE	0.25
HYDROCORTISONE SODIUM SUCCINATE	0.25
MEPREDNISONE	1.25
METHYLPREDNISOLONE	1.25
METHYLPREDNISOLONE ACETATE	1.25
METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
PARAMETHASONE	2.5
PREDNISOLONE	1
PREDNISOLONE ACETATE	1
PREDNISOLONE SODIUM PHOSPHATE	1
PREDNISOLONE SODIUM SUCCINATE	1
PREDNISONE	1
PREDNISONE ACETATE	1
TRIAMCINOLONE	1.25
TRIAMCINOLONE ACETATE	1.25
TRIAMCINOLONE ACETONIDE	1.25

Combination Products: Prednisone Conversion Factors (mg)		
Preferred term	**Ingredients**	**Conversion factor for converting to a prednisone-equivalent dose**
CELESTONA BIFAS	Betamethasone acetate + Betamethasone sodium phosphate	8.3333`
DEPO-MEDROL MED LIDOKAIN	Methylprednisolone + Lidocaine	1.25

CELESTAMINE	Betamethasone + Dexchlorpheniramine maleate	8.3333`
SYNBETAMINE	Betamethasone + Dexchlorpheniramine maleate	8.3333`

13.4.5. SLE Allowable and Prohibited 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', 'INTRA-ARTICULAR', 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", "BUCCAL", "PARENTERAL", "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) or "MERCAPTOPURINE" (oral route) AND route of administration is not "TOPICAL" or "OPHTHAMLIC" AND not classified above as "ANTIMALARIALS".
NSAIDs	Set to NSAIDs if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'M01A'. Glucosamine and Chondroitin are not considered NSAIDs
Aspirin	Set to "ASPIRIN" if CMDECOD contains "ACETYLSALICYLIC ACID" or "ACETYLSALICYLATE LYSINE".
Prohibited	Set to "PROHIBITED" if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04AB' or 'V98' or if any of the following conditions are met, if CMDECOD equals "INVESTIGATIONAL DRUG", "ADALIMUMAB", "ETANERCEPT", "INFLIXIMAB", "CERTILIZUMAB", "TOCILIZUMAB", "GOLIMUMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "CANAKINUMAB", "USTEKINUMAB", "BRODALUMAB", "SECUKINUMAB", "IXEKIZUMAB", "EPRATUZUMAB", "TABALUMAB", "ATACICEPT", "IMMUNOGLOBULIN" (IV route), "CYCLOPHOSPHAMIDE" (IV route) or "LEUKAPHERSIS". No programmatic checks are carried out for live vaccines, as this is carried out instream.

13.4.6. Coronavirus Disease 2019 (COVID-19) Environment Onset Date

A COVID-19 environment onset date has been defined by GlaxoSmithKline for each Country as:

Country	COVID-19 Environment Onset Date
Argentina	10/FEB/2020
Germany	10/FEB/2020
Japan	28/FEB/2020
Mexico	10/FEB/2020
Netherlands	10/FEB/2020
Spain	10/FEB/2020
United States	10/FEB/2020

This represents the best estimate of the outbreak of COVID-19 within each Country at this time.

13.5. Appendix 5: Reporting Standards for Missing Data

13.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject primary study completion (i.e. as specified in the protocol) was defined as completing Parts A and B of the study, up to and including the Week 52 visit. Additionally, subjects who elect not to join the optional Part B will be considered to have completed Part A if all visits up to Week 12 (Day 81/85) are completed. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Section 13.1: Assessment Windows or will be summarized as withdrawal visits.

13.5.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries will be documented along with the reason for exclusion in the clinical study report.

13.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow for the possibility of partial dates.
Concomitant Medications/ Medical History	• Missing concomitant medication start date (CMSTDT) is imputed as treatment start date (TRTSDT) unless: ○ concomitant medication end date (CMENDT) is prior to treatment start date (TRTSDT), whether CMENDT is complete (DD/MM/YY) or partial (some combination of CMENDT day, month or year imputed) OR ○ The month or month and year of the partial CMSTDT are different from the month and/or year of TRTSDT OR ○ "Taken prior to study?" is checked. If any of the above conditions are met then CMSTDT is imputed with Jan for missing month and 01 for missing day, whatever is applicable. The recorded partial date will be displayed in listings. • Completely missing end dates for concomitant medications (CMENDT) will not be imputed, and the medication will be considered ongoing. If month and year are

Element	Reporting Detail
	present, then set to the earlier of (last contact date and last day of that month). If only year present, then set to the earlier of (31DEC of the year and last contact date).

13.6. Appendix 6: Abbreviations & Trade Marks

13.6.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amininotransferase
ANA	Anti-nuclear Antibody
Anti-dsDNA	Anti-double-stranded DNA
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLyS	B Lymphocyte Stimulator
BMI	Body Mass Index
C3/C4	Complement Factor C3 and C4
Cavg	Average Concentration
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum Concentration
Cmin	Minimum Concentration
CMQ	Customized MedDRA Query
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CPMS	Clinical Pharmacology Modelling & Simulation
CRP	C-reactive Protein
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DP	Decimal Places
dsDNA	Double Stranded Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EW	Early Withdrawal
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HZ	Herpes Zoster
ICE	Intercurrent Events
ICF	Informed Consent Form
IDSL	Integrated Data Standards Library
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMMS	International Modules Management System

Abbreviation	Description
ITT	Intent-To-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LLN	Lower Limit of Normal
LOQ	Limit of Quantitation
MAP	Modelling and Analysis Platform
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non-melanoma skin cancer
NSAID	Nonsteroidal Anti-Inflammatory Drug
OI	Opportunistic Infections
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PISR	Post-injection systemic reactions
PK	Pharmacokinetic
PopPK	Population PK
PRT	Pharmacokinetics Review Team
PSAP	Program Safety Analysis Plan
PT	Preferred Term
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneously
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SELENA	Safety of Estrogen in Lupus National Assessment
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SoA	Schedule of Activities
SOC	System Organ Class
SRT	Safety Review Team
TB	Tuberculosis
TFL	Tables, Figures & Listings
ULN	Upper Limit of Normal

13.6.2. Trademarks

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13.7. Appendix 7: List of Data Displays

13.7.1. Data Display Numbering

RAP generated displays follow the Format AX.YY, where:

A refers to the type of output i.e.

- T = Table
- L = Listing
- F = Figure

X refers to the section i.e.

- 1 = Study population
- 2 = Efficacy
- 3 = Safety
- 4 = Biomarkers
- 5 = Pharmacokinetic

YY is an incremental count with a new number for every output.

13.7.2. Mock Example Shell Referencing

Example displays are provided in the document 'TFL Mock Outputs MID200908'.

13.7.3. Deliverables

Delivery	Description
Primary SAC	Primary Statistical Analysis Complete

14. ATTACHMENTS

14.1. Attachment 1: AESI Preferred Term Definitions

The AESI definitions under the current version of MedDRA at the time of reporting will be found via the following IMMS pathname:

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/