Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for BEL116027 A Phase IV, Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment with Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects
Compound Number	:	GSK1550188
Effective Date	:	30-JAN-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BEL116027.
- This RAP is intended to describe the final analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete deliverable.

RAP Author(s):

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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 for Protocol 116027:

Revision Chronology:		
2012N154810_00	22-Aug-2013	Original
2012N154810_01	04-Oct-2013	Amendment 01
2012N154810_02	14-Jan-2014	Amendment 02
2012N154810_03	01-Apr-2014	Amendment 03
2012N154810_04	31-Aug-2015	Amendment 04
2012N154810_05	03-Dec-2015	Amendment 05
2012N154810_06	12-Sep-2017	Amendment 06

2. KEY PROTOCOL INFORMATION

A total of approximately 71 subjects (10 in the treatment holiday group, 26 in the treatment control group, and 35 in the long-term discontinuation group) will be enrolled in this study. The total sample size is based on practical considerations on the availability of subjects from other ongoing belimumab studies, rather than on statistical considerations. Since this is a non-randomized study, results will be descriptive only, and not intended to be inferential. No power calculations were made in the determination of sample size for this study. However, the total of subjects is expected to provide adequate information to characterize time to SLE flare.

Table 1 Flare Rates from Pooled BLISS Studies

ISE Table	Analysis	Placebo	1 mg/kg	10 mg/kg
T57	Percentage of Subjects with Flare Over 52 Weeks	81.5%	74.6%	74.6%
TAC411	Percentage of Subjects with Flare Over 52 Weeks Post Week 24	68.5%	54.7%	57.5%
TAC613	Percentage of Subjects with Flare Over 52 Weeks Among SRI Wk 52 Responders	73.4%	69.8%	67.4%

2.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 2 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Partial prothrombin time (PTT) is collected	• Activated partial prothrombin time (aPTT) time is analyzed	• aPTT was collected instead of PTT
• Section 8.1.3 states that for the primary analysis of the additional efficacy and biomarkers, the baseline will be defined as study Day 0 of the original parent study. Additionally, for some of the endpoints, a secondary analysis will be performed by defining the baseline as Day 0 of the BEL116027 study.	• The baseline for each endpoint is defined per Section 6.1 of the protocol. .	• The protocol was inconsistent in the definition of baseline. See RAP Section 5.3 for clarification
• Immunogenicity is listed as a secondary endpoint in Protocol Section 6.1.2., but as an exploratory laboratory parameter in the Time and Events table.	• Immunogenicity is defined as a secondary endpoint.	• The protocol was inconsistent, so the correct category was used in the RAP.
• Renal flares are not listed as an endpoint in Protocol Section 6.1.2 nor described in Protocol Section 8, but are defined in Protocol Section 6.1.4	• Renal flares are included as an exploratory endpoint in RAP Section 2.2.	• The protocol was inconsistent, so the endpoint was correctly specified in the RAP.
• The definition of renal flare contained a typographical error and referenced an increase rather than a decrease in GFR. This was corrected in a note to file.	• The RAP specifies the correct definition, referencing a decrease in GFR.	• The protocol was incorrect.
• Protocol Section 6.1.3 lists percent change in PGA.	• The RAP specifies change from baseline in PGA instead.	• Change from baseline is more clinically relevant and interpretable, particularly in the case of low baseline scores.
• Protocol Section 6.1.2 lists one time interval for percent change in B-cell subsets from Week 24, i.e., Week 24 to 52.	• In addition to this, the RAP specifies percent change from Week 24 to 32 and Week 24 to 40.	• The additional time intervals facilitate interpretation of the changes following the treatment holiday phase.
• The protocol Section 6.1.2 does not list the CD19+ B-cell subset.	• The RAP adds the CD19+ B-cell subset.	• This subset is collected and clinically important.
• The protocol Section 6.1.3 Other Endpoints includes percent change in prednisone dose and percent of subjects with prednisone dose reduced to <7.5mg/day from ≥7.5mg/day..	• These two exploratory endpoints were not analysed	• The two secondary prednisone endpoints (Protocol Section 6.1.2) will be analysed as they are most descriptive in that they assess daily prednisone use. Given the reduced sample size from

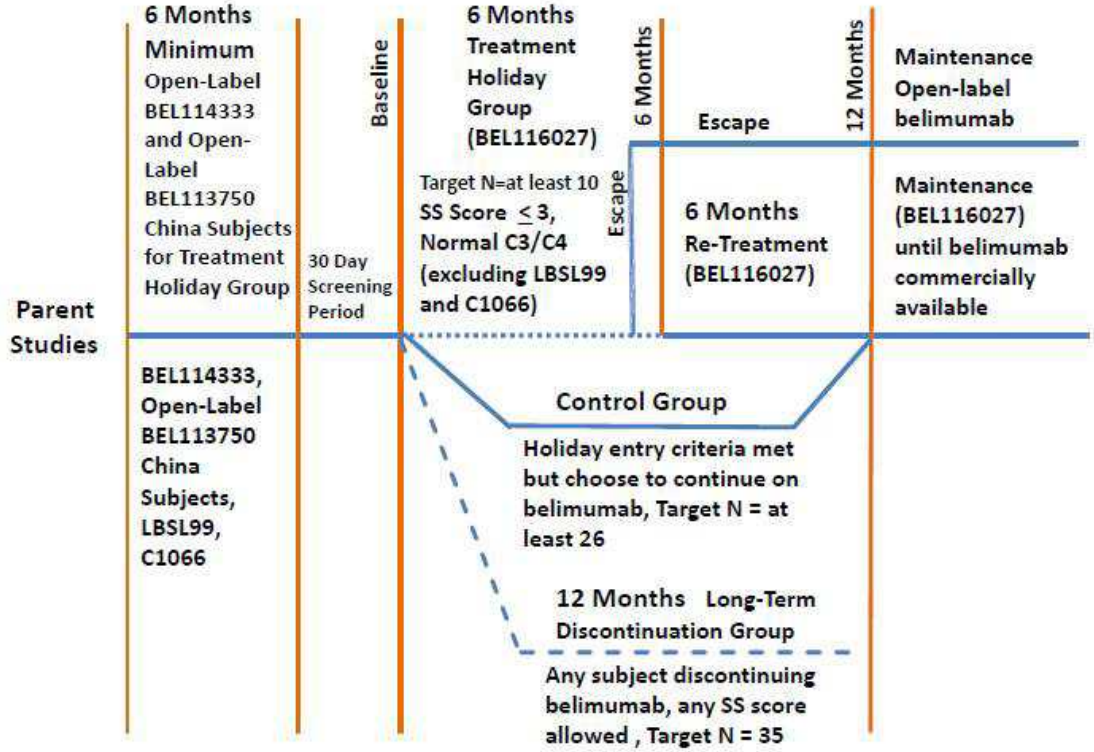
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
		the original protocol, these two endpoints allow sufficient evaluation of the impact of the treatment holiday.
• Section 6.1.2 lists percent change from baseline in B-Cells, immunoglobulins and auto-antibodies	• Change from baseline will also be presented for these parameters.	• Change from baseline added based on regulatory feedback on other studies in the belimumab development program.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Characterize the efficacy of a 24-week withdrawal followed by a 28-week reintroduction of intravenous belimumab therapy compared with uninterrupted intravenous belimumab therapy for 52 weeks in subjects with low SLE disease activity receiving belimumab 10 mg/kg plus standard of care, as measured by time to first flare.	• Time to any SLE Flare Index flare.
Secondary Objectives	**Secondary Endpoints**
• Evaluate the rate of any flare.	• Rate of any SLE Flare Index flare per subject year. • Time to first SLE Flare Index severe flare.
• Assess safety.	• Adverse events • AESI • Laboratory parameters • Vital signs
• Assess SLE disease activity.	• Number of subjects in the treatment holiday and long-term discontinuation group with evidence of rebound (defined as a SELENA SLEDAI score during the first 24 weeks that exceeds the baseline SELENA SLEDAI score in the subjects' respective original parent study). • SELENA SLEDAI scores change from baseline.
• Assess immunogenicity.	• Response (Negative, Transient Positive, Persistent Positive) by Visit and Across All Visits
• Assess markers of autoimmune response (e.g., immunoglobulins, complement.)	• Change and Percent change from baseline in IgG, IgM, IgA, anti-dsDNA, ANA, C3, and C4. • Shifts from baseline in IgG, IgM, IgA, anti-dsDNA, ANA, C3 and C4. • Change and Percent change in absolute B cell subsets

Objectives	Endpoints
	(CD19+, CD20+, CD20+/27+ memory, CD20+/27– naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells) at Weeks 0, 8, 16, 24, 32, 40 and 52 and from Weeks 24 to 52.
• Assess changes in corticosteroid use.	• Number of days of daily prednisone dose ≥7.5 mg/day and/or increased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52. • Number of days of daily prednisone dose ≤7.5 mg/day and/or decreased by 25% from Day 0 of this study to Week 24, from Day 0 of this study to Week 52, and from Week 24 to Week 52.
Exploratory/Other	Exploratory/Other Endpoints
	• Time to first renal flare • Time to first renal flare among subjects with baseline proteinuria >0.5g/24hr equivalent • Change from Baseline in PGA • Change and percentage change from Baseline in BLyS Protein • SLICC/SDI • Change from Baseline

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• A phase IIIB, multi-center open-label, non-randomized study.
Dosing	• **Treatment Holiday (TH) group**: Temporary discontinuation (24 weeks) and re-introduction of belimumab 10 mg/kg therapy. The target enrolment for this group is 10 subjects. • **Treatment Control (TC) group:** Continued treatment with belimumab 10 mg/kg. The target enrolment for this group is 26 subjects. • **Long-term Discontinuation (LTD) group**: Discontinued therapy with belimumab 10 mg/kg and are expected to remain off belimumab therapy for at least 12 months but remain on standard of care therapy. The target enrolment for this group is 35 subjects.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Non-randomized, open label
Interim Analysis	• The protocol indicated that an interim analysis of the data in this trial may be performed to support a submission to regulatory authorities relating to marketing authorization (e.g., to summarize and submit

Overview of Study Design and Key Features	
	this long-term safety data to regulatory authorities in the initial BLA and other marketing authorization submissions). Additional interim analyses may be required to support subsequent safety updates to regulatory authorities. No interim analyses were conducted.
Sample Size	• The total target sample size was 71 subjects and 80 were enrolled. The target sample size for subjects in the treatment holiday and control groups was 10 (12 enrolled) and 26 (29 enrolled) subjects respectively. A target sample size of 35 (39 enrolled) subjects in the long-term discontinuation group was anticipated. .

Note: Subjects from China participated in BEL113750 OL phase rather than in BEL114333,and were therefore eligible to enter BEL116027 from BEL113750 OL, per a China country-specific protocol amendment 01.

2.4. Statistical Hypotheses / Statistical Analyses

Since this is a non-randomized study, results will be descriptive only, and any comparisons are not intended to be inferential.

3. PLANNED ANALYSES

3.1. Interim Analyses

The protocol indicated that an interim analysis of the data in this trial may be performed to support a submission to regulatory authorities relating to marketing authorization (e.g., to summarize and submit this long-term safety data to regulatory authorities in the initial BLA and other marketing authorization submissions). Additional interim analyses may be required to support subsequent safety updates to regulatory authorities. No interim analyses were conducted.

The SRT performs in stream adjudication of subject-level safety data for Adverse Events of Special Interest (AESIs; serious and non-serious) in accordance with the GSK Standard Operating Procedures (SOPs) and the belimumab Program Safety Analysis Plan (PSAP). AESIs include malignancy; serious hypersensitivity and post-infusion systemic reactions; potential opportunistic infections; other infections of interest but not generally considered opportunistic i.e. Mycobacterium Tuberculosis and Herpes Zoster; suicide/self-injury; and fatalities.

AESIs are flagged in the clinical trial database, according to SRT adjudication. The SRT performs a periodic review of instream study data (at least every 6 months), reviewing the cumulative incidence of AEs, SAEs, and adjudicated AESIs. These periodic reviews of cumulative adverse event incidence are compared with previous SRT reviews and where appropriate, the pivotal SLE pooled data to assess for any new safety signals.

3.2. Final Analyses

The final planned primary analyses will be performed after the database cleaning activities have been completed and final database release and database freeze has been declared by Data Management:

database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

In this open-label, non-randomized study, for dispensing of study drug, randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprises all subjects who enroll in the study, including screen failures	• Study population
Intent-To-Treat	• Comprises all subjects who enroll in the study, excluding screen failures.	• Study population • Efficacy • Safety • Biomarker
PK	• Comprises all subjects included in the ITT population for whom at least one post belimumab treatment PK sample was obtained and analyzed.	• PK

1. **NOTES:**

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be identified in the Protocol Deviation Management Plan (PDMP).

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

- 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.

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.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Group Code	Group Description	Description	Order [1]
3	Long Term Discontinuation Group	Long-term Discontinuation	1
2	Control Group	Treatment Control	2
1	Treatment Holiday Group	Treatment Holiday	3

NOTES:

1. Order represents treatments being presented in TFL, as appropriate. Some Tables will only present TC and TH groups.
2. In applicable data listings, Screen Failures will be presented first followed by LTD, TC and TH.

5.2. Parent Studies

Subjects were eligible to enter BEL116027 from one of four continuation studies, having entered the continuation study from a respective parent study. The possible study participation sequences are as follows:

Parent Study	Continuation Study	Subjects
BEL113750 DB[1]	BEL113750 OL[1]	Subjects from China
BEL112341[2]	BEL114333	Some subjects from Japan
BEL113750	BEL114333	Subjects from Korea and some subjects from Japan
BEL110751	BEL112233 (C1066)	Subjects from US
LBSL02	LBSL99 (BEL112626)	Subjects from US

1. BEL113750 was both the parent and continuation study number for subjects enrolled in China.
2. Subjects from Japan who participated in study BEL112341 were eligible to enrol into the BEL114333 continuation phase per a BEL114333 protocol amendment, to allow them continued access to study agent until belimumab was commercially available in Japan.

5.3. Baseline Definitions

5.3.1. Baseline Definitions[1]

The baseline (BL) definition is dependent upon the endpoint being analyzed.

- For the SELENA SLEDAI (including rebound), immunoglobulins, auto-antibodies, complement, BLyS and B-cell endpoints, baseline is defined as the Day 0 assessment in the subject's respective parent study, prior to exposure with study treatment (whether placebo or belimumab). Baseline data for these

parameters will be extracted from the ADaM data sets from the double blind study (LBSL02, BEL110751, BEL113750 or BEL112341)from which the patients are enrolled.

- For the SLE flares, SLE severe flares, SLICC, prednisone (7 day average prior to Day 0), PGA, and immunogenicity[2], endpoints, baseline is the Day 0 assessment in BEL116027.
- For other endpoints, baseline is the Day 0 assessment in BEL116027[2].

[1]Feeder study BEL114333 database had not yet completed at the time of BEL116027 Last Patient Last Visit. Consequently, baseline data for BEL114333 patients has not been fully cleaned when extracted from that study's database for reporting.

[2]Assessments covered for both Day 0 in BEL116027 and the Exit/Follow-up visit of the feeder continuation studies were only to be performed once and were to be recorded in the appropriate case report forms for each study. For Day 0 values not recorded in BEL116027 CRF but exist in the feeder study, the data will be extracted from the appropriate feeder study for inclusion in analysis

In the displays, the baseline value/visit will be denoted as Baseline.

See Section 13.4.1 for a diagram depicting the baseline definitions and phases.

5.3.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.3.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.4. Multicentre Studies

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

Since this is a non-randomized study, results will be descriptive only, and there will be no methods applied to address multiple centers.

5.5. 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: Protocol Deviation Management and Definitions for Per Protocol Population
13.2	Appendix 2: Schedule of Activities
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance
13.9	Appendix 9: Adverse Events of Special Interest
13.11	Appendix 10: Abbreviations & Trade Marks
13.12	Appendix 11: List of Data Displays
13.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Demography, Baseline Characteristics and Medical History Analyses

The study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, medical conditions, prior and concomitant medications, and exposure and treatment compliance will be based on the ITT population, or for the Screened population where specified. Data will be presented by treatment group and for all subjects combined, unless otherwise specified.

Full details of data displays being presented in Appendix 11: List of Data Displays.

Completion and withdrawal status by treatment phase is defined in Section 13.6.2.

6.2. Baseline Disease Activity and Other Baseline Endpoints

A summary of baseline disease activity will be provided, including counts and percentages for categorical endpoints and descriptive statistics for the continuous endpoints and scores.

Table 3 provides indicators of baseline disease activity that will be summarized. Some of these parameters will be summarized on the by visit summary for that parameter according to the table specifications.

Table 3 Baseline Disease Activity Endpoints

Endpoint	Categories & Summaries at Baseline
SELENA-SLEDAI category	Continuous Categorical • 0, 1, 2, 3
SELENA SLEDAI by organ domain and item at baseline	Categorical • Presented if Yes
Complement & BLyS Levels	**Complement C3 and C4 (mg/dL)** Continuous Categorical • Positive, Negative • Low, Normal, High (See Section 13.6.6 for definitions) **BLyS Protein [ng/mL]** Continuous Categorical • Below LLOQ: <0.061 ng/mL for China samples and <0.02048 ng/mL for all others
SLE Flare Index	Categorical • At least 1 flare, At least 1 severe flare
PGA	Continuous Categorical • 0-1, >1 – 2.5, > 2.5
SLICC/ACR Damage Index	Continuous Categorical • 0, 1, > 1

Endpoint	Categories & Summaries at Baseline

Proteinuria (based on spot urine using protein: creatinine mg/mg ratio)	Continuous
	Categorical (units are g/24hr equivalent)
	• ≤ 0.5, > 0.5
	• Subcategories of > 0.5
	  • >0.5 - < 1
	  • 1 - < 2
	  • ≥ 2

B cells: CD19+ CD20+ CD20+/27+ memory CD20+/27– naïve CD20+/69+ activated CD20+/138+ plasmacytoid CD19+/27^{BRIGHT}/38^{BRIGHT} SLE subset CD20-/138+ plasma	Continuous
Autoantibody Levels	**Anti-dsDNA [IU/mL]** Continuous Categorical • Positive: >=30 IU/mL • Negative: <30 IU/mL
	ANA [Titer] Continuous Categorical • Positive: Index >=0.80 • Negative: Index <0.80
	aCL Status Categorical Positive, Negative, Missing (See Section 13.6.6 for definitions)
anti-dsDNA and/or ANA positive	Categorical • Yes, No
Immunoglobulin Levels (IgG, IgA, and IgM [g/L])	Continuous Categorical **IgG** • Low: < 6.94 g/L, High: > 16.18 g/L **IgM** Low: < 0.48 g/L, High: > 2.71 g/L **IgA** • Low: < 0.81 g/L, High: > 4.63 g/L

Endpoint	Categories & Summaries at Baseline
Allowable SLE Medication Usage	Categorical: • 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 • Traditional Chinese Medicine - Glycosides of Paeony/Tripterygium
Average daily prednisone dose (mg/day) at baseline	Continuous Categorical • 0, >0 to ≤7.5, >7.5
PT/aPTT	Continuous

6.3. Study Population Data for Maintenance Phase Subject Profile

Basic demography information will be listed on the subject profile.

7. EFFICACY ANALYSES

For all efficacy analyses, results for the TH group will be presented for the treatment holiday (TH) and re-start (RS) phases separately.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The time to the first SFI flare over 52 weeks will be estimated for the treatment groups using the product-limit method.

Analyses of SFI flare (defined as mild, moderate, or severe) will be performed on the SELENA SLEDAI SLE flare index. Note: Flares in this study are analysed using the modified SLE flare index where severe flares that are triggered only by an increase in SELENA SLEDAI score to greater than 12 are not categorized as severe in the analysis.

7.1.2. Summary Measure

Only post-baseline flares will be considered in these analyses. Flares (not subjects) occurring on the Day 0 visit date should be removed from the analysis set prior to determining the first flare.

Data observed at or prior to the baseline visit (see Section 5.3.1) will not be included in this analysis.

Time to first SFI flare is defined as the number of days from baseline date (see Section 5.3.1) to the date the subject has a flare (event date – baseline visit date + 1).

See Section. 13.6.3 for additional details.

7.1.3. Population of Interest

The primary efficacy analyses will be based on ITT population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The disposition of subjects as it relates to intercurrent events is defined as follows:

Subject Disposition	Event Met	Event Date [2]
Subject has a SFI flare or takes a prohibited medication		
Subject has a SFI flare during the study [1]	Yes	Date of first SFI flare
Subject takes a prohibited medication [1]	Yes	Date of prohibited medication
Subject does not have a SFI flare and did not take a prohibited medication.		
Subject withdraws from the study or is lost to follow-up	No	Censored at last available date where flare is assessed.
Subject dies during the study	No	Censored at date of death.

Subject completes the study	No	Censored at last study visit where flare is assessed.

[1] If a subject has a SFI flare and takes a prohibited medication, the event date is the earliest of the first SFI flare date and takes a prohibited medication date.
[2] If a subject meets multiple criteria, then the event date is the earliest date.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

The table will display the number and percentage of subjects with a SFI flare, as well as the median, 25th, and 75th percentile of days to first SFI flare, estimated using the product-limit method. For subjects who experience a SFI flare, the study day of the SFI flare will be summarized and the table will display the median, 25th and 75th percentiles and minimum and maximum.

A cumulative incidence curve for time to first SFI flare will also be produced for the 52-week treatment phase.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Rate of Flares

The unadjusted rate of flares per subject-year over 52 weeks will be summarized by treatment group.

7.2.1.2. First Severe SFI Flare

The time to the first severe SFI flare over 52 weeks will be estimated for the treatment groups using the product-limit method.

7.2.1.3. Rebound

Rebound is defined as a SELENA SLEDAI score during the first 24 weeks that exceeds the baseline SELENA SLEDAI score in the subject's respective original parent study.

7.2.1.4. SELENA SLEDAI Scores

SELENA SLEDAI assessments consist 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 maximum theoretical score is 105 (all 24 descriptors

present simultaneously) with 0 indicating inactive disease (marked 'No'), but in practice few subjects have scores > 45 [Buyon, 2005; Petri, 2005].

See Section 13.6.3 for further details.

7.2.2. Summary Measure

7.2.2.1. Rate of Flares

The total number of flares, total subject-years of follow-up in the time interval, and the unadjusted rate per subject-year will be presented.

7.2.2.2. First Severe SFI Flare

See Section 7.1.2.

7.2.2.3. Rebound

The frequencies and percentages of subjects who rebound will be presented by visit through the Week 24 visit, and at any time during the first 24 weeks.

7.2.2.4. SELENA SLEDAI Scores

Summary statistics for the change from baseline in SELENA SLEDAI scores will be presented at each visit in the 52-week treatment phase.

7.2.2.5. Changes in Corticosteroid Use

The frequencies and percentages of subjects who meet each definition will be presented at each visit in the 52-week treatment phase. Steroid doses will be converted to the prednisone-equivalent dose per the derivations in Section. 13.6.3

7.2.3. Population of Interest

The secondary efficacy analyses for all endpoints will be based on the ITT population.

For rebound, the analysis also will be performed by the SELENA SLEDAI score at the BEL116027 Day 0 visit, categorized as ≤3 and >3.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

7.2.4.1. Rate of Flares and First Severe SFI Flare

See Section 7.1.4.

If a subject withdraws from the study, dies or takes a prohibited medication, the subject will be considered as having a SFI flare.

7.2.4.2. Rebound and SELENA SLEDAI Scores

Missing data will be imputed using the principle of Last Observation Carried Forward (LOCF). For the TH group, LOCF will not be applied across the TH and RS phases. If an individual SS item data is missing at the first timepoint in the RS phase, the item will be considered not present.

7.2.4.3. Changes in Corticosteroid Use

7.2.4.3.1. Number of days of daily prednisone dose ≥7.5 mg/day and/or increased by 25%

The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication, the subject will be considered to have met this endpoint criteria (i.e, dose ≥ 7.5 mg/day and/or increased by 25%) after the date of dropout or the date that the medication is started, whichever comes first, up until the visit date, and for those days in intervals for subsequent attended visits. Before this date, the evaluated endpoint will be assessed using available data.

7.2.4.3.2. Number of days of daily prednisone dose ≤7.5 mg/day and/or decreased by 25%

The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication, the subject will be considered a non-responder for this endpoint criteria (i.e., dose >7.5 mg/day and/or did not decreased by 25%) after the date of dropout or the date that the medication is started, whichever comes first, and for those days in intervals for subsequent attended visits. Before this date, the evaluated endpoint will be assessed using available data.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint / Variables

7.3.1.1. Physician Global Assessment (PGA)

The change from baseline in PGA score will be assessed at each visit in the 52-week treatment phase. See Section. 13.6.3 for additional details on the instrument.

7.3.1.2. SLICC/SDI

The change from baseline in SLICC/SDI score will be assessed at each visit in the 52-week treatment phase.

7.3.1.3. Renal Flare

The time to the first renal flare over 52 weeks will be estimated for the treatment groups using the product-limit method. See Section 13.6.3 for additional details.

7.3.2. Summary Measure

7.3.2.1. Physician Global Assessment (PGA) and SLICC/SDI

These endpoints will be analyzed using summary statistics.

7.3.2.2. Renal Flares

Only post-baseline renal flares will be considered in these analyses. Renal flares (not subjects) occurring on the Day 0 visit date should be removed from the analysis set prior to determining the first renal flare.

Data observed at or prior to the baseline visit (see Section 5.3.1) will not be included in this analysis.

Time to first renal flare is defined as the number of days from baseline date (see Section 5.3.1) to the date the subject has a renal flare (event date – baseline visit date + 1).

7.3.3. Population of Interest

The analyses for all exploratory endpoints will be based on the ITT population.

For renal flares, the analysis will be repeated for subjects with baseline proteinuria proteinuria >0.5g/24hr equivalent.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

7.3.4.1. Physician Global Assessment (PGA)

Missing data will be imputed using LOCF. For the TH group, LOCF will not be applied across the TH and RS phases.

7.3.4.2. SLICC/SDI

Missing data due to study withdrawal will be imputed using LOCF. For the TH group, LOCF will not be applied across the TH and RS phases.

The SLICC/ACR Damage Index increases over time. Once a subject meets the criteria for positive scoring of an item, that item should always be marked as present, even if the subject subsequently recovered.

In the event the SLICC/ACR Damage Index is scored inconsistently (a decrease relative to previous items has occurred) and the data are unable to be queried and/or corrected, a worst observation carried forward (WOCF) approach will be used at the item level for the SLICC/ACR Damage Index questions. These WOCF values will then be used to calculate the total score which will be the value summarized and displayed for reporting.

7.3.4.3. Renal Flare

The disposition of subjects as it relates to intercurrent events is defined as follows:

Subject Disposition	Event Met	Event Date [2]
Subject has a renal flare or takes a prohibited medication		
Subject has a renal flare [1]	Yes	Date of first renal flare
Subject takes a prohibited medication [1]	Yes	Date of prohibited medication
Subject does not have a renal flare and did not take a prohibited medication		
Subject withdraws	No	Censored at last flare assessment date
Subject dies	No	Censored at date of death
Subject completes	No	Censored at the Week 52 study visit

[1] If a subject has a renal flare and takes a prohibited medication, the event date is the earliest of the first renal flare date and takes a prohibited medication date.
[2] If a subject meets multiple criteria, then the event date is the earliest date.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.4. Efficacy Data for Maintenance Phase Subject Profile

Flare data will be listed on the subject profile.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), serious adverse events (SAEs), and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 11: List of Data Displays.

Adverse events will be coded to the current MedDRA dictionary version available at the time of reporting.

Only treatment emergent AEs will be summarized (see Section 13.4.1). Any AEs that were ongoing in the upon entry into this will be listed and flagged with a footnote

An overall summary of AEs will be presented showing the number (%) of subjects with at least one of the following: AE, related AE, SAE, severe AE, SAE and/or severe AE, AE resulting in study treatment discontinuation, and deaths.

The number of events and the number (%) of subjects experiencing an AE by SOC, SOC and PT, and PT will be summarized for each of the AE categories below.

- All
- Serious
- Severe
- Study agent Related
- Resulting in discontinuation of study treatment

The data will be sorted by overall decreasing frequency of the SOC, by overall decreasing frequency of the SOC and then decreasing frequency of PT within the SOC, and by overall decreasing frequency of the PT, as applicable. Only SOCs with observed AE PTs will be presented. If the frequency for any two or more adverse events is equal, the events will be presented in alphabetical order by SOC/PT as applicable.

Summaries of AEs frequency by SOC and severity will also be provided. For these displays, 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.

The hierarchical relationship between MedDRA SOCs, PTs, and verbatim text will be displayed in a table for all AEs.

A listing of which subjects reported each AE will be produced. AEs will be grouped and sorted by SOC and PT. A listing of Infusion Related Systemic Reactions will be produced.

8.2. Adverse Events of Special Interest Analyses

8.2.1. Endpoint / Variables

8.2.1.1. Adverse Events of Special Interest

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 adverse events of special interest, 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. The details of the planned displays are provided in Appendix 11: List of Data Displays.

Adverse events of special interest for belimumab have been identified over the course of the development program. The Benlysta Program Safety Analysis Plan (PSAP) includes the definitions and adjudication criteria for the AESI. The definitions are based on standard and custom MedDRA queries (SMQs and CMQs). Categorizations for the AESI are listed in Section 13.9.

GSK will adjudicate neoplasms of unspecified malignancy, opportunistic infections, herpes zoster, serious suicide, and serious PISR events as described in the PSAP. In addition, GSK will review malignancy events to prevent counting an event multiple times in the case where a given malignancy has multiple events (e.g., a diagnostic test and the diagnosis). GSK will review all fatal events and assign a category of death.

8.2.1.2. Post-infusion systemic reactions by infusion

For the TH group in the RS phase, summaries of post-infusion systemic reactions will be presented by the first six infusions in the RS phase and PT for the following categories:

- Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion)
- Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion)
- Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK adjudication
- Serious Delayed Acute Hypersensitivity Reactions per GSK adjudication
- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK adjudication

8.2.2. Summary Measure

8.2.2.1. Adverse Events of Special Interest

An overall summary of AESIs by category 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 will be presented.

Infection AESIs that are serious, severe, serious/severe, and that lead to discontinuation will be presented by category and PT.

8.2.2.2. Post-infusion systemic reactions by infusion

The number and percentage of subjects with at least one occurrence and the number of events will be presented.

8.2.3. Population of Interest

The analyses will be based on the ITT population.

8.2.4. Strategy for Intercurrent (Post-Randomization) Events

For both endpoints, observed data will be used with no imputation.

8.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.3. 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. The details of the planned displays are in Appendix 11: List of Data Displays.

An issue was identified at Q2 Solutions (central lab) in Valencia, California, USA, regarding equipment malfunction which affected some serum creatinine results reported from one of the analyzers used at the lab. Unusually high serum creatinine results were noted for two different GSK clinical trials, and further investigation revealed one of the analyzers had been producing intermittent high serum creatinine results between 01 October 2016 to 13 January 2017, potentially due to an intermittent wash line blockage of the analyzer. BEL116027 investigators were notified of this issue by a Dear Investigator Letter (DIL) 22 February 2017. The subsequent evaluation concluded that there was no impact on data integrity and patient safety for clinical trial BEL116027. Therefore, there will be no modification to the analysis of serum creatinine. BEL116027 investigators were notified by a follow up DIL dated 25 July 2017, and the root cause was identified as a sporadic failure of the wash system due to debris causing intermittent obstruction.

Baseline is defined as described in Section 5.2.

A list of laboratory parameters collected and definition of the toxicity grades are provided in Appendix 8: Values of Potential Clinical Importance.

Listings will be generated for all laboratory results, and additionally for Grade 3 or Grade 4 laboratory toxicity results.

Line graphs will be produced for each analyte displaying the mean value by visit and treatment group.

8.3.1. Endpoint / Variables

8.3.1.1. Clinical Laboratory Results

Laboratory parameters which are continuous numeric values will be analyzed using summary statistics, and those with categorical results will be summarized using frequencies and percentages.

8.3.1.2. Clinical Laboratory Toxicity Grades

The endpoints evaluated will be:

- Worst toxicity grade
- Worsening by at least 2 toxicity grades

Toxicities will be reported as derived by the central laboratory, as protocol toxicity grading was applied.

For potassium, glucose, calcium, and sodium, toxicities are bi-directional (i.e., high and low directions) and both will be summarized by name of the toxicity.

- Potassium: hypokalemia, hyperkalemia
- Glucose: hypoglycemia, hyperglycemia
- Calcium: hypocalcemia, hypercalcemia
- Sodium: hyponatremia, hypernatremia

For example, calcium will have two toxicity sections, one for hypocalcemia and one for hypercalcemia and mapped to their high or low form as:

- RESULT < (LLN+ULN)/2 = “Hypo” toxicity
- RESULT > (LLN+ULN)/2 = “Hyper” toxicity

8.3.1.3. Clinical Laboratory Reference Range Shifts

For laboratory tests without toxicity grades, shifts relative to the normal range will be summarized for each analyte as shifts ‘to low’ and shifts ‘to high.’

For the ‘to low category’ the percentage of subjects with at least one low post-baseline value relative to the baseline (i.e. baseline and post baseline data available) will be displayed using the categories: no shift to low and normal/high to low.

For the ‘to high category’ the percentage of subjects with at least one high post-baseline value relative to baseline (i.e. baseline and post baseline data available) will be displayed using the categories: no shift to high and normal/low to high.

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.

8.3.1.4. Immunoglobulin Results Relative to the Lower Limit of Normal

Immunoglobulins (IgG, IgA, IgM) will be classified relative to the reference range for the following categories: < LLN and ≥ LLN.

8.3.2. Summary Measure

8.3.2.1. Clinical Laboratory Results

Laboratory parameters which are continuous numeric values will be analyzed using summary statistics, and those with categorical results will be summarized using frequencies and percentages. Results will be presented by visit during the 52-week treatment phase, and at any time post-baseline where specified.

8.3.2.2. Clinical Laboratory Toxicity Grades

The frequencies and percentages of subjects meeting each of the toxicity grade endpoints will be summarized by visit during the 52-week treatment phase, and at any time post-baseline where specified.

8.3.2.3. Clinical Laboratory Reference Range Shifts

The frequencies and percentages of subjects meeting each shift criteria will be summarized by visit during the 52-week treatment phase.

8.3.2.4. Immunoglobulin Results Relative to the Lower Limit of Normal

The frequencies and percentages of subjects who are <LLN and ≥LLN will be summarized by visit during the 52-week treatment phase. The analyses will be repeated for the subgroup of patients who are ≥LLN and who are <LLN at baseline, respectively.

8.3.3. Population of Interest

For all clinical laboratory endpoints, the analyses will be based on the ITT population.

8.3.4. Strategy for Intercurrent (Post-Randomization) Events

For all clinical laboratory endpoints, observed data will be used with no imputation.

8.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including immunogenicity and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

8.4.1. Endpoint / Variables

8.4.1.1. Immunogenicity

Serum samples for anti-belimumab antibody measurements will be obtained from subjects per the protocol

For the immunogenicity assessment, 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. Patients 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.

8.4.1.2. Vital signs

Vital signs will be collected per the protocol. Parameters along with units for reporting are listed below.

Vital Sign Parameter (Units)
Systolic Blood Pressure (sitting) (mmHg)
Diastolic Blood Pressure (sitting) (mmHg)
Heart Rate (beats/min)
Temperature (C)
Weight (kg)
BMI (kg / m^2)

8.4.2. Summary Measure

8.4.2.1. Immunogenicity

Immunogenic response will be summarized by visit and anytime postbaseline for the 52-week treatment phase.

Categories of response are Negative, Transient Positive (defined as a single positive response that does not occur at the final assessment, or Persistent Positive (defined as a positive response that occurs on at least 2 consecutive assessments or a single result at the final assessment).

8.4.2.2. Vital signs

Change from baseline in vital signs will be presented using summary statistics by visit.

Baseline body mass index (BMI) will be calculated from weight and height measurements.

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{[Height\ (m)]^2}$$

BMI will be derived at each visit using the baseline value for height and the weight at the visit. Since height is collected in centimeters (cm), it will be converted to meters (m) by dividing by 100 before using it in the formula above.

8.4.3. Population of Interest

For immunogenicity and vital signs endpoints, the analyses will be based on the ITT population.

8.4.4. Strategy for Intercurrent (Post-Randomization) Events

8.4.4.1. Immunogenicity

Observed data will be used with no imputation.

8.4.4.2. Vital signs

Observed data will be used with no imputation. If weight or height is missing, then BMI will be missing.

8.4.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.4.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.5. Safety Data for Maintenance Phase Subject Profile

AE data, grade 3 or 4 laboratory data, and immunogenicity data will be listed on the subject profile.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

The primary PK analysis will be of the serum belimumab concentrations.

9.1.1. Endpoint / Variables

Refer Section 13.5.3 Reporting Standards for Pharmacokinetic.

9.1.2. Summary Measure

Descriptive statistics for serum belimumab concentrations will be displayed for each visit. The tables will display the mean value, standard deviation, 95% CI of mean, geometric mean, % CV, 95% CI of geometric mean, median, 25th and 75th percentiles, minimum and maximum.

9.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Observed data will be used with no imputation.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Population Pharmacokinetic Analysis are not applicable to this study.

11. BIOMARKER ANALYSES

11.1. Primary Biomarker Analyses

11.1.1. Endpoint / Variables

Autoantibodies (anti-dsDNA, ANA), BLyS protein, B-cells (CD19+, CD20+, CD20+/27+ memory, CD20+/27–naïve, CD20+/69+activated, CD20+/138+plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells), immunoglobulins (IgG, IgA, and IgM), and complement (C3 and C4) will be assessed. See Section 13.6.6.2 for additional details.

11.1.2. Summary Measure

11.1.2.1. B-Cells

For the B-cells, the change and percent change from baseline in the original parent study will be summarized at Weeks 0, 8, 16, 24, 32, 40 and 52 and from Week 24 to 32, Week 24 to 40, and Week 24 to 52.

11.1.2.2. Autoantibodies, Immunoglobulins and Complement

For autoantibodies, immunoglobulins and complement, the change and percent change from baseline in the original parent study to each visit including the Day 0 visit in the 52-week treatment phase will be assessed.

Shifts from baseline in IgG, IgM, IgA, anti-dsDNA, ANA, C3 and C4.

11.1.2.3. BLyS Protein

The change and percent change from baseline in the original parent study to each visit in the 52-week treatment phase will be assessed.

11.1.3. Population of Interest

For all endpoints in Section 11.1.1, the primary biomarker analyses will be based on the ITT population.

11.1.4. Strategy for Intercurrent (Post-Randomization) Events

For all endpoints in Section 11.1.1, observed data will be used with no imputation.

11.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 11.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

11.2. Biomarker Data for Maintenance Phase Subjects

By subject line plots for subjects who enter the maintenance phase for all visits for each B-cell parameter will be presented.

12. REFERENCES

Alarcón-Segovia D, Tumlin JA, Furie RA, et al for the LJP 394 Investigator Consortium. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus. Arthritis Rheum. 2003;48(2):442–54.

Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: A randomized trial. Ann Intern Med 2005;142(12 Pt 1):953-62.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Eibl MM, Rosen FS. Intravenous gamma globulin and plasmapheresis. In: Frank MM,editor. Samter's Immunologic Diseases (5th ed.). Boston:Little, Brown, 1995:1529-36.

Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, Pien L, HaugMT, Gordon SM, Hague LK, Dresing JM, Evans-Walker T, Maurer JR.Hypogammaglobulinemia in lung transplat recipients. Transplantation. 2001;71(2):242-6.

Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353(24):2550-8.

Yamini MH, Avery RK, Mawhorter SD, Young JB, Ratliff NB, Hobbs RE, McCarthyPM, Smedira NG, Goormastic M, Pelegrin D, Starling RC. Hypogammaglobulinemiafollowing cardiac transplantation: a link between rejection and infection. J Heart Lung Transplant. 2001;20(4):425-30.

13. APPENDICES

13.1. Appendix 1: Protocol Deviation

See Section 4.1 for details.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

13.2.2. Time and Events Table (Year 1)

	Screen	Treatment Holiday Study														Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**--**	**--**
Study Day	**Up to -30** [1]	**0** [2]	**28 ±7d**	**56 ±7d**	**84 ±7d**	**112 ±7d**	**140± 7d**	**168 ±7d**	**196± 7d**	**224 ±7d**	**252 ±7d**	**280± 7d**	**308 ±7d**	**336 ±7d**	**364 ±7d or Exit**	**16-wk ±7d** [3]	**6 mo ±7d**
Study Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**--**	**--**
Written Informed Consent [4]	X																
Demography		X															
Medical History		X															
SLE History		X															
Therapy History		X															
Physical Examination		X															
Inclusion/Exclusion		X															
Efficacy Assessments																	
DAS: SS, SLE Flare Index, PGA [5]	X [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SLICC/ACR Damage Index		X						X							X		
Safety Assessments																	
Vital Signs [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height [6, 7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Symptom-driven Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record Concurrent Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments																	
Haematology & Modified Chem 20 (non-fasting) [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spot urine (protein to	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screen	Treatment Holiday Study														Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**--**	**--**
Study Day	**Up to -30** [1]	**0** [2]	**28 ±7d**	**56 ±7d**	**84 ±7d**	**112 ±7d**	**140± 7d**	**168 ±7d**	**196± 7d**	**224 ±7d**	**252 ±7d**	**280± 7d**	**308 ±7d**	**336 ±7d**	**364 ±7d or Exit**	**16-wk ±7d** [3]	**6 mo ±7d**
Study Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**--**	**--**
creatinine ratio) [8]																	
Pregnancy Test [6, 9]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	
Pharmacogenetic Sampling [10]		X															
aCL Autoantibody		X													X		
C3/C4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Anti-dsDNA Autoantibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ANA Autoantibodies		X						X							X		
IgG, IgA & IgM [11]		X		X		X		X		X		X		X	X		
PT/ PTT		X															
Exploratory Lab Assessments																	
Pharmacokinetic Sampling [12]		X		X		X		**X** [12]		X					X [12]		
Immunogenicity [6, 13]		X			X		**X** [13]	X			X				X	X	**X** [13]
BLyS Protein [14]						X		X		X							
B cell Markers [15]		X		X		X		X		X		X			X		**X**
Investigational Product (IP)																	
IP Administration [16]		X	X	X	X	X	X	X	X	X	X	X	X	X	***X***		

1. DAS = disease activity scales; SS = SELENA SLEDAI; SLE = systemic Lupus Erythematosus; PGA = Physician's Global Assessment; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; PT/PTT = prothrombin time/partial thromboplastin time; BlyS = B Lymphocyte Stimulator; IP = investigational product; aCL = anticardiolipin
2. A screening visit of up to 30 days prior to the Day 0 visit will be scheduled for subjects in the treatment holiday and control groups for assessment of SELENA SLEDAI score to assess eligibility.
3. The EXIT Visit in the respective feeder continuation studies will serve as the Day 0 visit for all 3 subject groups in this study. Assessments covered for both this study at Day 0 and the Exit visit of the feeder continuation studies need only be performed once and recorded in the appropriate case report forms for each study. Subjects in the control group must be able to receive the 1st dose of belimumab on Day 0 of this study on average 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the feeder continuation study.
4. The 16 week follow-up visit will occur at approximately 16 weeks after last dose of investigational product for subjects in the control group who withdraw at any time during the study, or for subjects in the treatment holiday group who withdraw from the study from Week 24 onwards (Visit 7) during the belimumab re-introduction period. The 16-week and 6 month follow-up visits do not apply to subjects in the long-term discontinuation group.
5. Obtain written informed consent to participate in this study at the Screening visit.

6. Guidelines for scoring proteinuria for SELENA SLEDAI are provided in protocol Section 6.3.1.1 .
7. Complete assessment prior to belimumab dosing for subjects in the control group (to Week 48) and for subjects in the treatment holiday group (during Weeks 24 to 48 or earlier in the event of a flare). Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
8. For any subject whose weight changes by more than 5% from that recorded at Day 0, use the weight at the current visit for calculating the belimumab dose to be administered. Height measured only at Day 0.
9. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
10. Urine pregnancy test results for women of child-bearing potential must be available prior to dosing (during Weeks 0 to 48 in the control group and during Weeks 24 to 48 or earlier in the event of a flare in the treatment holiday group).Can be performed at any time during the visit for females of child-bearing potential in the long-term discontinuation group.
11. PGx sampling from consenting subjects recruited from all studies except from study BEL114333. PGx informed consent must be obtained prior to sampling.
12. Serum immunoglobulin isotypes: IgG, IgM, IgA.
13. Pharmacokinetic sampling at select sites for subjects in the control and treatment holiday groups; subjects in the treatment holiday group can have PK sampling performed at any time during the visit between Weeks 0 and 16. Otherwise, if on a dosing day, sampling must be performed **prior** to dosing. Collect blood samples pre-dose and post-dose at the end of the infusion at Weeks 24 and 52 (or earlier if belimumab is re-started before Week 24 in the event of a severe flare by using the escape option). Subjects in the long-term discontinuation group will have one PK sampling performed at any time during the visit between Weeks 0 and 24. PK sampling for the long-term discontinuation group is not performed after Week 24. Long-term discontinuation subjects withdrawing before Week 24 will have one PK sampling performed at any time during the EXIT visit. PK sampling for long-term discontinuation subjects withdrawing after Week 24 is not performed at the EXIT visit.
14. Blood sample for immunogenicity will be taken at Weeks 12, 24, 36 and 52 for all three groups. In addition, a blood sample for immunogenicity will also be taken **4 weeks prior** to the reintroduction of belimumab (at Week 20 since belimumab will be reintroduced at Week 24) in the treatment holiday group. A blood sample for immunogenicity must be taken at least 6 months after the final dose of investigational product for any subjects in the control group or treatment holiday group who had an anti-belimumab antibody response at the 16-week follow-up visit (or at the last immunogenicity assessment if 16-week follow-up is not available). **Note** that serum samples for immunogenicity must be collected pre-dose at the time of dosing from subjects in the treatment holiday group who experience a severe flare prior to Week 24 and consequently receive open-label belimumab as rescue. Immunogenicity blood sample will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
15. Measured in treatment holiday group at Weeks 16 and pre-dose at Week 24. Measured in long-term discontinuation group at Weeks 16, 24 and 32. Not measured in control group.
16. Biological Markers include FACS of peripheral lymphocytes: B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27– naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27^{BRIGHT}/38^{BRIGHT} SLE subset and CD20-/138+ plasma cells). Note: B cell markers will not be collected at the 6-month follow up visit for subjects in the long-term discontinuation group as this visit does not apply to this subject group.
17. Only subjects in the control group will receive belimumab 10 mg/kg during Weeks 0 through 20 inclusive; subjects in the control group must be able to receive the **first** dose of belimumab **in this study** 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in their **previous** open-label continuation study Subjects in the control group and treatment holiday groups will receive belimumab from Weeks 24 through 48 although subjects in the treatment holiday group may be treated with belimumab **prior** to Week 24 as determined by the investigator in the event of increased SLE activity. When belimumab therapy is re-started, subjects in the treatment holiday group will remain under clinical supervision for 3 hours after completion of the first 2 infusions. At the **Week 52** visit, only subjects in the treatment holiday and control groups who are continuing belimumab therapy beyond this time will be dosed.

13.2.3. Time and Events Table (Additional Years)

Study Visit (Weeks) [1]	4	8	12	16	20	24	28	32	36	40	44	48
Study Day	**28 ±7d**	**56 ±7d**	**84 ±7d**	**112 ±7d**	**140 ±7d**	**168 ±7d**	**196 ±7d**	**224 ±7d**	**252 ±7d**	**280 ±7d**	**308 ±7d**	**336 ±7d**
Efficacy Assessments												
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, and PGA [2]						X						X
SLICC/ACR Damage Index												X
Safety Assessments												
Symptom-driven Physical Exam						X						X
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [3, 4]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Haematology & Modified Chem 20 (non-fasting) [3, 5]						X						X
Urinalysis [5, 6]						X						X
Spot urine (protein to creatinine ratio) [3, 5, 6]						X						X
Urine Pregnancy Test [3, 5, 7]	X	X	X	X	X	X	X	X	X	X	X	X
C3, C4, Anti-dsDNA Autoantibodies [3, 5]						X						X
IgG [3, 5, 8]												X
IgA & IgM [3, 5, 8]												X
Exploratory Lab Assessments												
Immunogenicity [3, 9]						X						X
B cell Markers [10]												X
Investigational Product												
Belimumab Administration [4, 11]	X	X	X	X	X	X	X	X	X	X	X	X

1. Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study.
2. Guidelines for scoring proteinuria for SELENA SLEDAI are provided in protocol Section 6.3.1.1.
3. Assessments performed prior to dosing.
4. For any subject whose weight changes by more than 5% from that recorded at Day 0, use the weight at the current visit for calculating the belimumab dose to be administered.
5. During “Additional years”, investigators can obtain any of the same laboratory assessments that are mentioned for Year 1 (haematology, modified Chem 20, urinalysis, spot urine to creatinine ratio, urine pregnancy, C3, C4, anti-ds DNA autoantibodies, IgG, IgA, and IgM), as unscheduled laboratory tests at any time during Year 2 and beyond, if clinically indicated. Any additional laboratory tests beyond this, if not related to the protocol, will be the responsibility of the investigator and subject.
6. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
7. Results of urine pregnancy tests in women of child-bearing potential must be available prior to belimumab dosing.
8. Serum immunoglobulin isotypes: IgG, IgM, IgA.
9. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
10. Biological Markers include FACS of peripheral lymphocytes: B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27– naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset and CD20-/138+ plasma cells).
11. After completion of the Week 48 visit during year 1 of the study, subjects in the treatment holiday and control groups can continue to receive belimumab therapy at 4-weekly intervals in the maintenance phase of this study. Subjects who withdraw from belimumab therapy during this maintenance phase will complete the Exit and follow-up visits detailed in the Year 1 Time and Events Table. The Exit visit Schedule should be scheduled 4 weeks after the final belimumab dose and the 16-week follow-up visit 16 weeks after the final belimumab dose.

13.3. Appendix 3: Assessment Windows

13.3.1. Mapping of the Maintenance Phase Visits for Subjects with an Escape Visit

In the eCRF, the next visit provided following the Escape visit is the Year 2 Week 8 visit, when chronologically the next visit would be the Year 2 Week 4 visit. Therefore, the maintenance phase visits for subjects with an Escape visit will be re-mapped in the ADaM analysis data sets to the maintenance phase visit, so that the visits align chronologically with those for subjects who complete the 52-week treatment phase and subsequently enter the maintenance phase.

If an Escape visit is present, mapping will occur as follows:

	SDTM Variable	**ADAM Variable**
Domain	**VISITNUM** **VISIT**	**AVISITN** **AVISIT**
All	190 ESCAPE	190 ESCAPE
All	220 YEAR 2 WEEK 8	210 YEAR 2 WEEK 4
All	230 YEAR 2 WEEK 12	220 YEAR 2 WEEK 8
All	240 YEAR 2 WEEK 16	230 YEAR 2 WEEK 12
The mapping will continue in this pattern for subsequent visits.		

13.3.2. Mapping of Week 16 and 6-month Follow-up Visits

The 16-week and 6-month follow-up visits will be re-mapped in the ADaM analysis data sets so that they sort in chronological sequence when using the numeric visit number.

	SDTM Variable	ADAM Variable
Domain	**VISITNUM** **VISIT**	**AVISITN** **AVISIT**
All	170 16 WK FOLLOW-UP	9100 16 WK FOLLOW-UP
All	180 6 MO FOLLOW-UP	9200 6 MO FOLLOW-UP

13.3.3. Analysis Visit and Analysis Visit Number

The data are analyzed according to the planned visit assignment in the data.

Exit/withdrawal visits must be slotted to the appropriate planned visit according to the study phase. This will only be done for subjects that withdrew early and did not complete the 52-week treatment phase. Unscheduled laboratory visits will also be slotted to the appropriate planned visit.

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

Analysis Visit	Analysis Visit Number	Target Study Day[1]	Interval Start Day	Interval End Day
Screening	10	-34	na	na
52-week Treatment Phase visits:				
Baseline	20	1	na	na
Week 4	30	29	22	42
Week 8	40	57	43	70
Week 12	50	85	71	98
Week 16	60	113	99	126
Week 20	70	141	127	154
Week 24	80	169	155	182
Week 28	90	197	183	210
Week 32	100	225	211	238
Week 36	110	253	239	266
Week 40	120	281	267	294
Week 44	130	309	295	322
Week 48	140	337	323	350
Week 52	150	365	351	378

Analysis Visit	Analysis Visit Number	Target Study Day[1]	Interval Start Day	Interval End Day
[1]Day 0 visit date in study 116027 = Study Day 1.				

13.3.4. Windows for Assessment of Post-injection/infusion sensitivity reactions (PISR) and hypersensitivity reactions (HSR)

The windows for assessment of PISR/HSR, as described in the AESI definitions in Section 13.9.2, are as follows:

Date of Infusion		
Day 1	Day 2	Day 3
SMQ narrow, broad and algorithmic searches (On day of injection/infusion or within 3 days of injection/infusion)		

13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

13.4.1. Treatment Phases

- Visits, assessments and events will be classified according to the time of occurrence relative to the following cut-point dates for each treatment group.
- For convenience and ease of data presentation, the 52-Week Treatment Phase has the same name designation for all three treatment groups, even though the LTC group does not receive treatment at all during this phase and the TH group receives treatment for only the second half of the phase.
- Only the TC and TH groups are eligible to participate in the Maintenance Phase.
- If an AE start date falls on the Day 0 date, then it will be considered treatment emergent (i.e., fall in the 52-week treatment phase). If a concomitant medication start date falls on the Day 0 visit date, the concomitant medication will be considered to fall in the 52-week treatment phase. Any other assessments that fall on the Day 0 visit date will be considered to occur in the pre-study phase.
- For the TC group, if the first infusion date differs from the Day 0 visit date, then the first infusion date will be used as the phase cut-point.
- Other than Day 0, if an assessment or event occurs on the same date as a phase cut-point, then the event will be considered to fall in the previous phase. For example, if a new prednisone dose starts on the same date as the Week 24 visit date and then continues for a total of 7 days, then the first day of that prednisone dose will fall into the Holiday Phase and the remaining 6 will fall into the Re-start phase.
- For AEs, if the AE Onset date is missing, then the AE will be considered to occur in the 52-week treatment phase.
- For the TH group, a subject who re-starts treatment prior to Week 24 will not have a Re-Start phase.

13.4.1.1. Treatment Holiday Group

Endpoint	Day 0 Visit Parent Study	Day 0 Visit BEL116027 Study	Week 24/ TX Re-start Visit	Week 52/ Exit/Escape Visit	Week 16 Follow-up Visit
Baseline					
Flare, PGA, Prednisone, SLICC	N/A	52-Week Treatment Phase		Maintenance Phase	N/A
		Holiday Phase	Re-start Phase		
Baseline					
SS, Auto-antibodies Immunoglobulins, B-cells [1], BLyS	Pre-Study Phase	52-Week Treatment Phase		Maintenance Phase	N/A
		Holiday Phase	Re-start Phase		
Baseline					
Rebound [2]	Pre-Study Phase	52-Week Treatment Phase		N/A	N/A
		Holiday Phase	N/A		
Baseline					
Adverse Events, Lab Parameters, Vital Signs, Con Meds Immunogenicity [1]	N/A	52-Week Treatment Phase		Maintenance Phase	N/A
		Holiday Phase	Re-start Phase		

N/A = Not Applicable.

[1] Immunogenicity and B-cells may also be collected at the 6-month follow-up visit. The 6-month follow-up visit is not represented in the diagram since it does not define a treatment phase of the study.

[2] Rebound is only assessed up to the Week 24/Treatment re-start visit.

13.4.1.2. Treatment Control Group

Endpoint	Day 0 Visit Parent Study	Day 0 Visit BEL116027 Study [1]	Week 24 Visit	Week 52/ Exit Visit	Week 16 Follow -up Visit
Baseline					
Flare, PGA, Prednisone, SLICC	N/A	52-Week Treatment Phase		Maintenance Phase	N/A
Baseline					
SS, Auto-antibodies Immunoglobulins, B-cells [2], BLyS	Pre-Study Phase	52-Week Treatment Phase		Maintenance Phase	N/A
Baseline					
Rebound [3]		52-Week Treatment Phase			
	Pre-Study Phase	First 24 Weeks	N/A	N/A	N/A
Baseline					
Adverse Events, Lab Parameters, Vital Signs, Con Meds , Immunogenicity [2]	N/A	52-Week Treatment Phase		Maintenance Phase	N/A

N/A = Not Applicable.

[1] If the first infusion date differs from the Day 0 visit date, then the first infusion date will be used as the phase cut-point.

[2] Immunogenicity and B-cells may also be collected at the 6-month follow-up visit. The 6-month follow-up visit is not represented in the diagram since it does not define a treatment phase of the study.

[3] Rebound is only assessed up to the Week 24 visit.

13.4.1.3. Long-term Discontinuation Group

Endpoint	Day 0 Visit Parent Study	Day 0 Visit BEL116027 Study	Week 24 Visit		Week 52/ Exit Visit
Baseline					
Flare, PGA, Prednisone, SLICC	N/A	N/A	52-Week Treatment Phase		N/A
Baseline					
SS, Auto-antibodies Immunoglobulins, BLyS	N/A	Pre-Study Phase	52-Week Treatment Phase		N/A
Baseline					
Rebound	N/A	Pre-Study Phase	52-Week Treatment Phase		N/A
			First 24 Weeks	N/A	
Baseline					
Adverse Events, Lab Parameters, Vital Signs, Con Meds	N/A	N/A	52-Week Treatment Phase		N/A

N/A = Not Applicable.

Treatment State	Treatment Group	Definition
Treatment Emergent	TH, LTD	AE Onset Date ≥ Day 0 visit date
Treatment Emergent	TC	AE Onset Date ≥ Date of First Infusion in BEL116027
Onset Time Since 1st Dose (Days)	TH, TC	If Date of First Infusion in BEL116027> AE Onset Date: = AE Onset Date - Date of First Infusion in BEL116027 If Date of First Infusion in BEL116027≤ AE Onset Date = AE Onset Date - Date of First Infusion in BEL116027+1 =Missing otherwise.
Onset Time Since Study Start (Days)	TH, TC, LTD	If Day 0 visit date > AE Onset Date: = AE Onset Date – Day 0 visit date If Day 0 visit date ≤ AE Onset Date = AE Onset Date - Day 0 visit date +1 =Missing otherwise.
Duration (Days)	TH, TC, LTD	AE Resolution Date – AE Onset Date + 1
Drug-related	TH, TC, LTD	If relationship is marked 'YES' on Inform/CRF OR value is missing.

1. NOTES:

- If the AE Onset date is missing, then the AE will be considered as treatment emergent.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	US1SALX00259
HARP Compound and Reporting effort	GSK1550188/BEL116027/final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0).	
Generation of RTF Files	
• RTF files will be generated for all tables in the final_cdisc RE	

13.5.2. 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
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

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 agent 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
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will be included in figures unless their inclusion contributes adversely to

visual presentation or interpretation of the figure. • 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.	

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log transformed data and between geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	N, n mean, 95% CI, standard deviation (SD), median, 25^{th} and 75^{th} percentile, minimum and maximum will be reported.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the Day 0 Visit Date (i.e., Day 1) to the assessment date or visit date of interest (Ref Date)
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Day 0 Visit Date → Study Day = Ref Date – Day 0 Visit Date
  • Ref Data ≥Day 0 Visit Date → Study Day = Ref Date –Day 0 Visit Date + 1

13.6.2. Study Population

Demographics
Study Phases Definitions for Disposition

• Completion/withdrawal for the 52-Week Treatment Phase will be derived as follows:
  o Withdrawn if the subject completion status is marked as No and the subject has no visits during the maintenance phase.
  o Complete if the subject completion status is marked as Yes and the subject has no visits during the maintenance phase.
• Completion/withdrawal for the Maintenance Phase will be derived as follows:
  o Withdrawn if the subject completion status is marked as No and the subject has at least one visit during the maintenance phase.
  o Complete if the subject completion status is marked as Yes and the subject has at least one visit during the maintenance phase.

Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.
• Analysis age is derived in years relative to the Day 0 visit date, and is calculated in SAS as follows:
Analysis Age (years) = INTCK('year', Date of Birth, Day 0 Date) - (MONTH(Day 0 Date) < MONTH(Date of Birth)

Demographics
or (MONTH(Day 0 Date) eq MONTH(Date of Birth) and DAY(Day 0 Date) < DAY(Date of Birth)))

Proteinuria

- For analysis, urine protein in g/24-hour will be approximated by the urine protein:creatinine ratio (uPCR).
- The value for reporting and analysis is stored in the uPCR result variable corresponding to the original unit in the SI dataset. Depending on the study, units for uPCR may be reported in g/g or mg/mg. As long as the units are the same in the numerator and denominator, the ratio will be the same.
- The SI dataset standard unit is reported in mg/mmol is not used for reporting and analysis purposes in this study.

Concomitant medications

- Concomitant medications are defined as
  a. Medications that start on or before the Day 0 visit date and end on or after the Day 0 visit date, or
  b. Medications that start after the Day 0 visit date
- Medications that meet criterion 'a' are considered to be in use at baseline.
- Medications will be assigned to the 52-week treatment or maintenance phases, as per the definitions in Section 13.4.1.
- 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 treatment and if the month and year are the same or later, then the medication will be considered concomitant.

Allowable SLE Medications at Baseline

There are 5 medication categories that are evaluated. These medication categories are defined in the table below and stored in the variable CMSCAT. Only medications providing systemic exposure are evaluated. Systemic exposure is based on the route of administration. A flag variable for systemic exposure when CMSCAT is not blank is defined below and stored in the variable SYSTEMIC. The medication must have one of the defined medication categories below (CMSCAT ne blank) and must provide systemic exposure (SYSTEMIC='Y').

Medication Category (CMSCAT)	Rule
Anti-malarials	Set CMSCAT to "ANTIMALARIALS" if the preferred term begins with "QUINACRINE", "QUININE", "HYDROXYCHLOROQUINE", "MEPACRINE", or "CHLOROQUINE"
Steroids	Set CMSCAT to 'STEROIDS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02'

Allowable SLE Medications at Baseline	
Immunosuppressants	Set CMSCAT to 'IMMUNOSUPPRESSANTS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04A' or the preferred term begins with "CYCLOPHOSPHAMIDE" or "MERCAPTOPURINE".
NSAIDs	Set CMSCAT to NSAIDs if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'M01A'.
Aspirin	Set CMSCAT to "ASPIRIN" if CMDECOD contains "ACETYLSALICYLIC ACID" or "ACETYLSALICYLATE LYSINE".
Prohibited	Set to "PROHIBITED" if any of the following conditions are met, if CMDECOD equals "INVESTIGATIONAL DRUG", "IMMUNOGLOBULIN", "ADALIMUMAB", "ETANERCEPT", "INFLIXIMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "GOLIMUMAB", "CERTOLIZUMAB" ***and/or*** *A review of the surgeries/procedures form indicates the subject had "PLASMAPHERESIS".*
Traditional Chinese medications Glycosides of Paeony and Tripterygium	These medications will be identified based on a clinical review of all the concomitant medications assigned the following drug collection codes in the GSK drug dictionary: 50119401, 54654601, 40987301, 50192401, 53020201, 53060901, 53766001, 53927401, 53959101, 53959201, 53990601, 54619401, 54731901, 54908201, 59164101
Systemic (SYSTEMIC)	Rule
Blank	If CMSCAT=blank
Y	'Y' if CMSCAT ne blank and the route of administration is "INTRADERMAL" "PO" "INTRAMUSCULAR", "INTRAVENOUS", "ORAL", or "SUBCUTANEOUS"
N	'N' otherwise and CSMCAT ne blank

Treatment Compliance
• Treatment compliance for patients completing the 52 week treatment phase or withdrawals is calculated as: $$treatment\ compliance\ (\%) = 100 \times \frac{Number\ of\ infusions\ prescribed - Number\ of\ infusions\ missed}{Number\ of\ infusions\ prescribed}$$ • Prescribed number of infusions will be 7 for the TH arm and 13 for the TC arm, except for TH subjects who escape to the Maintenance Phase. For TH subjects who escape, the treatment compliance will be missing. The Week 52 infusion is considered to be the first infusion of the maintenance phase. • NB: for withdrawals the number of infusions prescribed is the number from Day 0 up to the withdrawal date

Extent of Exposure
• Number of days of exposure to study treatment during the 52-week Treatment Phase will be calculated based on the formula: **Duration of Exposure in Days = (Date of last infusion in BEL116027 52-week treatment Phase– Date of first infusion in BEL116027) + 28** • The Week 52 infusion is considered to be the first infusion in the Maintenance Phase, and will not be considered in this calculation. • Subjects who were enrolled in the TH and TC groups but did not receive an infusion will be categorised as having zero days of exposure. • Exposure will not be calculated for the LTD group. • Only complete dates will be used when calculating duration of exposure. • Exposure will not be adjusted for skipped infusions.

13.6.3. Efficacy

SLE Flares and Severe Flares, and Renal Flares
Baseline Flares
• Baseline flares will be summarized using the data from the eCRF SFI data collection for the Day 0 visit. Per eCRF completion guidelines, the data collected at the Day 0 visit represents the flare data since the previous visit (i.e. the last visit in the feeder continuation study).
SLE Flares and Severe SLE Flares

SLE Flares and Severe Flares, and Renal Flares

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

- 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 modified 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 modified SELENA SLEDAI score.
- If it's found that the change is not actually ≥ 3, and no other reasons are checked,

SLE Flares and Severe Flares, and Renal Flares

then the flare will not be counted.

Renal Flares

A SLE Renal flare is defined as the occurrence of at least 1 or more of the following in 2 or more consecutive visits during the study. (NB: at least 1 of the same criteria must be present on at least 2 consecutive visits)

Increased Proteinuria (using spot urine)

A reproducible increase in 24-hour urine protein levels (as measured in uPCR) to:

- >1g if the baseline (Day 0)value was <0.2g

OR

- >2g if the baseline (Day 0) value was between 0.2g and 1g

OR

- More than twice the value at baseline (Day 0) if the baseline value (Day 0)was >1g

Impaired Renal Function

- A reproducible decrease in GFR of >20%, accompanied by proteinuria (>1), and/or cellular (RBC and WBC) casts.
- [Alarcón-Segovia, 2003].

GFR is estimated by the Cockcroft-Gault equation [Cockcroft, 1976] for creatinine clearance in mL/min.

Cockcroft-Gault Equation

$$Cl_{cr}\ (mL/min) = \frac{(140\text{-age (yrs)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ if female}$$

"Reproducible" requires the criterion to be met at two consecutive visits, including unscheduled visits.

The following table identifies the lab parameters to be used to evaluate the criteria in the renal flare definition above.

Criterion	Parameter	SI Dataset LBTESTCD
Proteinuria	Urine Protein:Creatinine Ratio (mg/mg)	PRTCRT_URQ
GFR	Creatinine Clearance estimated by the Cockcroft-Gault equation (mL/min)	CRTCE_PLR
Cellular casts:		
WBC cellular casts	WBC cellular casts	WBCSTM_URQ
dysmorphic RBCs	dysmorphic RBCs	DRBCM_URQ

SLE Flares and Severe Flares, and Renal Flares

Derivation for rates of SFI flares

- Within a treatment group, the unadjusted flare (severe flare) rate per subject-year in a given phase will be calculated as:

Unadjusted flare (severe flare) rate per subject-year =

total number of flares (severe flares) in the phase / total number of years of follow-up time in the phase.

- The calculation will not include baseline flares in the 116027 study.

Follow-up time derivation for rates of SFI flares

Phase	Treatment Group	Definition
52-week Treatment Phase	TC, LTD	(Week 52/Exit visit date – Day 0 date + 1)/ 365.25.
TH Phase	TH	(Week 24/TX re-start date – Day 0 date + 1)/ 365.25.
RS Phase	TH	(Week 52/Exit visit – Week 24/TX re-start date)/ 365.25.

SELENA SLEDAI Organ System Domains

SELENA SLEDAI assessments consist 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 maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No'), but in practice few subjects have scores > 45 [Buyon, 2005; Petri, 2005].

Organ system domain scores are the sum of the weights of items within the organ domain as defined in the table below.

In this study, proteinuria is evaluated using spot-urine protein [represented as protein-creatinine ratio or PC Ratio (Add ref to 9.3.13) in the laboratory dataset] in lieu of the 24-hour urine collection. PC ratio in mg/mg is considered equivalent to g/24-hr urine protein.

If the P/C ratio value is missing, then the value from the previous visit will be used. Specifically, the assessment for proteinuria indicated on the CRF will be used to calculate the SELENA SLEDAI score.
In the eCRF, laboratory items on the SLEDAI may also be ticked 'unknown' to indicate the lab test was not available. The laboratory items are: urinary casts, hematuria, proteinuria, pyuria, low complement, increased DNA binding, thrombocytopenia, and leukopenia. Responses of 'Unknown' will be managed via LOCF

List of organ systems, items, and weights for the assessments are provided.

Organ System	Descriptor	Weight
[1] CNS	Seizure	8
	Psychosis	8
	Organic Brain Syndrome	8
	Visual Disturbance	8
	Cranial Nerve Disorder	8
	Lupus Headache	8
	CVA	8
[2] Vascular	Vasculitis	8
[3] Musculoskeletal	Arthritis	4
	Myositis	4
[4] Renal	Urinary Casts	4
	Hematuria	4
	Proteinuria	4
	Pyuria	4
[5] Mucocutaneous	Rash	2
	Alopecia	2
	Mucosal Ulcers	2
[6] Cardiovascular & Respiratory	Pleurisy	2
	Pericarditis	2
[7] Immunologic	Low Complement	2
	Increased DNA Binding	2
[8] Constitutional	Fever	1
[9] Hematologic	Thrombocytopenia	1
	Leukopenia	1

PGA

- The PGA is collected on a 10cm visual analogue scale (VAS).
- The standard scoring range for the PGA is 0 to 3, and the score will be rescaled for standard reporting by multiplying the collected score by 3/10.
- During study conduct, it was noted that some sites erroneously received PGA scales that were 9.5cm in length due to a printing error, and some subjects utilized these scales before the error was discovered. Per Notes to File (08Jan2015, and 20Sep2017), an evaluation was performed and the decision was taken that this would result in minimal differences and not expected to affect any outcomes, and therefore it was unnecessary to adjust the analysis.

Prednisone Equivalent Conversion

Identification of Steroids

- A concomitant medication is identified as a steroid if
  - At least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02.' AND
  - The route meets the following criteria:
    - Provides systemic exposure: oral, subcutaneous, intramuscular, intradermal, and intravenous.
    - Although not systemic, intra-articular steroids are also identified for

prohibited medication rules.

  - Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).

- Steroid doses will be converted to the prednisone-equivalent dose.
- At data base release, 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 or intra-articular 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 or intra-articular 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).
  - Prednisone Equivalent Daily Dose (mg) = Collected Dose (mg) x Conversion Factor x Frequency Factor

Average Daily Dose Derivation

- Average daily prednisone dose at baseline is based on all days from the Screening visit date up to and including the Day 0 visit date.
- Post-baseline, average daily prednisone dose is based on all days between visits including the current visit date.
- Average Daily Dose (mg/day) = Sum of Prednisone Equivalent Daily Dose (mg) across all days in the visit interval / Number of days in the visit interval

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
CELESTONA BIFAS	7.5
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.3333
DEFLAZACORT	0.8333
DEPO-MEDROL MED LIDOKAIN	1.25
DEXAMETHASONE	6.6667
DEXAMETHASONE ACETATE	6.6667
DEXAMETHASONE SODIUM PHOSPHATE	6.6667
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
Frequency Factors	
Frequency	**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
QAM	1
QD	1
QH	24
QHS	1
QID	4
QOD	1/2
QPM	1
QW	1/7
QWK	1/7
TID	3
TIW	3/7
UNK	null
2 TIMES PER WEEK	2/7
3 TIMES PER WEEK	3/7
EVERY 2 WEEKS	1/14
EVERY 3 WEEKS	1/21
EVERY 4 Weeks	1/28
EVERY WEEK	1/7

13.6.4. Safety

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
- PISR per Anaphylactic Reaction CMQ broad search
- PISR per Anaphylactic Reaction CMQ algorithmic search
- Serious Anaphylaxis per Sampson Criteria per GSK adjudication
- Serious Acute PISR/Hypersensitivity Per GSK adjudication
  - Serious Acute PISR Excluding Hypersensitivity per GSK adjudication

Adverse Events
Adverse Events of Special Interest (AESI)
• Serious Acute Hypersensitivity Reactions per GSK adjudication • Serious Delayed Acute Hypersensitivity Reactions per GSK adjudication • Serious Delayed Non-Acute Hypersensitivity Reactions per GSK adjudication 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 • Opportunistic ▪ Recurrent ▪ Disseminated • Sepsis 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 adjudication • Suicidal Behaviour ▪ Completed Suicide • Suicidal Ideation • Self-injurious Behaviour without Suicidal Intent • Deaths

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 • Example 3: 0 Significant Digits = '< x' becomes x – 1

13.6.5. Pharmacokinetic

Belimumab concentration
• Assign zero to NQ values (Refer to GUI_51487 for further details)

13.6.6. Biomarker

13.6.6.1. Autoantibody, Complement, Immunoglobulins, and BLyS Protein

Biomarker Categorical Definitions
Anti-ds DNA
• Positive: ≥ 30 IU /mL • Negative: < 30 IU /mL
ANA
• Positive: index ≥ 0.80 • Negative: index < 0.80
aCL status
• Positive: if any of the three isotypes IgG, IgA or IgM are above the lower limit of quantification • Negative: if at least one isotype is non-missing and none of the isotypes are above the lower limit of quantification • Missing: if all three isotypes are missing
BLyS Protein
• Below LOQ: <0.02048 ng/mL • Above LOQ: ≥0.02048 ng/mL
C3
• Positive: < 90 mg/dL • Negative: ≥ 90 mg/dL • Low: < 90 mg/dL • High: > 180 mg/dL
C4
• Positive: < 10 mg/dL • Negative: ≥ 10 mg/dL • Low: < 10 mg/dL • High: > 40 mg/dL
Immunoglobulin G
• Low: < 6.94 g/L • Normal/High: ≥ 6.94 g/L
Immunoglobulin A
• Low: < 0.81 g/L • Normal/High: ≥ 0.81 g/L
Immunoglobulin M
• Low: < 0.48 g/L • Normal/high: ≥ 0.48 g/L

13.6.6.2. B-cell Subsets

Flow Assays

B-cells can be assayed using 3 different flow panels (identification of the flow panel responsible for each record is stored in BIMETHCD in the data transfer): Not all assays

will have the full list of B-cells assessed, but data relating to CD19 B-cells are collected using all 3 assay methods, i.e. concentration of CD19 cells from the TBNK panel and CD19 event counts on the Plasma and Transitional panels (see detail in the table below).

Because the numbers of cells observed for the rare B-cell subsets are small, the concentration data cannot be adequately summarised in the units provided in the SI/SDTM data. Therefore, these subsets are normalized and converted to an appropriate unit of measurement, i.e. count/mL. To normalize a rare B-cell subset and convert to count/mL, the CD19+ B-cell event count from the same flow panel as the B-cell subset being converted is used in the derivation. For example, the CD19+ event count from the plasma flow panel is used to normalize B-cell subsets found in the plasma panel, whereas the CD19+ event count from the transitional panel is used when converting rare B-cell subsets from the transitional panel. The study RAP should detail which rare B-cell subsets will be normalized and converted.

Source data

Below are the important variables included in a source data transfer for the B-cells to be reported in this study.

Flow Panel	Biomarker testing method code	Biomarker category code (BICATCD)[1]	Analyte name	Biomarker test code (BITESTCD)	Units of Measurement (BIORRESU)
TBNK	FLWTBNK	CD19	CD19+	CONC	GI/L
TBNK	FLWTBNK	CD19	CD19+	%LYMPH	%
PLASMA	FLWPLSM	CD19	CD19+	EVENTS	EVENTS
TRANSITIONAL	FLWTRANS	CD19	CD19+	EVENTS	EVENTS
PLASMA	FLWPLSM	CD20	CD20+	CONC	GI/L
PLASMA	FLWPLSM	CD20	CD20+	%CD19+	%
PLASMA	FLWPLSM	CD20	CD20+	EVENTS	EVENTS
PLASMA	FLWPLSM	CDX136	Naïve CD20+ CD27-	CONC	GI/L
PLASMA	FLWPLSM	CDX136	Naïve CD20+ CD27-	%CD19+	%
PLASMA	FLWPLSM	CDX136	Naïve CD20+ CD27-	EVENTS	EVENTS
PLASMA	FLWPLSM	CDX137	Memory CD20+ CD27+	CONC	GI/L
PLASMA	FLWPLSM	CDX137	Memory CD20+ CD27+	%CD19+	%
PLASMA	FLWPLSM	CDX137	Memory CD20+ CD27+	EVENTS	EVENTS
PLASMA	FLWPLSM	CDX141	Activated CD20+ CD69+	CONC	GI/L
PLASMA	FLWPLSM	CDX141	Activated CD20+ CD69+	%CD19+	%
PLASMA	FLWPLSM	CDX143	Plasma CD20- CD138+	CONC	GI/L
PLASMA	FLWPLSM	CDX143	Plasma CD20- CD138+	%CD19+	%
PLASMA	FLWPLSM	CDX143	Plasma CD20- CD138+	EVENTS	EVENTS
PLASMA	FLWPLSM	CDX145	Plasmacytoid CD20+ CD138+	CONC	GI/L
PLASMA	FLWPLSM	CDX145	Plasmacytoid CD20+ CD138+	%CD19+	%
PLASMA	FLWPLSM	CDX145	Plasmacytoid CD20+ CD138+	EVENTS	EVENTS
PLASMA	FLWPLSM	CDX156	SLE Subset CD27+CD38+CD19+	CONC	GI/L
PLASMA	FLWPLSM	CDX156	SLE Subset CD27+CD38+CD19+	%CD19+	%
PLASMA	FLWPLSM	CDX156	SLE Subset CD27+CD38+CD19+	EVENTS	EVENTS

[1]Note: The SI data for Activated B-cells includes BICATCD=CDX141 for its concentration and %CD19 records, and CDX155 for its EVENTS record. For all other B-cell subsets, the BICATCD is the same for all 3 records.

B-cell unit conversions and Normalization of Rare B-cell Subsets

The Benlysta program standard is to report common B-cells (CD19, CD20, naïve, and memory) in counts per microliter (uL). Common B-cells are not normalized but they must be converted to uL for reporting. To convert values reported from GI/L (= 10^9/L) to count per uL (= cells/mm^3), multiply the value by 10^3 or 1000.

Example: (0.25 GI/L) x (1000) = 250/uL

Rare B-cell subsets are reported in counts per milliliter (mL). Rare B-cell subsets reported in GI/L will be converted to cells/ml using the following formula:

Normalized count/mL = (rare cell events) / (CD19+ events) * (CD19+ count/uL) * 1000

Note, the total B-cell (CD19+) concentration from the TBNK panel should be converted to count/uL prior to the normalization and conversion of the Rare B-cell subset.

Example: Normalization and conversion of Plasma CD20-CD138+ to count/mL

Given:

- Plasma CD20-CD138+ number of events = 16
- CD19+ number of events on Plasma panel = 10250
- CD19+ concentration on TBNK panel = 0.35 GI/L

Then:

Plasma CD20-CD138+ Normalized (count/mL) = 16 / 10250 * (0.35*1000) * 1000 = 546.34 count/mL

Reporting B cell subsets

The table below includes variables, labels and details of derivations used in the reporting of the B-cell subsets for this study.

B-cell subset label for displays	Lab Test Code (LBTESTCD)	Derivation for Normalization and / or Conversion of B-cell Subsets
Common B-cells		
CD19 (/uL)	CD19	May require conversion to /uL
CD20 (/uL)	CD20	May require conversion to /uL
Naive CD19+CD20+CD27- (/uL)	CDX136	May require conversion to /uL
Naive CD19+CD20+CD27- (%CD19)	CDX13619	N/A
Memory CD19+CD20+CD27+ (/uL)	CDX137	May require conversion to /uL
Memory CD19+CD20+CD27+ (%CD19)	CDX13719	N/A
Rare B-cells		
Activated CD19+CD20+CD69+ Normalized (COUNT/mL)	CDX141N	CDX155 EVENTS, CD19 EVENTS from Plasma Panel and CD19 concentration from TBNK Panel

Plasma CD19+CD20-CD138+ Normalized (COUNT/mL)	CDX143N	CDX143 EVENTS, CD19 EVENTS from Plasma Panel and CD19 concentration from TBNK Panel
Plasmacytoid CD19+CD20+CD138+ Normalized (COUNT/mL)	CDX145N	CDX145 EVENTS, CD19 EVENTS from Plasma Panel and CD19 concentration from TBNK Panel
SLE Subset CD19+CD38b+CD27b+Lymph Normalized (COUNT/mL)	CDX156N	CDX156 EVENTS, CD19 EVENTS from Plasma Panel and CD19 concentration from TBNK Panel

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	Subject study completion (i.e. as specified in the protocol) was defined as s • Treatment holiday group: completion of the 24-week treatment holiday period plus the belimumab re-introduction treatment period to Week 52. • Control and long-term discontinuation groups: completion of all visits to Week 52. For reporting purposes, withdrawal from the maintenance phase is defined in Section 13.6.2. Withdrawn subjects were not replaced in the study 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 Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

13.7.2. 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 and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
LOCF	• In the LOCF dataset, missing values will be carried forward from the previous, non-missing available on-treatment assessment. • For the TH group, LOCF will not be applied across the TH and RS phases.
SLICC/ACR Damage Index	• Missing data due to prohibited medication or study withdrawal will be imputed using LOCF • For the TH group, LOCF will not be applied across the TH and RS phases.
SELENA SLEDAI,	• Missing data will be imputed using LOCF. • For the TH group, LOCF will not be applied across the TH and RS phases.

Element	Reporting Detail
Rebound, PGA	• If an individual SELENA SLEDAI item data is missing at the first timepoint in the RS phase, the item will be considered not present.
Reduction in Daily Prednisone Dose	• The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication prior to a scheduled visit, the subject will be considered a non-responder (i.e. no reduction in prednisone) for that and subsequent visits.
Average daily prednisone dose	• Observed data will be used with no imputation.
Auto-antibodies, immunoglobulins, biomarkers, BLyS protein	• Observed data will be used with no imputation
Immunogenicity	• Observed data will be used with no imputation.

13.7.2.1. 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 allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the Day 0 visit date (LTD and TH arms) or the study treatment start date (TC arm) will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications and Medical History	• 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 treatment and if the month and year are the same or later, then the medication will be considered concomitant.

13.7.3. Handling of Prohibited Medications, Withdrawals and Deaths

Element	Reporting Detail
Time to SFI Flares	• Evaluated up to Week 52 • If a subject takes a prohibited medication during the time period being analyzed, the subject will be considered as having a SFI flare at the start date of the prohibited medication. • If a subject withdraws from the study, the will be censored at last flare assessment date • If a subject dies, censor at the date of death
Time to Renal Flare	• Evaluated up to Week 52 • If a subject withdraws from the study, the will be censored at last renal flare assessment date • If a subject dies, censor at the date of death
Number of SFI Flares	• If a subject withdraws from the study, dies or takes a prohibited medication, the subject will be considered as having a SFI flare.
Number of days of daily prednisone dose ≥7.5 mg/day and/or increased by 25%	• The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication, the subject will be considered to have met this endpoint criteria (i.e, dose ≥ 7.5 mg/day and/or increased by 25%) after the date of dropout or the date that the medication is started, whichever comes first, up until the visit date, and for those days in intervals for subsequent attended visits. Before this date, the evaluated endpoint will be assessed using available data.
Number of days of daily prednisone dose ≤7.5 mg/day and/or decreased by 25%	• The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication, the subject will be considered a non-responder for this endpoint criteria (i.e., dose >7.5 mg/day and/or did not decreased by 25%) after the date of dropout or the date that the medication is started, whichever comes first, and for those days in intervals for subsequent attended visits. Before this date, the evaluated endpoint will be assessed using available data.
Reduction in Daily Prednisone Dose	• The Dropout (DO)/Prohibited Medication (PM)=Non-responder (NR) imputation will be applied. If a subject withdraws from the study and/or receives a protocol-prohibited medication prior to a scheduled visit, the subject will be considered a non-responder (i.e. no reduction in prednisone) for that and subsequent visits.

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

The following laboratory parameters are collected per the protocol.

<table>
<tr><th>Hematology</th><th>Urinalysis</th><th>Modified Chem-20</th></tr>
<tr><td>Total white blood cell count
Differential:
Absolute Neutrophils
Segmented Neutrophils
Band Neutrophils
Myelocytes
Metamylocytes
Promyelocytes
Lymphocytes
Monocytes
Eosinophils
Basophils
Hemoglobin
Hematocrit
Red blood cell (RBC) count
Platelet count
Prothrombin time (PT)
Partial thromboplastin time (PTT)</td><td>Protein
Glucose
Ketones
Occult blood
Microscopic examination including:
WBC per hpf
RBC per hpf
Dysmorphic RBC
Casts (specified by type e.g., RBC, WBC)
Spot Urine (protein : creatinine ratio)
Urine Pregnancy</td><td rowspan="4">Electrolytes:
Sodium
Potassium
Magnesium
Chloride
Carbon dioxide
Calcium adjusted for Albumin
Inorganic Phosphate

Enzymes:
SGOT (AST)
SGPT (ALT)
Alkaline Phosphatase
Gamma glutanyl transpeptidase (GGT)
Lactic dehydrogenase (LDH)

Other:
Creatinine
Blood urea nitrogen (BUN)
BUN/creatinine ratio
Bilirubin, total
Protein, total
Albumin
Uric acid
Glucose
Hepatitis B Viral DNA PCR Quantitative (HBV DNA)
Estimated Creatinine Clearance/ GFR (Cockroft-Gault)

Liver event follow-up assessments:
Hepatitis A IgM antibody
HBsAg and hep B Core antibody (IgM)
Hepatitis C RNA
Hepatitis delta antibody
Cytomegalovirus IgM antibody
Epstein-Barr viral capsid antigen IgM antibody
Hepatitis E IgM antibody
CPK
Anti-smooth muscle antibody
Type 1 anti-liver kidney microsomal antibodies
PK
IgG
Fractionated bilirubin
Serum acetaminophen</td></tr>
<tr><td colspan="2">Biological Markers</td></tr>
<tr><td colspan="2">BLyS protein
Serum complement (C3 and C4)
B-cell subtypes

Immunoglobulins
Serum immunoglobulin isotypes: IgG, IgM, IgA

Immunogenicity</td></tr>
<tr><td colspan="2">Autoantibodies
ANA
Anti-dsDNA
aCL</td></tr>
</table>

13.8.2. Adverse Event and Laboratory Value Severity Grade Tables

HEMATOLOGY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin	> 9.5 - 11.0 g/dL	> 8.0 – 9.5 g/dL	6.5 - 8.0 g/dL	< 6.5 g/dL
Leukocytes	3000-3999/mm3	2000-2999/mm3	1000-1999/mm3	< 1000/mm3
Absolute Neutrophil Count	1500-1999/mm3	1000-1499/mm3	500-999/mm3	< 500/mm3
Platelets	75,000 - 99,999/mm3	50,000 – 74,999/mm3	25,000 - 49,999/mm3	< 25,000/mm3
Prothrombin Time (PT)	> 1.0-1.25 x ULN*	> 1.25-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0 x ULN
Partial Thromboplastin Time (PTT)	> 1.0-1.66 x ULN	> 1.66-2.33 x ULN	> 2.33-3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0-10.0 %	10.1-15.0 %	15.1-20.0 %	> 20%
				(continued)

1. *ULN = Upper Limit of Normal Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out patient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused
Modified from DMID Adult Toxicity Tables, 2001(continued)				

Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium				
Hyponatremia	130-135 meq/L	123-129 meq/L	116-122 meq/L	< 116 meq/L
Hypernatremia	146-150 meq/L	151-157 meq/L	158-165 meq/L	> 165 meq/L
Potassium				
Hypokalemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalemia	5.6-6.0 meq/L	6.1-6.5 meq/L	6.6-7.0 meq/L	> 7.0 meq/L
Phosphate				
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL	1.0-1.4 mg/dL	< 1.0 mg/dL
Calcium- (Corrected For Albumin)				
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2-1.4 meq/L	0.9-1.1 meq/L	0.6-0.8 meq/L	< 0.6 meq/L
Albumin				
Hypoalbuminemia	3.00-3.49 g/dL	2.50-2.99 g/dL	2.00-2.49 g/dL	< 2.00 g/dL
Bilirubin (Total)				
Hyperbilirubinemia (Total)	> 1.0-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5-5 x ULN	> 5 x ULN
Glucose				
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycemia	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
(nonfasting & no prior diabetes)				
Triglycerides	151-399 mg/dL	400-750 mg/dL	751-1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES (continued)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric Acid				
Hyperuricemia	7.5-10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	> 15.0 mg/dL
Liver Transferases (AST, ALT, and GGT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Pancreatic Enzymes				
Amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
*Hypoglobulinemia (IgG)**	550-700 mg/dL	400-549 mg/dL	250-399 mg/dL	< 250 mg/dL

(continued)

1. *Eibl , 1995; Goldfarb, 2001; Yamini, 2001. Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

GASTROINTESTINAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalization required for IV treatment req
Diarrhea	Mild or transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting (continued)

Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
RESPIRATORY	MILD	MODERATE	SEVERE	POTENTIALLY LIFE-THREATENING
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalizes with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalization with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O2 therapy

Adverse Event and Laboratory Value Severity Grade Tables (continued)

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dispstick				
Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 Hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 to < 10 RBC/hpf	Gross, No clots ≥ 10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required
				(continued)
RBC = red blood cell; hpf = high power field. Modified from DMID Adult Toxicity Tables, 2001				

Adverse Event and Laboratory Value Severity Grade Tables (continued)

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self
				(continued)

Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood		none	Severe mood changes requires medical intervention	Acute psychosis requiring hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk
				(concluded)

Modified from DMID Adult Toxicity Tables, 2001

13.9. Appendix 9: Adverse Events of Special Interest

The primary source for rules governing identification, adjudication, and reporting of Adverse Events of Special Interest is the Program Safety Analysis Plan (PSAP). AESI are defined using preferred terms from the current version of MedDRA. The intent is to update these definitions semi-annually using the newest MedDRA version. Preferred terms used in the current and prior versions of MedDRA can be found in IMMS at the following path /Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_201.csv.

13.9.1. Malignant neoplasms

Malignant neoplasms are identified using the sub-SMQs of Malignant or unspecified tumours (20000091), malignancy related conditions (20000092), haematological malignant tumours (20000227), non-haematological malignant tumours (20000228), haematological tumours of unspecified malignancy (20000229) and non-haematological tumours of unspecified malignancy (20000230) under the current version of MedDRA. The sub-SMQ of Malignant or unspecified tumours contains two further subcategories: "Malignant Tumours" and "Tumours of unspecified malignancy." Tumours of unspecified malignancy will be reviewed by GSK and identified as malignant or non-malignant for reporting.

Malignancies other than those in the "Tumours of unspecified malignancy" category will be categorized as hematologic, skin, or solid, based on a CMQ developed by the MAH. In addition, the following customizations have been made since MedDRA v19.1:

- The term "Paraneoplastic glomerulonephritis" has been removed from the SMQ as it is a complication of malignancy.
- The term "Mismatch repair cancer syndrome" has been added as a tumour of unspecified malignancy
- The term "Malignant meningioma metastatic" has been added as a solid tumor type.
- The term "Marginal zone lymphoma recurrent" has been added as a hematological tumor type.
- The term "Skin neoplasm bleeding" has been added as a tumour of unspecified malignancy.
- The term "Astroblastoma" has been added as a solid tumour type.
- The term "Epstein Barr virus positive mucocutaneous ulcer" has been added as a hematological tumour type.
- The term "Langerhans cell sarcoma" has been added as a solid tumour type.
- The term "Naevoid melanoma" has been added as a skin tumour type.
- The term "Nasopharyngeal cancer metastatic" has been added as a solid tumour type.
- The term "Phospaturic mesenchymal tumour" has been added as a solid tumour type.
- The term "Primary gastrointestinal follicular lymphoma" has been added as a hematological tumour type.

- The term “Squamous cell breast carcinoma” has been added as a solid tumour type.
- The term “Transformation to acute myeloid leukaemia” has been added as a hematological tumour type.
- The term “FIP1L1/PDGFR alpha fusion kinase positive” has been added as a hematological tumour type.
- The term “Gleason grading score” has been added as a solid tumour type.
- The term “Oncotype test” has been added as a solid tumour type.
- The term “Intestinal metastasis” has been added as an unspecified tumour type.
- The term “Maternal cancer in pregnancy” has been added as an unspecified tumour type.
- The term “Microsatellite instability cancer” has been added as an unspecified tumour type.
- The term “Pulmonary tumour thrombotic microangiopathy” has been added as an unspecified tumour type.
- The term “Tumour cavitation” has been added as an unspecified tumour type.
- The term “Malignant urinary tract obstruction” has been added as a solid tumour type.

Non-melanoma skin cancer (NMSC) will be categorized using a CMQ developed by the Marketing authorization holder (MAH)

Note beginning with MedDRA v20.0 in 2017, there will be two new sub-SMQs of Hematological Malignancies. These do not result in any changes to how malignant neoplasms are identified.

13.9.2. Post-infusion systemic reactions

Post-infusion systemic reactions will be identified using a customization of the Anaphylactic Reaction SMQ (20000021). This SMQ includes a broad list of preferred terms including symptoms of systemic injection/infusion reactions and hypersensitivity reactions and anaphylaxis. For the Anaphylactic Reaction query, 4 categories of preferred terms are considered, including a set of core anaphylactic terms (Category A), upper airway/respiratory terms (Category B), angioedema/urticaria/pruritus/flush terms (Category C), and cardiovascular/hypotension terms (Category D).

The customizations of the SMQ involve terms in Categories A, B and C. Category A has been modified to include the following additional terms: “Infusion-related reaction”, “Drug hypersensitivity”, “Hypersensitivity”, and “Urticarial vasculitis”. Category B has been modified to include the following additional terms: “Oropharyngeal oedema” and “Pharyngeal oedema”. Category C has been modified to include the following additional term: “Fixed eruption”. GSK has also removed three terms that are not relevant for an analysis of hypersensitivity reactions to belimumab (“Anaphylactic transfusion reaction”, “Dialysis membrane reaction”, and “First use syndrome”). Anaphylactic transfusion reaction is an adverse event associated with a blood transfusion, not related to study

medication. First use syndrome and dialysis membrane reaction are associated with adverse events related to kidney transplants and dialysis, not related to study medication.

Algorithmic Search Criteria

The post-infusion systemic reactions per Anaphylactic Reaction SMQ algorithmic search are defined as follows:

Subjects must have the following associated with the same infusion/injection:

a. at least 1 AE coding to a Category A preferred term *or*

b. 2 AEs, 1 coding to a Category B preferred term and the other coding to a Category C preferred term *or*

c. 2 AEs, 1 coding to a Category D preferred term and the other coding to either a Category B preferred term or to a Category C preferred term.

For the algorithmic search, if any event at a given infusion/injection meets the definition under criteria a, b or c, then all events in Categories A, B, C and D associated with that injection/infusion will be considered AESI.

For CSR reporting, all post-infusion systemic reaction AESIs defined via narrow, broad, or algorithmic search, the AEs need to have occurred on the day of an infusion/injection or within 3 days after an infusion/injection. See Section 13.3.4 for the definition of the 3-day assessment window. GSK will review all serious events identified via the broad search occurring within 21 days after an infusion/injection, and adjudicate these events as post-infusion systemic reactions or hypersensitivity reactions per the criteria in Section 13.9.10.2. Adverse events with partial or missing start dates will be included unless there is evidence through comparison of partial dates to suggest otherwise.

Sampson Criteria

Sampson et al define anaphylaxis as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance. In addition, one of the following 3 criteria must be met: (1) acute onset of illness with involvement of skin or mucosal tissue, accompanied with either respiratory compromise, reduced blood pressure, or hypotension-related symptoms of end-organ dysfunction (2) reduced blood pressure associated with a known allergen or (3) two or more of the following that occur rapidly after exposure to an allergen: a) involvement of skin-mucosal tissue b) respiratory compromise c) reduced blood pressure d) persistent GI symptoms.

With the exception of GI symptoms, all symptoms required to assess anaphylaxis per Sampson criteria would be identified by Broad Anaphylaxis SMQ or the Anaphylactic Reaction SMQ algorithmic. Therefore, any events falling under the below criteria will be adjudicated by GSK prior to database release to determine if serious anaphylaxis per Sampson criteria is met.

Possible cases of serious anaphylaxis per Sampson criteria will be identified as follows:

a. Any Infusion/Injection-related Reaction per Anaphylactic Reaction SMQ broad

search SAE which occurs on the day of an injection.

b. Any AE or SAE in the "Gastrointestinal disorders" SOC that occurs on the day that criterion in a) above is met.

c. Any anaphylaxis and hypersensitivity reactions per Anaphylactic Reaction SMQ algorithmic search SAE which occurs on the day of an infusion/injection.

13.9.3. Infections

The infections of special interest are described below.

13.9.3.1. Opportunistic Infections

Opportunistic infections will be identified using a broad CMQ developed by the MAH. Any events falling under these preferred terms will be adjudicated by GSK prior to database release to determine if criteria are met for an opportunistic infection, per the criteria in Section 13.9.10.3.

13.9.4. Mycobacterium Tuberculosis

Tuberculosis events will be identified using a CMQ developed by the MAH. Any events falling under these preferred terms will be adjudicated by GSK prior to database release to determine if criteria are met for an opportunistic infection (Section 13.9.10.3).

13.9.5. Herpes Zoster

Herpes Zoster events will be identified using a CMQ developed by the MAH. Additional manual adjudication by GSK prior to database release will identify events that are recurrent or disseminated (Section 13.9.10.3).

13.9.6. Pneumonia

Pneumonia events will be identified using a CMQ developed by the MAH. Pneumonia events will not be reported separately, but are being flagged in the event further evaluation is necessary.

13.9.7. Sepsis

Sepsis events will be identified using a CMQ developed by the MAH.

13.9.8. Depression/suicide/self-injury

13.9.8.1. Depression (excluding suicide and self-injury)

Depression events will be identified using a CMQ including the preferred terms from the depression (excluding suicide and self injury) SMQ (20000035) plus additional terms added by the MAH.

13.9.8.2. Suicide and Self-Injury

Suicide and self-injury events will be identified using the SMQ (20000035) preferred terms.

13.9.9. Fatalities

All fatalities will be identified in the clinical database and subsequently adjudicated by the GSK SRT into a general category of death (Section 13.9.10.5).

Post-study fatalities that are captured in ARGUS prior to CSR approval, but are not captured in the clinical database, will be described within the CSR text but cannot be included in statistical post-text displays.

13.9.10. GSK SRT Adjudication of Adverse Events of Special Interest

Adverse events of special interest (AESI) are identified per the preferred terms and other criteria described in Section 13.9. The following AESI are adjudicated at the subject level by the GSK SRT during regular SRT meetings or during quarterly adjudication. The adjudication occurs prior to database release and is performed for reporting purposes, per the criteria described below.

Assignment of adjudication flags in the clinical database will occur as part of the quarterly SRT review process. In addition, as part of individual study close-out procedures, the adjudications should be finalized as follows:

- Just preceding data base release (DBR), allowing time to send queries or update the eCRF/database as necessary prior to DBR.
- After DBR to provide final confirmation of adjudications and ensure there are no new AESI or relevant data changes to adjudicated events since the pre-DBR adjudication. This would be a requirement for declaring data a freeze (DBF).

13.9.10.1. Malignancies

All malignancies identified via the preferred terms will be reviewed by GSK SRT. The classification of malignancies as solid tumor, hematological, and skin will be reviewed against the verbatim term to confirm an appropriate and accurate preferred term has been assigned, or to recommend follow-up with the investigator for additional specificity on the verbatim term. In addition, malignancies that are flagged more than once, e.g., based on a term for both a diagnostic procedure and a diagnosis, will be adjudicated as one event.

Tumors of unspecified malignancy, as identified via preferred terms, will be reviewed clinically by the GSK SRT for reporting. In general, non-serious events in the tumours of unspecified malignancy with insufficient information will be categorized as not malignant. Serious adverse events with insufficient information will be categorized as either not malignant or malignant based on the type of tumor and likelihood the tumor type is malignant (e.g., thyroid nodules are common in SLE patients and are generally not

malignant; tumor types with higher likelihood for malignancy would be assumed to be malignant).

13.9.10.2. Serious hypersensitivity and post-infusion systemic reactions

Before the data base is released, GSK SRT will review all serious cases identified from the Broad Anaphylaxis SMQ as described in Section 13.9, applying clinical judgment to determine if the preferred terms are indicative of a hypersensitivity or infusion/injection reaction. Time to onset after an infusion/injection and details provided in the clinical narratives with respect to the nature and likely cause of the events are taken into consideration. Time to onset within 24 hours is generally applied to post infusion/injection reactions. The GSK SRT adjudicates serious hypersensitivity reactions into a category based primarily on time to onset: acute (onset ≤ 1 day), delayed acute (onset 2-3 days), or delayed, non-acute (onset 4-21 days). In addition to time to onset, description of associated symptoms is taken into account for this categorization.

In addition, possible cases of serious anaphylaxis per Sampson criteria will be identified per the criteria in Section 13.9. Any events falling under these criteria will be adjudicated by GSK prior to database release to determine if serious anaphylaxis per Sampson criteria is met.

13.9.10.3. Potential opportunistic infections

Opportunistic infections (OIs) will be identified using a list of preferred terms, designed to cast a wide net for events potentially indicative of an opportunistic infection. Any identified events will be adjudicated by the GSK SRT prior to database release to determine if criteria are met for an opportunistic infection. Targeted follow-up is sought for events with insufficient information. In general, potential OIs that are non-serious with insufficient information to adjudicate will be considered non-opportunistic. Potential OI SAEs with insufficient information to adjudicate will be considered opportunistic. See below for a list of agreed upon pathogens and infections considered to be opportunistic for the purpose of adjudication.

Pathogens and Infections Considered Opportunistic:

- Acinetobacter infection
- Aspergillosis
- Blastomycosis, extrapulmonary
- Candidiasis of esophagus, bronchi, trachea or lungs
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis infection, chronic intestinal (greater than 1 month duration)
- CMV disease other than liver, spleen, or nodes
- Herpes simplex – bronchitis, pneumonitis, or esophagitis
- Herpes Zoster (adjudication details are below)
- Histoplasmosis disseminated or extrapulmonary
- Human polyomavirus infection
- Isosporiasis, chronic intestinal (greater than one month duration)

- Listeriosis
- Mycobacterium avium complex or M. Kansasii, disseminated or extrapulmonary
- Nocardiosis
- Other non-tuberculous mycobacterium (NTM) infections (other species or unidentified species), disseminated or extrapulmonary*
- Polyomavirus (JC virus or BK virus) associated nephropathy (including PML)
- Pneumocystis jiroveci infection
- Toxoplasmosis of brain

* Extra pulmonary NTM infections are generally considered an OI unless the affected extra pulmonary area followed a wound or trauma.

In addition, GSK SRT will review all SAEs, including those coded under preferred terms not in the preferred term definition, and utilizing the supplemental/narrative information, will adjudicate the SAEs as OI if warranted based on medical judgment.

Other Infections of Interest but not generally considered opportunistic:

- Mycobacterium tuberculosis (adjudication details are below)

Herpes Zoster

Herpes Zoster events will be identified per preferred terms. Adjudication by GSK SRT will identify events that are recurrent or disseminated. Herpes Zoster is considered disseminated if there is involvement of other organs other than the skin or if skin lesions (1) cross the midline of the body or (2) are in non-adjacent dermatomes or (3) are located in more than three adjacent dermatomes. Herpes zoster is considered an opportunistic infection if it is adjudicated as recurrent or disseminated. However, there may be some uncommon occurrences of a herpes zoster case that is adjudicated as an OI but is neither recurrent or disseminated.

Mycobacterium Tuberculosis

Tuberculosis (TB) cases are reviewed by the GSK SRT to determine if a case is an OI. The following principles are applied: Pulmonary TB in an endemic area is not considered an OI. Pulmonary TB in a non-endemic area would be considered an OI unless the subject had close contact with a person infected with TB. Extra pulmonary TB is generally considered an OI unless the affected extra pulmonary area followed a wound or trauma.

13.9.10.4. Suicide/self-injury

Suicide and self-injury SAEs will be identified using the preferred terms and subsequently adjudicated into the following categories:

Adjudicated Category
Suicidal Behaviour
Completed Suicide
Suicidal Ideation
Self-Injurious Behaviour without Suicidal Intent

In addition, GSK SRT will review all SAEs, including those coded under preferred terms not in the definition, and utilizing the supplemental/narrative information, will adjudicate the SAEs as suicide/self-injury if warranted based on medical judgment.

13.9.10.5. Fatalities

All fatalities will be identified in the clinical database and subsequently adjudicated by the GSK SRT into a general category of death.

All fatalities will be adjudicated into one of the following categories:

Adjudicated Category of Death
SLE-Related
Infectious
Vascular
Gastrointestinal
Respiratory
Malignancy
Hypersensitivity
Suicide
Surgical Complication
Unknown
Hematologic
Trauma

Additional ‘categories of death’ may be added in the future should a fatality not clearly fit into one of the ‘categories’ listed above. The ‘categories’ will not change unless agreed upon by the GSK SRT.

13.10. Appendix 10: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
aCL	Anti-cardiolipin Antibody
ACR	American College of Rheumatology
AE	Adverse Event
AESI	AEs of Special Interest
Anti-dsDNA	Anti-double-stranded DNA
ANA	Anti-nuclear Antibody
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
C3 / C4	Complement 3 / Complement 4
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CS	Clinical Statistics
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DO	Dropout
DOB	Date of Birth
DP	Decimal Places
DQE	Data Quality Evaluation Report
eCRF	Electronic Case Report Form
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
GUI	Guidance
hpf	High-power Field
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IgA, G, M	Immunoglobulin A, G, M
IM	Intramuscular
IMMS	International Modules Management System
ITT	Intention-to-treat
IV	Intravenous
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification
LTD	Long-term discontinuation
MedDRA	Medical Dictionary for Regulatory Activities
MHE	Mental Health Enhanced Score
NMSC	Non-melanoma skin cancer
NR	Non-responder
OI	Opportunistic Infections
PCI	Potential Clinical Importance
PD	Pharmacodynamic

Abbreviation	Description
PDMP	Protocol Deviation Management Plan
PGA	Physician's Global Disease Assessment
PK	Pharmacokinetic
PM	Prohibited medication
PopPK	Population Pharmacokinetic
PSAP	Program Safety Analysis Plan
PT	Preferred Term/Prothrombin Time
PTT	Partial thromboplastin Time
QC	Quality Control
RAP	Reporting and Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red blood cell
RS	Re-start Phase
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SELENA	Safety of Estrogen in Lupus National Assessment
SI	System independent
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operation Procedure
SS	SELENA SLEDAI
TC	Treatment Control
TH	Treatment Holiday
TLFs	Tables, Listings, and Figures
TX	Treatment
ULN	Upper Limit of Normal
uPCR	Urine Protein: Creatinine Ratio.
VAS	Visual Analogue Scale
WOCF	Worst Observation Carried Forward

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
BENLYSTA
BLyS

Trademarks not owned by the GlaxoSmithKline Group of Companies
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13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.17	1.1 to 1.1
Efficacy	2.1 to 2.12	2.1 to 2.3
Safety	3.1 to 3.52	3.1 to 3.6
Pharmacokinetic	4.1 to 4.1	4.1 to 4.2
Biomarker	5.1 to 5.23	5.1 to 5.10
Section	**Listings**	
ICH Listings	1 to 39	
Other Listings	40 to 51	

13.11.2. Deliverables

Priority	Description
H	Included in Headline Data Package

13.11.3. Study Population Tables

Study Population Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results denoted by H**
Subject Disposition				
1.1.	ITT	Subject Enrollment		
1.2.	ITT	Enrolment by Country and Site	EudraCT/Clinical Operations	
1.3.	Screened	Study Populations	IDSL	
1.4.	Screened	Screening Status and Reasons for Failing Screening	Journal Requirements	
1.5.	ITT	Subject Disposition for the Subject Conclusion Record (52-Week Treatment Phase)	ICH E3, FDAAA, EudraCT	
1.6.	ITT	Subject Disposition for the Subject Conclusion Record (Maintenance Phase)	ICH E3, FDAAA, EudraCT	
1.7.	ITT	Time to Withdrawal from the Study	Benlysta Standard	
1.8.	ITT	Subject Disposition at Each Study Epoch	ICH E3	
Protocol Deviation				
1.9.	ITT	Subjects with Important Protocol Deviations	ICH E3	
Demographic and Baseline Characteristics				
1.10.	ITT	Demographic and Baseline Characteristics	ICH E3, FDAAA, EudraCT	H
1.11.	ITT	Age Ranges	EudraCT	
1.12.	ITT	Race and Racial Combination Details	ICH E3, FDA, FDAAA, EudraCT	
Current and Prior Medical History				
1.13.	ITT	General Medical History	ICH E3	

Study Population Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results denoted by H**
Baseline Disease Activity and SLE Medication Use				
1.14.	ITT	Baseline Disease Activity	Benlysta Standard	H
1.15.	ITT	SELENA SLEDAI Organ and Item Involvement at Baseline	Benlysta Standard	H
1.16.	ITT	Allowable SLE Medication Usage at Baseline	Benlysta Standard	
1.17.	ITT	Steroid, Anti-malarial and Immunosuppressant Use at Baseline	Benlysta Standard	

13.11.4. Study Population Figures

Study Population: Figure				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Time to Withdrawal				
1.1	ITT	Time to Withdrawal	Study Population	H

13.11.5. Efficacy Tables

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results denoted by H**
Flares				
2.1.	ITT	Time to First SFI Flare to Week 52	Primary endpoint	H
2.2.	ITT	SFI Flares per Subject-year from Day 0 to Week 52	Secondary endpoint	
2.3.	ITT	Time to First SFI Severe Flare to Week 52	Secondary endpoint	H
2.4.	ITT	Time to First Renal Flare to Week 52	Exploratory endpoint	H
2.5.	ITT	Time to First Renal Flare to Week 52 [1] Among Subjects with Baseline Proteinuria >0.5g/24hr Equivalent	Exploratory endpoint	
Rebound and SELENA-SLEDAI				
2.6.	ITT	SELENA SLEDAI Rebound (LOCF) (52-Week Treatment Phase)	Secondary endpoint	H
2.7.	ITT	SELENA SLEDAI Change from Baseline (LOCF) (52-Week Treatment Phase)	Secondary endpoint	
PGA				
2.8.	ITT	PGA Change from Baseline (52-Week Treatment Phase)	Other/exploratory endpoint	
Prednisone				
2.9.	ITT	Number of Days of Daily Prednisone Dose >=7.5 mg/day and/or Increased by 25%	Secondary endpoint	
2.10.	ITT	Number of Days of Daily Prednisone Dose <=7.5 mg/day and/or Decreased by 25%	Secondary endpoint	

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results denoted by H**
2.11.	ITT	Prednisone Percent Change from Baseline (52-Week Treatment Phase)	Other/exploratory endpoint	
2.12.	ITT	Prednisone Reduced to <= 7.5 mg/day by Visit (DO/TF=NR) among Subjects with Baseline Prednisone Dose > 7.5 mg/day (52-Week Treatment Phase)	Other/exploratory endpoint	

13.11.6. Efficacy Figures

Efficacy: Figures				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Flares				
2.1.	ITT	Time to First SFI Flare to Week 52	Primary endpoint	H
2.2.	ITT	Time to First Severe SFI Flare to Week 52	Secondary endpoint	H
Rebound and SELENA-SLEDAI				
2.3.	ITT	SELENA SLEDAI Change from Baseline by Visit (LOCF) (52-Week Treatment Phase)	Secondary endpoint	

13.11.7. Safety Tables

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
Concomitant Medications				
3.1.	ITT	Concomitant Medications by ATC Level 1 and ATC Level 4 Term for the 52-Week Treatment Phase	ICH E3	
Study Agent Exposure				
3.2.	ITT	Study Agent Exposure (52-Week Treatment Phase)	ICH E3	
SLICC				
3.3.	ITT	SLICC/ACR Damage Index Change from Baseline (52-Week Treatment Phase)	Other/exploratory endpoint	
Adverse Events				
3.4.	ITT	Adverse Events (52-Week Treatment Phase)	Benlysta standard	H
3.5.	ITT	Adverse Events by SOC (52-Week Treatment Phase)	Benlysta standard	
3.6.	ITT	Serious Adverse Events by SOC (52-Week Treatment Phase)	Benlysta standard	
3.7.	ITT	Study Agent Related Adverse Events by SOC (52-Week Treatment Phase)	Benlysta standard	
3.8.	ITT	Adverse Events Resulting in Study Agent Discontinuation by SOC (52-Week Treatment Phase)	Benlysta standard	

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
3.9.	ITT	Adverse Events by SOC and PT (52-Week Treatment Phase)	ICH E3	H
3.10.	ITT	Serious Adverse Events by SOC and PT (52-Week Treatment Phase)	Benlysta Standard	H
3.11.	ITT	Study Agent Related Adverse Events by SOC and PT (52-Week Treatment Phase)	ICH E3	
3.12.	ITT	Adverse Events Resulting in Study Agent Discontinuation by SOC and PT (52-Week Treatment Phase)	IDSL	H
3.13.	ITT	Adverse Events by PT (52-Week Treatment Phase)	Benlysta Standard	
3.14.	ITT	Serious Adverse Events by PT (52-Week Treatment Phase)	Benlysta Standard	
3.15.	ITT	Study Agent Related Adverse Events by PT (52-Week Treatment Phase)	Benlysta Standard	
3.16.	ITT	Adverse Events Resulting in Study Agent Discontinuation by PT (52-Week Treatment Phase)	Benlysta Standard	
3.17.	ITT	Common (>5%) Non-Serious Adverse Events by SOC and PT (52-Week Treatment Phase) (Number of Subjects and Occurrences)	FDAAA, EudraCT	
3.18.	ITT	Serious Adverse Events by SOC and PT (52-Week Treatment Phase) (Number of Participants and Occurrences)	FDAAA, EudraCT	H
3.19.	ITT	Adverse Events by SOC and PT and Maximum Severity (52-Week Treatment Phase)	IDSL	

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
3.20.	ITT	Relationship Between System Organ Class and Verbatim Text (52-Week Treatment Phase)	IDSL	
3.21.	ITT	Adverse Events of Special Interest by Category (52-Week Treatment Phase)	Benlysta Standard	H
3.22.	ITT	Adverse Events of Special Interest by Category and Infusion for Treatment Holiday Group Re-Start Phase	Benlysta Standard	
Laboratory Parameters				
3.23.	ITT	Laboratory Results by Visit: Hematology (52-Week Treatment Phase		
3.24.	ITT	Laboratory Results by Visit: Liver Function (52-Week Treatment Phase)		
3.25.	ITT	Laboratory Results by Visit: Electrolytes (52-Week Treatment Phase)		
3.26.	ITT	Laboratory Results by Visit: Other Chemistries (52-Week Treatment Phase)		
3.27.	ITT	Laboratory Results by Visit: Urinalysis (52-Week Treatment Phase)		
3.28.	ITT	Laboratory Results by Visit: Immunoglobulins (52-Week Treatment Phase)		
3.29.	ITT	Worst Laboratory Toxicity Grade: Hematology (52-Week Treatment Phase)	ICH E3	

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
3.30.	ITT	Worst Laboratory Toxicity Grade: Liver Function (52-Week Treatment Phase)	ICH E3	
3.31.	ITT	Worst Laboratory Toxicity Grade: Electrolytes (52-Week Treatment Phase)	ICH E3	
3.32.	ITT	Worst Laboratory Toxicity Grade: Other Chemistries (52-Week Treatment Phase)	ICH E3	
3.33.	ITT	Worst Laboratory Toxicity Grade: Urinalysis (52-Week Treatment Phase)	ICH E3	
3.34.	ITT	Worst Laboratory Toxicity Grade: Immunoglobulins (52-Week Treatment Phase)	ICH E3	
3.35.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Hematology (52-Week Treatment Phase)	Benlysta Standard	
3.36.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Liver Function (52-Week Treatment Phase)	Benlysta Standard	
3.37.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Electrolytes (52-Week Treatment Phase)	Benlysta Standard	
3.38.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Other Chemistries (52-Week Treatment Phase)	Benlysta Standard	
3.39.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Urinalysis (52-Week Treatment Phase)	Benlysta Standard	
3.40.	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Immunoglobulins (52-Week Treatment Phase)	Benlysta Standard	
3.41.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Hematology (52-Week Treatment Phase)	Benlysta Standard	

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
3.42.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Liver Function (52-Week Treatment Phase)	Benlysta Standard	
3.43.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Electrolytes (52-Week Treatment Phase)	Benlysta Standard	
3.44.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Other Chemistries (52-Week Treatment Phase)	Benlysta Standard	
3.45.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Urinalysis (52-Week Treatment Phase)	Benlysta Standard	
3.46.	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Immunoglobulins (52-Week Treatment Phase)	Benlysta Standard	
Immunoglobulins				
3.47.	ITT	Immunoglobulin Levels below the Lower Limit of Normal (LLN) by Visit (52-Week Treatment Phase)	Benlysta Standard	
3.48.	ITT	Immunoglobulins below the Lower Limit of Normal (LLN) at each Visit among Subjects with Immunoglobulins >= LLN at Baseline (52-Week Treatment Phase)	Benlysta Standard	
3.49.	ITT	Immunoglobulins above the Lower Limit of Normal (LLN) at each Visit (52-Week Treatment Phase)	Benlysta Standard	
3.50.	ITT	Immunoglobulins above the Lower Limit of Normal (LLN) at each Visit among Subjects with Immunoglobulins <= LLN at Baseline (52-Week Treatment Phase)	Benlysta Standard	
Immunogenicity				
3.51.	ITT	Immunogenic Response by Visit (52-Week Treatment Phase)	Benlysta Standard	

Safety: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority Headline Results Denoted by H**
Vital Signs				
3.52.	ITT	Vital Signs Change from Baseline by Visit (Observed) (52-Week Treatment Phase)	ICH E3	

13.11.8. Safety Figures

Safety: Figures				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Laboratory				
3.1.	ITT	Laboratory Results by Visit: Hematology (52-Week Treatment Phase)		
3.2.	ITT	Laboratory Results by Visit: Liver Function (52-Week Treatment Phase)		
3.3.	ITT	Laboratory Results by Visit: Electrolytes (52-Week Treatment Phase)		
3.4.	ITT	Laboratory Results by Visit: Other Chemistries (52-Week Treatment Phase)		
3.5.	ITT	Laboratory Results by Visit: Other Chemistries (52-Week Treatment Phase)		
3.6.	ITT	Laboratory Results by Visit: Immunoglobulins (52-Week Treatment Phase)		

13.11.9. Pharmacokinetic Tables

Pharmacokinetic: Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Belimumab Concentrations				
4.1.	PK	Belimumab Concentrations (ug/ml)		

13.11.10. Pharmacokinetic Figures

Pharmacokinetic: Figures				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Belimumab Concentrations				
4.1.	PK	Median Belimumab Concentrations (ug/mL): 52-Week Treatment Phase		
4.2.	PK	Geometic Mean Belimumab Concentrations (ug/mL): 52-Week Treatment Phase		

13.11.11. Biomarker Tables

Biomarker Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Autoantibodies				
5.1.	ITT	Autoantibody Levels Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.2.	ITT	Autoantibody Levels Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.3.	ITT	Autoantibody Levels Change from Baseline by Visit among Subjects Positive at Baseline (Observed) (52-Week Treatment Phase)		

Biomarker Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
5.4.	ITT	Autoantibody Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (Observed) (52-Week Treatment Phase)		
5.5.	ITT	Autoantibody Levels Shift from Baseline by Visit (Observed) (52-Week Treatment Phase)		
Complement				
5.6.	ITT	Complement Levels Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.7.	ITT	Complement Levels Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.8.	ITT	Complement Levels Change from Baseline by Visit among Subjects Low at Baseline (Observed) (52-Week Treatment Phase)		
5.9.	ITT	Complement Levels Percent Change from Baseline by Visit among Subjects Low at Baseline (Observed) (52-Week Treatment Phase)		
5.10.	ITT	Complement Levels Shift from Baseline by Visit (Observed) (52-Week Treatment Phase)		

Biomarker Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Immunoglobulins				
5.11.	ITT	Immunoglobulins Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.12.	ITT	Immunoglobulins Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.13.	ITT	Immunoglobulins Change from Baseline by Visit among Subjects Low at Baseline (Observed) (52-Week Treatment Phase)		
5.14.	ITT	Immunoglobulins Percent Change from Baseline by Visit among Subjects Low at Baseline (Observed) (52-Week Treatment Phase)		
5.15.	ITT	Immunoglobulin Levels Shift from Baseline by Visit (Observed) (52-Week Treatment Phase)		
B-cells				
5.16.	ITT	B-cells Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.17.	ITT	B-cells Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.18.	ITT	B-cells Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.19.	ITT	B-cells Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.20.	ITT	B-cells Change from Week 24 by Visit (Observed) (Maintenance Phase)		

Biomarker Tables				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
5.21.	ITT	B-cells Percent Change from Week 24 by Visit (Observed) (Maintenance Phase)		
BLyS Protein				
5.22.	ITT	BLyS ProteinChange from Baseline by Visit (Observed) (52-Week Treatment Phase)		
5.23.	ITT	BLyS Protein Percent Change from Baseline by Visit (Observed) (52-Week Treatment Phase)		

13.11.12. Biomarker Figures

Biomarker Figures				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Autoantibodies				
5.1.	ITT	Autoantibody Levels Percent Change from Baseline by Visit (52-Week Treatment Phase)		
5.2.	ITT	Autoantibody Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (52-Week Treatment Phase)		
Complement				
5.3.	ITT	Complement Levels Percent Change from Baseline by Visit (52-Week Treatment Phase)		
5.4.	ITT	Complement Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (52-Week Treatment Phase)		

Biomarker Figures				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Immunoglobulins				
5.5.	ITT	Immunoglobulin Levels Percent Change from Baseline by Visit (52-Week Treatment Phase)		
5.6.	ITT	Immunoglobulin Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (52-Week Treatment Phase)		
BLyS Protein				
5.7.	ITT	BLyS Protein Percent Change from Baseline by Visit (52-Week Treatment Phase)		
B cell Subsets				
5.8.	ITT	B Cell Percent Change from Baseline by Visit (52-Week Treatment Phase)		
5.9.		B Cell Percent Change from Week 24 by Visit (52-Week Treatment Phase)		
5.10.	ITT	B Cell Absolute Values by Visit and Subject for Subjects who Enter the Maintenance Phase		

13.11.13. ICH Listings

ICH: Listings				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Subject Disposition				
1.	Screened	Reasons for Screen Failure	Journal requirements	
2.	Screened	Re-Screened Subjects		
3.	ITT	Subject Disposition and Population Status	ICH E3	
4.	ITT	Previous Trial History	ICH E3	
5.	ITT	Reasons for Study Withdrawal	ICH E3	
Protocol Deviations				
6.	Screened	Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	
7.	Screened	Important Protocol Deviations	ICH E3	
Demographic and Baseline Characteristics				
8.	ITT	Demographic and Baseline Characteristics	ICH E3	
9.	ITT	General Medical History	ICH E3	
10.	ITT	Subjects Who Took Prohibited Medications	Study specific	
Prior and Concomitant Medications				
11.	ITT	Concomitant Medications	ICH E3	
Exposure and Treatment Compliance				
12.	ITT	Study Agent Administration	ICH E3	
Adverse Events				
13.	ITT	All Adverse Events	ICH E3	

ICH: Listings				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
14.	ITT	Subject Numbers for Individual Adverse Events	ICH E3	
15.	ITT	Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	
Serious and Other Significant Adverse Events				
16.	ITT	Serious Adverse Events	Study specific/ ICH E3 (other significant events)	
17.	ITT	Deaths	ICH E3	
18.	ITT	Non-Fatal Serious Adverse Events	ICH E3	
19.	ITT	Study Treatment Related Adverse Events	Study specific/ ICH E3 (other significant events)	
20.	ITT	Adverse Events Resulting in Study Treatment Discontinuation	ICH E3	
21.	ITT	Pre-treatment Adverse Events	Study specific/ ICH E3 (other significant events)	
22.	ITT	Adverse Events of Special Interest	Study specific/ ICH E3 (other significant events)	
23.	ITT	Malignancy Adverse Events of Special Interest	Study specific/ ICH E3 (other significant events)	
24.	ITT	Reasons for Considering as a Serious Adverse Event	ICH E3	
25.	ITT	Infusion Related Systemic Reactions	Study specific	
26.	ITT	Concomitant Procedures/Surgery	Study specific	
Vital Signs				
27.	ITT	Vital Signs	IDSL	
All Laboratory				
28.	ITT	Laboratory Results: Hematology		

ICH: Listings				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
29.	ITT	Laboratory Results: Liver Function		
30.	ITT	Laboratory Results: Electrolytes		
31.	ITT	Laboratory Results: Other Chemistries		
32.	ITT	Laboratory Results: Urinalysis		
33.	ITT	Laboratory Results: Immunoglobulins		
34.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Hematology		
35.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Liver Function		
36.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Electrolytes		
37.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Other Chemistries		
38.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Urinalysis		
39.	ITT	Grade 3 or Grade 4 Laboratory Toxicity Results: Immunoglobulins		
Hepatobiliary (Liver)				
40.	ITT	Liver Monitoring Stopping Event Reporting		
41.	ITT	Medical Conditions for Participants with Liver Stopping Events		
42.	ITT	Substance Use for Participants with Liver Stopping Events		

13.11.14. Non-ICH Listings

Non-ICH: Listings				
No.	**Population**	**Title**	**Programming Notes**	**Priority**
Efficacy Endpoints				
43.	ITT	SFI Flares	Study specific	
44.	ITT	SELENA-SLEDAI Analysis Results	Study specific	
45.	ITT	Physician's Global Assessment (PGA) Analysis Results	Study specific	
46.	ITT	Average Daily Prednisone Dose	Study specific	
Immunogenicity				
47.	ITT	Immunogenicity Results	Study specific	
SLICC				
48.	ITT	SLICC/ACR Damage Index Analysis Results	Study specific	
Belimumab PK Concentration				
49.	PK	Serum Belimumab PK Concentration-Time Data	Study specific	
Biomarkers				
50.	ITT	Autoantibody and Complement Results	Study specific	
51.	ITT	B Cell Results	Study specific	

13.12. Appendix 12: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request