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

Title	:	Reporting and Analysis Plan for GSK1550188 Study BEL114333. A multicentre, continuation study of belimumab in subjects with systemic lupus erythematosus (SLE) who completed the phase III study BEL113750 in Northeast Asia or completed the open-label extension of HGS1006-C1115 in Japan.
Compound Number	:	GSK1550188
Effective Date	:	31-MAY-2019

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the final Clinical Study Report for Protocol BEL114333, which was a continuation study of belimumab in Japan and Korea subjects with systemic lupus erythematosus (SLE) who completed the phase III study BEL113750 in Northeast-Asia or who completed the open-label extension of HGS1006-C1115 in Japan (in this document referred to as GSK study number BEL112341).
- This RAP is intended to describe the evaluation of the long-term safety and efficacy of belimumab in subjects with SLE in Japan and Korea, following completion of BEL113750 and BEL112341.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1 As described in the file note sign off was by email on 31-May-2019. Details are found in the file note in TMF.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP

Purpose	• The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BEL114333, which was a continuation study of intravenous (IV) belimumab in Japan and Korea subjects with systemic lupus erythematosus (SLE) who completed the Phase III study BEL113750 in Northeast-Asia (China, Japan, Korea) or who completed the Phase III subcutaneous (SC) open-label extension of HGS1006-C1115 (Japanese subjects only).
	  • In this document, HGS1006-C1115 is referred to as GSK study number BEL112341.
	  • The complete results for all countries for study BEL112341 (using the SC formulation) and BEL113750 DB study have been previously reported.
	• The study (BEL114333) included Japan and Korea, while the OL extension of study BEL113750 included China, of which the study design was similar. Thus, the reporting of OL data will be similar for both studies.
	  • Due to process changes in China, the clinical trial permit for a separate OL extension was not available in time for China double-blind subjects to smoothly transition into study BEL114333 without interruption.
	• Per protocol amendment 3, study BEL114333 was extended to allow Japanese subjects to enter, who had completed the 6 month OL extension of BEL112341, after receiving 52 weeks of blinded SC treatment on study BEL112341.
	• The BEL114333 study RAP is intended to describe the evaluation of the long-term safety and efficacy of belimumab in subjects with SLE in Japan and Korea.

Protocol	• The BEL114333 RAP is based on the following study documents: • Protocol amendment 3 (Dated: 16/MAY/2014) of study BEL114333 (GSK Document No. YM2010/00145/03). • Final Case Report Form (eCRF) Version 3 (dated: 17/NOV/2017). • Program Safety Analysis Plan (PSAP) for GSK1550188 Version 6 (October 02 2018). Note: for reporting purposes the most current version of the PSAP and associated MedDRA version at the time of the database release (DBR) will be used. Sections of the PSAP that are relevant to reporting are given in the BEL114333 RAP, Appendix 10: PSAP Sections for AESI Reporting.
Primary Objective	• The primary objective of BEL114333 is to evaluate long-term safety and tolerability of belimumab in subjects with SLE in Japan and Korea.
Primary Endpoint	• Multiple safety endpoints (SAEs, AEs, AESIs, haematology and clinical chemistry parameters, immunogenicity, vital signs).
Study Design	• BEL114333 provides Japan and Korea subjects who completed study BEL113750 and Japan subjects who completed the open-label extension of BEL112341 with the option of receiving IV belimumab, as an add-on to their

Overview	Key Elements of the RAP
	standard of care SLE therapy. In this document, BEL113750 and BEL112341 are collectively referred to as the 'parent' studies. All eligible subjects will receive IV belimumab 10 mg/kg every 4 weeks irrespective of their randomised treatment (placebo vs. belimumab) in the parent study. This is an optional study in which eligible subjects will be enrolled at the discretion of the investigator and consent of the subject. The study will provide data on long-term safety and efficacy of belimumab in Japan and Korea. • This study is being closed as belimumab commercial supply is now available in Japan and Korea, and the study has met the protocol-defined criteria for stopping.
Planned Analyses	• Safety and efficacy endpoints will be assessed using counts (percentages) and summary statistics. • The data will be reported by years of belimumab treatment beginning at the first dose of belimumab, which will include subjects who received belimumab treatment during the parent study. See Section 2.4.1.
Analysis Populations	• All Japan and Korea subjects who enrolled in study BEL114333 and received at least one dose of open-label (IV) belimumab treatment.
Hypothesis	• No formal statistical hypothesis testing. Data from all subjects as one total belimumab treatment group will be presented. Any comparisons between parent study randomised treatment groups will be purely descriptive. See Section 2.4.1.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Study Completion Status		
Section 3.1. Study Design Study completion is defined as: • IV belimumab becomes commercially available in the respective countries. • Upon the decision of the sponsor to close/terminate the study.	Definition has been revised to include "the subject transferred to a different protocol".	The BEL114333 protocol intent was to include this additional criterion. Similar definition is contained within the BEL113750 OL (China only) Phase of the protocol.
Safety		
Section 8.1.3 Safety The frequency of AEs will be tabulated by treatment groups, according to the treatment assignment during the respective DB phase of study BEL113750 or BEL112341 (C1115).	Although the adverse events in this section were initially intended to be summarised by parent study randomised treatment groups, the safety data will actually be shown as one total belimumab group.	Similar approach to other Long-Term Continuation (LTC) studies, allowing meaningful comparisons between study BEL114333 and the LTC studies.
Section 8.1.3 Safety The number of subjects with AEs and the incidence rate of AEs will be summarised in each 6-month time interval.	Adverse events will be summarised by year interval.	For consistency with the LTC studies.
Section 8.1.3 Safety	AE of Special Interest (AESI) will also be summarised.	AESI (serious and non-serious) of scientific and medical interest specific for GSK are being reported across the Benlysta program.
Section 8. Data Analysis and Statistical Considerations. Immunogenicity and B cell marker data collected at the 6-month post-treatment visit will be reported separately as an addendum to the clinical study report.	Not required.	The data base will be locked once all subjects have completed their last visit of BEL114333. All data will be included in the BEL114333 CSR.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Efficacy		
Section 8.1.1. Primary Efficacy Analysis and Section 8.1.2 Analysis of Additional Efficacy and Biomarkers Subjects who received subcutaneous (SC) belimumab in the BEL112341 study before joining the BEL114333 study will be evaluated separately.	Although the efficacy data for BEL112341 subjects in this section were to be analysed separately, the data will be combined with the data from subjects who received IV belimumab in the BEL113750 parent study.	There are no clinically significant differences in the results between these studies in terms of which formulation was used. Hence, the data from these 25 SC subjects can be aggregated with the subjects who received the IV formulation, unless otherwise stated.
Section 6.2.1.2 Secondary [Efficacy] Endpoints Baseline will be defined as study Day 0 of the respective studies BEL113750 or BEL112341.	For subjects randomised to placebo during the parent study BEL113750, baseline will be defined as study Day 0 of the study BEL114333. For subject randomised to placebo in the parent study BEL112341, baseline will be defined as study Day 0 of the open-label extension of BEL112341.	For consistency with the LTC studies, baseline is defined as the last available value prior to the initiation of treatment with belimumab. No additional analyses are planned as mentioned in the protocol, for placebo.
Section 6.2.1.1 Primary Endpoint The SRI response is defined as the primary efficacy endpoint.	The primary SRI response endpoint will be regarded as a key secondary endpoint for the study BEL114333.	The primary objective of the study BEL114333 is safety. Efficacy is considered as a secondary outcome.
Section 6.2.1.2 Secondary [Efficacy] Endpoints	PGA and BILAG components of the SRI response endpoint were added.	Additional analyses are being reported to enable the long-term data to be further evaluated.
Section 6.2.1.2 Secondary [Efficacy] Endpoints Number of days of daily prednisone dose $\leq$ 7.5 mg/day and/or reduced by 25% from baseline over time.	The threshold of a 25% reduction has been revised to 50%.	For consistency with the BEL113750 parent study definition of this endpoint. This endpoint was not considered in the parent study BEL112341.
Section 6.2.1.3 Other [Efficacy] Endpoints Duration of primary response [SRI] assessed every 24 weeks.	This endpoint has been removed.	Because the investigator has much more freedom in prescribing concomitant medications during the OL continuation study BEL114333, this could potentially confound evaluating the duration of the SRI response.
Section 6.2.1.3 Other [Efficacy] Endpoints	The following efficacy endpoints were added: • Change and percent	Additional analyses are being reported to enable the long-term, data to be further

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	change from baseline in SELENA SLEDAI. • SLICC/ACR Damage Index Worsening from baseline.	evaluated.
Section 6.2.1.3 Other [Efficacy] Endpoints Renal flare rate and time to first renal flare assessed over time. A SLE renal flare is defined as the occurrence of 1 or more of the following criteria (not shown here) in 2 or more consecutive visits during the study. See RAP, Section 8.2.8, for details of the criteria.	The renal flare definition has been revised for study BEL114333, as the occurrence of one or more of the following criteria (not shown here) at a single visit in which assessments are performed.	Assessments every 6 months during study BEL114333 will not allow the use of the same definition of renal flares as in the respective parent studies, which requires assessments to be performed at 2 or more consecutive monthly visits.
Section 8.1 Data Analysis Considerations	Although the efficacy data will be tabulated by parent study randomised treatment groups, as mentioned in the protocol, the graphical displays will be shown for the total Safety population only.	The graphs align with the interpretation of response over time rather than comparisons between treatment groups.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Evaluate long-term safety and tolerability of belimumab in subjects with SLE in Japan and Korea	The endpoints below will be used to assess this study objective.
	Adverse events (AEs)
	• Frequency and percentage of subjects with events. • Event rates adjusting for person-years on study agent.
	Laboratory Parameters
	• Observed and Change from Baseline by visit. • Laboratory reference shifts from baseline by visit. • Laboratory toxicity worsening of at least two grades from baseline by study year • Grade 3 or 4 laboratory abnormalities by visit and study year.
	Immunogenicity
	• Immunogenic response (anti-belimumab anti-bodies) by visit and study year.
	Biomarkers

Objectives	Endpoints
	• Percent change from baseline in immunoglobulins, auto-antibodies, and complement levels by visit. • Immunoglobulin values below the lower limit of normal by visit and study year. • Percent change from baseline in absolute B cell subsets.
Secondary Objectives	**SRI and Other Secondary Endpoints**

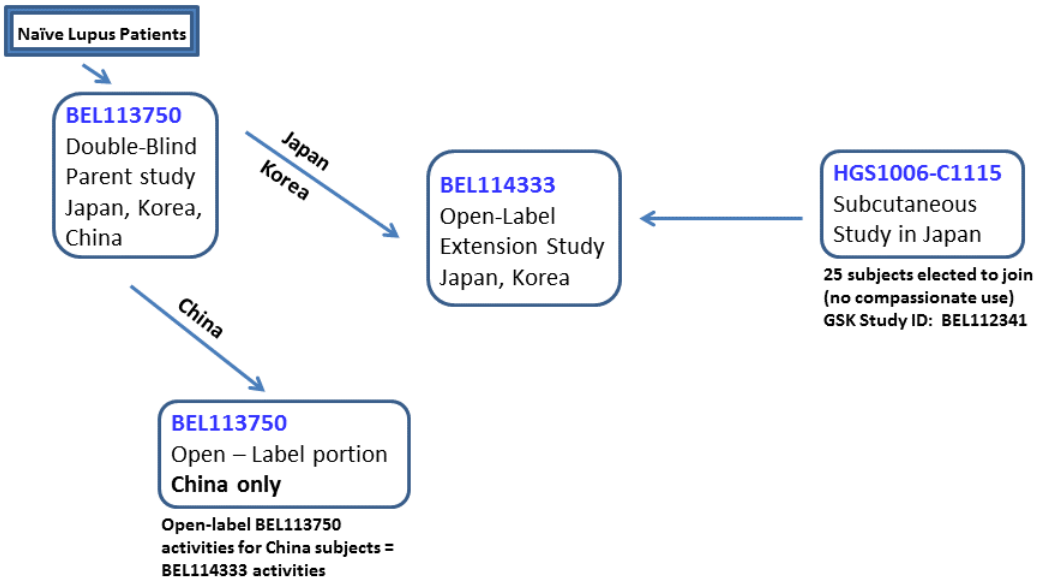
Evaluate the long-term efficacy of belimumab in subjects with SLE in Japan and Korea	• SRI response rate at each scheduled visit when complete efficacy evaluations occur (e.g., Week 24 and Week 48 for each year). An SRI response is defined as
	  • ≥4 point reduction from baseline in SELENA SLEDAI score,
	AND
	  • No worsening (increase of <0.30 points from baseline) in Physician's Global Assessment (PGA),
	AND
	  • No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment.
	• Percent of subjects with ≥4 point reduction from baseline in SELENA SLEDAI score assessed every 24 weeks
	• Percent of subjects with No Worsening in PGA compared to baseline (added to the RAP)
	• Percent of subjects with No new BILAG A organ domain or 2 new BILAG B organ domain scores compared to baseline (added to the RAP)
	• Number of days of daily prednisone dose ≤ 7.5 mg/day and/or reduced by 50% from baseline over time.
	• Time to first severe SLE Flare Index (SFI) flare assessed over time.

	Other Efficacy Endpoints
	Disease Activity
	• Absolute change and percent change from baseline in SELENA SLEDAI (added to the RAP) • Change in Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index assessed every 24 weeks. • SLICC/ACR Damage Index Worsening from baseline (added to the RAP). • Percent change from baseline in PGA assessed every 24 weeks.
	Flares
	• Time to first SFI flare assessed over time. • Time to first 1A/2B BILAG flare assessed over time. • Time to first BILAG A flare assessment over time.
	Organ-specific measures
	• Renal flare rate and time to first renal flare assessed over

Objectives	Endpoints
	time.
	• Percent change from baseline in proteinuria by visit.
	Prednisone
	• Percent change from baseline of prednisone dose at each scheduled visit. • Percent of subjects whose average prednisone dose has been reduced to ≤ 7.5 mg/day from >7.5 mg/day at baseline over time.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Multicentre, open-label, continuation study of intravenous (IV) belimumab plus standard of care in Japan and Korea subjects with SLE who completed the Phase III study BEL1123750 in Northeast-Asia or who completed the Phase III study SC open-label extension of BEL112341 (Japan subjects only). ○ The complete results for all countries for BEL112341 (using the SC formulation) and study BEL113750 have been previously reported. • Subjects in Japan and Korea randomised to placebo in the parent study BEL113750 began IV belimumab in BEL114333. Those initially randomised to belimumab in the parent study BEL113750 will continue IV belimumab. • Subjects in Japan randomised to placebo in parent study BEL112341 began SC belimumab in the open-label phase extension of BEL112341 and then changed to IV belimumab in BEL114333. Those initially randomised to SC belimumab in the parent study BEL112341 changed to IV belimumab at the start of BEL114333. • Subjects no longer receiving belimumab after their exit visit are expected to return for follow up visits. A 6 month FU visit was included for Japan in order to obtain B cells. However, immunogenicity draws at the 6 month FU visit were only obtained if there were positive immunogenicity results at the prior 16 week FU visit. Korean subjects were not required to collect B cells at the 6 month FU visit. Korea however only had 6 month FU visits scheduled for those subjects with prior positive immunogenicity results at the 16 week FU visit.
Dosing	• Belimumab 10 mg/kg IV infused over 1 hour every 28 days as add-on therapy to standard of care.

Overview of Study Design and Key Features	
	• The first dose in BEL114333 must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last IV dose for subjects enrolled from the parent study BEL113750. For subjects from the SC parent study BEL112341, the first IV dose in BEL114333 is targeted for 1 week after the last dose of SC belimumab (scheduled for Week 23 in the OL extension part of BEL112341). • If a subject misses 3 or more consecutive infusions during BEL114333, they should be withdrawn from the study.
Time & Events	• Refer to Appendix 1: Time & Events
Treatment Assignment	• Open-label – all subjects will receive IV belimumab
Interim Analysis	• None

2.4. Statistical Hypotheses

Since this is an open-label continuation, no formal statistical hypothesis testing will be performed. Any comparisons between the parent study randomised treatment groups will be purely descriptive.

2.4.1. Treatment Comparisons

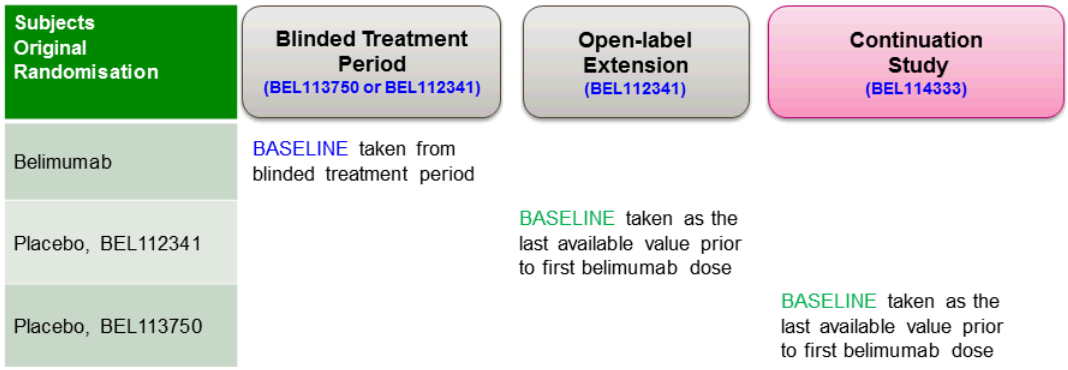
All subjects will be treated with open-label IV belimumab for the duration of the study BEL114333. The analyses will be performed on data from all subjects as one total belimumab treatment group by year of belimumab treatment.

As subjects started to receive belimumab treatment in the parent study, or the open-label extension of the parent study BEL112341, or the open-label study BEL114333, different time points to start of belimumab treatment will be used to define subject follow up in the analysis. See Figure 1.

Analyses will be based on all available follow-up from the first dose of belimumab treatment through to study end.

Additional safety (e.g., labs), efficacy and study population summaries will be presented by parent study randomised treatment groups (belimumab vs placebo); however, these comparisons will be descriptive in nature. For the remainder of the document, parent randomised treatment group will be used to refer to the treatment to which a subject was randomised in the parent study, irrespective of formulation.

Figure 1 First Belimumab Dose/Baseline Definition



Analyses will be based on all available data from the first belimumab dose through to study end, BEL114333. As subjects started to receive belimumab in the parent study, or the open-label extension of BEL112341, or the open-label study BEL114333, different timepoints to start of belimumab treatment are used in the analysis (as shown). Baseline is defined as the last available value prior to the first belimumab dose.

3. PLANNED ANALYSES

3.1. Interim Analyses

To date, no interim analyses pertaining to open-label safety data has been required to support regulatory submission activities for Japan, Korea and China.

3.1.1. Safety Reviews

The SRT regularly performs in stream data looks of the pooled open-label data from BEL114333, Japan and Korea subjects, and BEL113750, China subjects, to monitor the safety of these studies. These reviews are based on data from all subjects as one belimumab treatment group.

Additionally, the SRT performs in stream adjudication of subject-level data for Adverse Events of Special Interest (AESIs; serious and non-serious). See Appendix 10: PSAP Sections for AESI Reporting..

3.2. Final Analyses

Korean sites in BEL114333 were closed in 2015 (per the protocol-defined stopping criteria) because of approval and the commercial availability of Benlysta in Korea. The last subject visit in Korea was 27 April 2015.

The data base can be locked since all Japan and Korea subjects have completed their last visits of BEL114333. All Japanese subjects completed their latest visit, as appropriate, up to 6-month post-treatment follow-up visit. The 6-month FU serves as the last subject last visit. The last subject visit in Japan was on 13 September 2018.

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

All Subjects	• Japan and Korea subjects who were randomised in the DB 52-week parent study BEL113750. Additionally, participation in BEL114333 was extended to Japanese subjects in the parent study BEL112341, of which 30 subjects were randomised at the beginning of BEL112341 (but only 27 remained to enter the open-portion of BEL112341). A total of 25 of these 27 subjects elected to join BEL114333; the other 2 did not elect to join BEL114333. • This population, and all subsequently defined	• Enrolment and Population level displays for patient disposition

	populations below, will be based on data from all subjects as one total belimumab treatment group. Additional summaries will be presented by the parent randomised treatment groups. See Section 2.4.1.	
Screened	• All subjects in the All Subjects population who completed the parent studies BEL113750 (Japan and Korea) or BEL112341 (Japan only) and were eligible to enrol in BEL114333.	• Study Population
Enrolled	• All subjects who enrolled in BEL114333.	• Disposition-level displays
Safety	• All subjects in the Enrolled population who received at least one IV dose of belimumab during BEL114333. Analyses will be based on all available follow-up from the first dose of belimumab treatment through to study end. See Section 2.4. As such exposure data to belimumab will be included for subjects who received their first dose in the parent study, and subsequently enrolled in BEL114333. Note: although the OL analysis for Japan and Korea will be based on the Safety population, the definition is the same as the Efficacy population used for China (which excluded subjects from one site).	• Safety/Efficacy analyses and displays

Refer to Appendix 12: List of Data Displays which details the population used for each display.

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 summarised and listed. Note, only important protocol deviations that occurred during BEL114333 will be reported.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Version 3 (dated: June 21, 2017).
  - Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations for BEL114333 will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
11.1	Appendix 1: Time & Events Section 11.1.1: BEL114333 Protocol Defined Time & Events Section 11.1.2: Parent Study Protocol Defined Time & Events
11.2	Appendix 2: Assessment Windows Section 11.2.1: Year Intervals Section 11.2.2: Belimumab Visits
11.3	Appendix 3: Adverse Event Collapsing Rules and Assignment of Adverse Events to Study Year Section 11.3.1: Adverse Event Collapsing Section 11.3.2: Assigning Adverse Events to Study Year
11.4	Appendix 4: Data Display Standards & Handling Conventions Section 11.4.1: Study Treatment & Sub-group Display Descriptors Section 11.4.2: Baseline Definition
11.5	Appendix 5: Derived and Transformed Data Section 11.5.1: General Section 11.5.2: Study Population Section 11.5.3: Safety Section 11.5.4: Efficacy Section 11.5.5: Biomarkers
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data Section 11.6.1: Premature Withdrawals and Completion Section 11.6.2: Handling of Missing Data
11.7	Appendix 7: Methods for Handling Centres
11.8	Appendix 8: Examination of Covariates, Subgroups & Other Strata Section 11.8.1: Handling of Other Strata and Covariates Section 11.8.2: Handling of Subgroups
11.9	Appendix 9: Laboratory Parameters & Adverse Events Grading Tables Section 11.9.1: Laboratory Parameters Section 11.9.2: Adverse Event and Laboratory Value Severity Grade Tables
11.10	Appendix 10: PSAP Sections for AESI Reporting.

5.1. General Data Considerations

- This is a multi-centre study in Japan and Korea. There are no planned adjustments made for multiple centres or regions.
- As no formal hypotheses are being tested, there are no planned adjustments for multiple comparisons or multiplicity.
- As all subjects will be treated with belimumab and there are no hypothesis tests, no additional strata or covariates will be employed in the analyses. Subgroups will be defined for further exploration of the data in a descriptive fashion.
- Reporting of data is by year of belimumab treatment beginning on the date when subjects received their first dose of belimumab, irrespective of the formulation (Section 2.4.1 and Section 11.2.1).
- Baseline is defined as the last available value prior to the initiation of treatment with belimumab and will henceforth be referred to as 'Belimumab baseline'. See Appendix 4: Data Display Standards & Handling Conventions for more details on baseline definitions.
- For summaries performed by belimumab visit, placebo subjects are aligned based on start of exposure to belimumab (see Section 11.2.2 for details of the visit mapping).

  Note, for BEL114333, subjects randomized to belimumab in the parent study were off-set by an additional 4 weeks compared to the open-label visit schedule, in order to complete the final assessments at the parent study Week 52 visit. Therefore, the mapping was adjusted in order to align the ensuing open-label visits. This was achieved by mapping the parent study Week 52 visit to the Belimumab Visit Year 1 Week 48 (and dropping the parent study Week 48). Ongoing open-label visits will always align.

  Note, for subjects ongoing in BEL114333 at the time of study end, there is one year off-set between the parent randomised treatment groups until the last dose was administered in March 2018. Data for the last year will be limited to the belimumab group.
- There is a single data base that captures both parent study (i.e. DB phase of BEL113750) and open-label data for study BEL113750. The dividing line between parent study and open-label data is determined by the Day 365 visit. Any new data after this visit is regarded as open-label.

  Note, after the database was frozen for the parent study analysis (DB data), technical limitations required the entire data base to be open in order to enter open-label information. Thus, sites had the ability to also change data pertaining to the parent study.

  - A complete BEL113750 database extraction will be performed (because the DB data will be used in the open-label analyses). Note, there are differences between the prior DB data extraction by a different vendor/format and the open-label data. The complete extraction will enable all the data to be compatible.

- The complete extraction will be able to include any additional parent study information (e.g., SAEs, concomitant meds) entered by sites at any time from the start of the parent study, and will be included in aggregate reporting.

  Note any additional SAEs will also be mentioned separately in the open-label phase CSR.

The same database captures data for BEL114333. Similarly, the BEL114333 sites had the ability to also change data pertaining to the parent study BEL113750, per the above

- From the complete database, a selected data extraction of the BEL114333 data will be performed
- The DB data for Japan and Korea subjects will be extracted from the complete BEL113750 data (previously used for the BEL113750 – China OL analysis).

Lastly, the BEL112341 Japan subjects who entered BEL114333 will have all relevant data extracted from the complete BEL112341 database.

All relevant belimumab data from the parent studies and study BEL114333 will be aggregated.

Unless otherwise stated, the following statistics will be used to summarise the data:

- Continuous Variables: n, mean, standard deviation (SD), median, 25th & 75th percentiles, minimum and maximum.
- Categorical Variables: n, frequency counts and percentages.

Unless otherwise stated, the following rules will be implemented:

- Summaries by Visit: Only scheduled visits will be presented (i.e. that correspond to the timings of the open-label visits for BEL114333). Otherwise data not shown here will be displayed in listings, and used in derivations such as “any time post-baseline” summaries for laboratory data, time to event, etc. Exit visits will be slotted to the next 6 monthly scheduled visit for that year for efficacy endpoints (or next 12 monthly scheduled visit for SLICC). Otherwise, data will be summarised per the nominal visit.
- Due to the additional 6 month OL extension for SC subjects entering BEL114333, there is a 6 month off-set in the data capture between the parent studies. As a result, for SLICC, immunoglobulins and B cell subsets, captured on an annual basis in BEL114333, the data captured at each analysis visit stratifies by parent study. As such these endpoints will be tabulated by parent study, and the data will not be aggregated.
- Summaries by belimumab Treatment: Data will be mapped to the year by windowing starting at the time of first belimumab treatment.

- Listings: If endpoints reported, data will be presented in listings as required.
- Figures: error bars will be displayed.

Unless otherwise stated, no imputation for missing values will be conducted.

6. STUDY POPULATION ANALYSES

The study population analyses will be based on the Safety population, unless otherwise specified.

6.1. Overview of Planned Analyses

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Enrolment (All Subjects Population)	Y [1] [2]		
Enrolment by Site	Y [1]		
Belimumab Treated Subject-Years on Study	Y [3]		
Subject Disposition (All Enrolled Subjects Population)	Y [4]		
Reasons for Study Withdrawal			Y [5]
Study Completion Status per Protocol	Y [6]		Y [7]
Time to Withdrawal Prior to Study Closing	Y [8]	Y [8]	
Subject Completion Status per Protocol by Year Interval	Y [9]		
Inclusion/Exclusion Criteria			
Inclusion/Exclusion Criteria Deviations (All Enrolled Subjects Population)	Y [1]		Y
Protocol Deviations			
Subjects with Important Protocol Deviations (All Enrolled Subjects Population)	Y [1]		Y

NOTES :

- T = tables, F = Figures, L = Listings, Y = Yes display generated.

[1] Summarised by parent randomised treatment group and the total population.

[2] Summarises No. (%) of Japan and Korea subjects randomised & completed parent study BEL113750, and those subjects who were enrolled and included in the Safety population for BEL114333. Additionally, Japan subjects from BEL112341 are also summarised.

[3] Summarises person-years and cumulative person-years for time on belimumab treatment by year interval and parent randomised treatment group, and person-years for at any time post-baseline up to a subject's final contact. See Section 11.5.1 for definition of final contact.

[4] Summarises subject disposition per End of Treatment CRF page as determined by the investigator. Note, the CRF page does not include an option for selecting study completion. Thus, all subjects were indicated as being withdrawn.

[5] Listing indicates reasons and time of withdrawal per End of Treatment CRF page (see footnote 4).

[6] Summarises study completion status per protocol (completed, death, withdrawn [and reasons for withdrawal]). See Section 11.6.1 for definition of study completion.

[7] Listing indicates subject completion status (see footnote 6) and whether subjects are included in analysis populations.

[8] Kaplan-Meier plot of time (in days) to withdrawal (see footnote 6 for definition of withdrawal) and associated summary table. See Section 11.5.1 for derivation of time to withdrawal. Note: subjects who died or completed the study per the protocol, will be censored.

[9] Summarises No. (%) of subjects starting each year interval, and of those, the number completed, died and withdrawn [and reason for withdrawal], or ongoing in the study at the end of that year interval. Will be summarised using frequencies and percent. The denominator for each year will be the number of subjects who started each year of treatment.

6.2. Overview of Planned Demography & Baseline Characteristics Analyses

Table 4 provides an overview of the planned demography and baseline characteristics analyses, with full details of data displays being presented in Appendix 12: List of Data Display.

Table 4 Overview of Planned Demography & Baseline Characteristics & Medical History Analyses

Display Type	Data Display's Generated	
	Table	Listing
Demography & Baseline (BL) Characteristics		
Demographics & BL Characteristics	Y	Y (x6) [3]
Demographics & BL Characteristics by Age Group (< 65 vs ≥ 65 years)	Y (x2) [1]	
Demographics & BL Characteristics by Sex (Male vs Female)	Y (x2) [1]	
Demographics & BL Characteristics by BL SELENA SLEDAI (≤ 9 vs ≥ 10)	Y (x2) [1]	
Summary of Age Ranges (All Enrolled Subjects Population)	Y	
Race and Racial Combination Details (All Enrolled Subjects Population)	Y	Y
Medical History		
Medical History		Y [4]
Baseline Disease Activity		
Baseline Disease Activity	Y	
Baseline Disease Activity by Age Group (< 65 vs ≥ 65 years)	Y (x2) [1]	
Baseline Disease Activity by Sex (Male vs Female)	Y (x2) [1]	
Baseline Disease Activity by BL SELENA SLEDAI (≤ 9 vs ≥ 10)	Y (x2) [1]	
Other Baseline		
Allowable SLE Medication Usage at Baseline	Y	
ACR Classification Criteria at Parent Study Baseline	Y	
SELENA SLEDAI Organ & Item Involvement at Baseline	Y	
BILAG Grade by Organ Domain at Baseline	Y	
Complement Levels at Baseline	Y	
Autoantibody Levels at Baseline	Y	
Immunoglobulin Levels at Baseline	Y [2]	
B Cells at Baseline (Japan Only)	Y	

NOTES:

- BL= Baseline, T = Tables, L = Listings, Y = Display Generated, (xN) = Number of separate displays generated

[1] Separate displays generated for each sub-group level.

[2] Parameters summarised: IgG, IgM and IgA.

[3] Separate listings generated for [A] Demographic Characteristics [B] Anti-dsDNA, ANA, Complement Levels and SLE Medication Use [C] Disease Duration, PGA, SLICC/ACR Damage Index and Proteinuria Results [D] SELENA SLEDAI Results [E] BILAG Index Results [F] SLE Flare Index.

[4] Medical history data were collected at screening of the parent studies. The baseline definitions for the parent randomised treatment groups are different for the open-label analysis. See Figure 1. Thus, for subjects who were randomised to placebo in the parent study, any AEs with end dates prior to the first open-label belimumab dose (i.e. either in BEL112341 open-label extension or BEL114333), will be included as medical history terms. For subjects who were randomised to belimumab in the parent study, any AEs that started before the first belimumab dose in the parent study, will be included as medical history terms; any AEs that started on or after the first belimumab dose with end dates during the parent study will be summarised as AEs.

6.2.1. Demography

Baseline measurements for subjects are defined in Section 11.4.2. Data presentations will be summarized by parent randomized treatment group and overall.

Descriptive statistics will be used to summarize the continuous demographic and baseline characteristics of age at start of belimumab treatment (years), height (cm), weight (kg), BMI (kg/m^2).

Counts (%) of the following categorical demographic and baseline characteristics will be presented: sex, race, race category, ethnicity.

The summary of demographic and baseline characteristics will be repeated for subgroups, where the subgroup categories are defined in Appendix 8: Examination of Covariates, Subgroups & Other Strata.

6.2.1.1. Baseline Disease Characteristics

A summary of baseline disease activity will be provided, including counts and percentages for categorical endpoints defined in Table 5.

Descriptive statistics for the continuous scores will be presented for SELENA-SLEDAI, PGA and SLICC/ACR Damage Index. The summary of baseline disease activity will be repeated for subgroups. Refer to Appendix 8: Examination of Covariates, Subgroups & Other Strata.

Table 5 Baseline Disease Endpoints

Endpoint	Categories
BILAG Organ Domain Involvement	At least 1A or 2B, At least 1A, At least 1B, No A or B [1]
SELENA-SLEDAI	≤ 9 or ≥ 10
SLE Flare Index	No flare, At least 1 flare, At least 1 severe flare [2]
PGA	0 to 1, >1 to 2.5 or > 2.5
SLICC/ACR Damage Index	0, 1 or >1
Baseline Proteinuria (measured by spot urine protein creatinine ratio mg/mg)	≤ 0.5 or > 0.5 Subcategories of > 0.5 mg/mg: >0.5 to < 1, 1 to < 2 or ≥ 2

NOTES:

[1] "No A or B" is to mean "Neither A nor B", equivalently, "No A and No B", and not "No A or No B". A footnote should be added to the SAS output.

[2] See Section 11.4.2.3 for derivation of flare categories.

Table 6 provides indicators of baseline disease activity that will also be summarized.

Table 6 Baseline Indicators of Disease Activity

Baseline Indicator	Categories & Summaries at Baseline
SLE Disease Duration (yrs)	• Summary statistics
ACR Classification Criteria	• Count (%) with each symptom present and total at baseline, and total number of ACR criteria met. **NOTE:** ACR classification is collected at screening of the respective parent studies, and therefore based on parent study screening assessment.
SELENA-SLEDAI category	• Count (%) for each organ domain and item present.
BILAG	• Count (%) of each A – E score by organ domain.
Autoantibody Levels (anti-dsDNA, ANA)	• Count (%) for negative and positive (Anti-ds DNA: ≥ 30 IU/ml & ANA ≥ 0.80 Index [BEL113750] or ANA ≥ 80 Titer [BEL112341]) • Summary statistics for positive Anti-dsDNA and positive ANA.

Complement Levels (C3, C4)	• Summary Statistics.
	• Low, Normal, and High C3
	  ○ C3 count (%) of low (< 90 mg/dL), normal, and high (> 180 mg/dL)
	• Low, Normal, and High C4
	  ○ C4 count (%) of low (< 10 mg/dL), normal, and high (> 40 mg/dL).

Immunoglobulin Levels (IgG, IgA, and IgM [g/L])	• Summary statistics. • Count (%) below the lower limit of normal (LLN) and above upper limit of normal (ULN). See Section 11.5.5 for definitions.
Allowable SLE Medication Usage	• Counts (%) by class for: Steroid only, Immunosuppressant only, Anti-malarial only, Steroid and Immunosuppressant only, Steroid and Anti-malarial only, Immunosuppressant and Anti-malarial only, Steroid, Immunosuppressant and Anti-malarial only. • Counts (%) for preferred term within drug class (Steroid, Other Immunosuppressant/immunomodulatory Agents, Anti-malarial, NSAIDs and Aspirin).
Average daily prednisone dose (mg/day) at baseline	• Summary statistics. • Counts (%) for dose categories: 0, >0 to ≤ 7.5, >7.5 to ≤ 40 and >40 mg/day

7. SAFETY ANALYSES

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

7.1. Overview of Planned Medications and Exposure Analyses

Table 7 provides an overview of the planned analyses of medications and exposure, with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 7 Overview of Planned Medications & Exposure

Display Type	Absolute		
	Summary		Individual
	T	F	L
Medications			
Concomitant Medications by ATC Level 1 & ATC Level 4 Term	Y		Y [1]
Concomitant Medications by ATC Level 4 & Preferred Term	Y		Y [1]
Concomitant Procedures/Surgery			Y
SLE Medication Use by Year Interval	Y		
Prednisone and Other Corticosteroids by Year Interval	Y [2]		
Prednisone Dose Shifts from BL by Visit	Y		Y
Exposure			
Study Drug Exposure	Y		Y
Study Drug Administration			Y

NOTES:

- BL = Baseline, T = Table, F = Figure, L = Listing, Y = Yes display generated, (xN) = number of separate displays generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represent L related to any displays of individual subjects observed raw data.

[1] Listing by ATC code 1 and 4, Preferred and verbatim term.

[2] Maximum Daily Prednisone Equivalent Corticosteroid Daily Dose Category

7.1.1. Concomitant Medications

- Concomitant medications are defined as medications that started on or before the first dose of belimumab treatment, which continued during the belimumab treatment period, or medications that started after the first belimumab dose. See Section 11.6.2 for details of handling missing and partial dates.
- Summaries will be performed by the parent randomised treatment group and the total Safety population.
- Concomitant medications in BEL114333 will be coded and reported based on the current version of the GSK Drug Dictionary (version 1.6) at the time of study reporting (study BEL114333). To comply with fulfilling any PMDA regulations, the concomitant medications will also be coded using the WHO-DRUG dictionary. Outputs using the WHO-DRUG dictionary will be produced on request.

NOTE: the same version of the GSK Drug Dictionary which was used at the time of reporting the parent studies will be used for this current reporting (BEL113750, version 1.4; BEL112341, version 1.3). Any major coding discrepancies between different versions of GSK Drug can be addressed in a CSR appendix, if necessary.

- WHO coded medications will not be provided for BEL112341 because the BEL112341 reporting predates the PMDA regulations requiring WHO coded data. The BEL112341 data were only coded using GSK DRUG at the time of reporting (CSR effective date 26 Sep 2016). WHO coded medications will be provided for BEL113750.

Note: medications which do not have pharmacological properties are not coded to ATC descriptions, and therefore, will be assigned programmatically to an ATC Level 1 term of "PHARMACOLOGICAL PROPERTIES CANNOT BE REFERENCED". These medications are identified by a blank ATC Level 1 term (CMATC1).

For summaries performed by ATC Level 4, medications that have no ATC Level 4 term, will be summarised according to the lowest ATC level categorisation based on the level of specificity of the medication therapeutic action.

- Listings of concomitant medications will be presented.

7.1.1.1. Concomitant Medication Collapsing Rules

- Concomitant medications were collected in both the parent studies and study BEL114333.

- Due to the ongoing nature of some concomitant medications at the end of the parent study, some medications occur in both the parent study and study BEL114333.

- The following table shows where medications reside by their relationship to the parent study exit date or Year 1 Day 0 visit of the BEL114333 study.

Medication Occurrence	Database
CM starts and ends on/before parent study Exit Visit.	Parent study only
CM starts on/before Exit Visit in the parent study and ends either on/after Year 1 Day 0 of BEL114333, or after the Exit Visit but before Year 1 Day 0 of BEL114333 (where there is a gap between these visits). [1]	Parent study and BEL114333 [2]
CM starts after Exit Visit of the parent study and ends before Year 1 Day 0 of BEL114333 (where there is a gap between these visits).	BEL114333 only
CM starts after Exit Visit of the parent study and ends on/after Year 1 Day 0 of BEL114333 (where there is a gap between these visits).	BEL114333 only
CM starts and ends on/after Year 1 Day 0 of BEL114333.	BEL114333 only

[1] Records to be collapsed.

[2] Ongoing concomitant medications (CM) in the parent study BEL112341 were entered by site in the BEL114333 eCRF. Ongoing CMs in the parent study BEL113750 were programmatically added to the BEL114333 data transfer.

- Medications that occur in both the parent study and BEL114333 will be collapsed based on the following dataset attributes: GSK Drug Preferred Term, medication start date, dose, unit, frequency, route and reason/indication.
    - Medication end date should reflect the final date in BEL114333, as appropriate.

7.1.2. SLE Medications

- Corticosteroids, anti-malarials, other immunosuppressive/immunomodulatory agents, NSAIDs and Aspirin will be categorized based on the coded preferred terms, and summarized by yearly interval using frequencies (%).

- For summaries, all corticosteroids taken during belimumab treatment are converted to a prednisone equivalent dose (mg/day). This then can be used for the derivation of average daily dose, see Appendix 5: Derived and Transformed Data.

- Use of prednisone or other corticosteroids during the study were collected as a running log with other concomitant medications, and will be summarized using dose level categories: 0, > 0 to ≤ 7.5 or > 7.5 to ≤ 40, and > 40 mg/day.

7.1.3. Maximum Daily Prednisone Equivalent Corticosteroid Daily Dose Category

Prednisone equivalent corticosteroid daily dose will be mapped to belimumab visits occurring at Year 1 Day 0, as well as weeks 24 and 48 for each year per the definitions in Appendix 5: Derived and Transformed Data.

Maximum prednisone equivalent corticosteroid daily dose will be summarised within the year intervals.

Categories reported as
[1] No prednisone use (0 mg prednisone equivalent)
[2] > 0 to ≤ 7.5 mg prednisone equivalent
[3] > 7.5 to ≤ 40 mg prednisone equivalent
[4] > 40 mg prednisone equivalent
[5] Unknown

7.1.4. Shifts in Prednisone Average Daily Dose from Baseline

Shifts from average daily dose category at baseline will be summarised using frequencies and percentages, and be presented by the parent randomised treatment group and the total Safety population, for each visit.

Categories reported as [1] No prednisone use (0 mg prednisone equivalent)

[2] > 0 to ≤ 7.5 mg prednisone equivalent
[3] > 7.5 to ≤ 40 mg prednisone equivalent
[4] > 40 mg prednisone equivalent
[5] Unknown

No imputation will be performed for missing data.

7.1.5. Extent of Exposure and Study Drug Administration

- The extent of exposure to IV belimumab treatment through end of study will be assessed by examining the duration of exposure to belimumab in days and the total number of infusions a subject received. First and last infusion dates will be used, regardless of any intermittently missed infusions.
- Duration of exposure to IV belimumab (in days) will be calculated for each subject, as:

  Extent of Exposure (days) =
  Date of last exposure to IV treatment + 28 – Date of first exposure to IV treatment

  where

  - the first IV belimumab dose either occurred during the parent study BEL113750 (for subjects randomized to belimumab in BEL113750) or during BEL114333 (for everyone else).
  - the last IV belimumab dose occurred during BEL114333 for everyone. For any subjects who died within the 28 days after infusion, duration of exposure will be censored at the date of death.

- Only complete dates will be used when calculating duration of exposure.
- Summary statistics will be produced for the duration of exposure.

  NOTE: subjects from the parent study BEL112341 received SC belimumab prior to joining BEL14333. Their total duration to exposure is the sum of the exposure to both IV and SC (see details of exposure calculation for SC belimumab below).
- Summary statistics of the total number of infusions.

    - Additionally, the total number of infusions will also be summarized using counts and percentages using the following categories: 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59 and >60 (if applicable).

NOTE: for BEL112341 subjects only. The extent of exposure to SC belimumab during the parent study BEL112341 prior to joining BEL114333, will be assessed by examining the duration of exposure to SC belimumab in days and the total number of injections a subject received. First and last injection dates will be used, regardless of any intermittently missed injections.

- SC belimumab was administered weekly by injection. Duration of exposure to SC belimumab (in days) will be calculated for each subject, as:

  Extent of Exposure (days) =
  Date of last exposure to SC treatment + 7 – Date of first exposure to SC treatment

  where

  - the first SC belimumab dose either occurred during the DB portion of the parent study BEL112341 (for subjects randomized to belimumab in BEL112341) or the open-label portion of the parent study BEL112341 (for subjects randomized to placebo in BEL112341).
  - the last SC belimumab dose occurred during the open-label portion of BEL112341 for everyone.
  - Only complete dates will be used when calculating duration of exposure.
  - Summary statistics will be produced for the total number of injections.
    - Additionally, the total number of injections will also be summarized using counts and percentages using the following categories: 1 to 23, 24 to 76, and >76 (if applicable).

7.2. Overview of Planned Adverse Event Analyses

Table 8 provides an overview of the planned Adverse Event analyses, with full details of data displays being presented in Appendix 12: List of Data Displays. Data from all subjects as one treatment belimumab group will be presented.

Table 8 Overview of Planned Adverse Events Analyses

Endpoint	Absolute		
	Summary		Individual
	T	F	L
AE Summary by Year Interval	Y		
Cumulative AE Incidence Over Time		Y [4]	
Adverse Events by SOC			
AE by SOC	Y		
Serious AE by SOC	Y		
Severe AE by SOC	Y		
Study Drug Related AE by SOC	Y		
AE Leading to PD of Study Drug or WD from Study by SOC	Y		
Adverse Event Rates by SOC			
AE Rate by SOC	Y		
Serious AE Rate by SOC	Y		
Severe AE Rate by SOC	Y		
Study Drug Related AE Rate by SOC	Y		

Endpoint	Absolute		
	Summary		Individual
	T	F	L
AE Leading to PD of Study Drug or WD from Study Rate by SOC	Y		
Adverse Events by SOC & PT			
AE by SOC & PT	Y		Y [2]
Serious AE by SOC & PT	Y		Y [2]
Severe AE by SOC & PT	Y		
Study Drug Related AE by SOC & PT	Y		
AE Leading to PD of Study Drug or WD from Study by SOC & PT	Y		Y [3]
Subject Numbers by Individual AE by SOC & PT			Y [2]
Relationship between AE SOC, PT and Verbatim Text			Y [2]
Adverse Events by SOC & PT (Subgroups)			
AE by Age Group (< 65 vs ≥ 65 Years), SOC and PT	Y (x2) [1]		
AE by Gender (Male vs Female), SOC and PT	Y (x2) [1]		
AE by BL SELENA SLEDAI (≤ 9 vs ≥ 10), SOC & PT	Y (x2) [1]		
Adverse Events: Non-Serious, Serious & Fatal Serious by SOC & PT			
Fatal Serious Adverse Events			Y [2]
Non-Fatal Serious Adverse Events			Y [2]
Reason for Considering as a Serious Adverse Event			Y
Most Common (≥ 10%) Non-Serious Drug Related Adverse Events	Y		
Most Common (≥ 2%) Serious Drug Related Adverse Events	Y		
Common (≥ 5%) Non-Serious Adverse Events by SOC and PT (FDAAA)	Y		
Serious Adverse Events by SOC and PT (FDAAA)	Y		
Adverse Events by PT			
AE by PT	Y		
Serious AE by PT	Y		
Severe AE by PT	Y		
Study Drug Related AE by PT	Y		
AE Leading to PD of Study Drug or WD from Study by PT	Y		
Adverse Events by Maximum Severity			
AE by SOC & Maximum Severity	Y		
AE by SOC, PT & Maximum Severity	Y		

NOTES:

- BL = Baseline, PD = Permanent Discontinuation, WD = Withdrawal, T = Table, F = Figures, L = Listings, Y = Yes display generated, (xN) = Number of separate displays generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Separate displays generated for each level of the subgroup.
[2] Listing generated by SOC, PT and Verbatim Term.
[3] Listing generated for AE results in study drug discontinuation.
[4] Kaplan-Meier figure showing each AE category (all, related, serious, severe).

7.2.1. Adverse Events

- Data from all subjects as one belimumab group will be summarised.

- All adverse event tables will show the data by year interval at the start of an AE, and include a summary over the total post-baseline period. Year interval is defined in Appendix 2: Assessment Windows.
- Any AEs that started prior to the first IP administration in the parent study will not be reported. See Section 6.2, footnote 4 in Table 4 for relevance for such AEs as past medical history terms. Only treatment-emergent adverse events will be summarised.
    - Treatment-emergent AEs are defined as follows:
        - AEs that started on or after the first dose of belimumab treatment.
        - For those subjects who were randomised to placebo in the parent study, ongoing AEs that started before the first open-label belimumab dose (in either BEL112341 open-label extension or BEL114333) and worsened (severity, seriousness, relatedness) at any point during the open-label treatment.
    - Ongoing AEs that started before the first open-label belimumab dose which did not worsen during the open-label treatment (for those subjects who were randomised to placebo during the parent study) will not be considered treatment-emergent, but will be listed.
- Listings will be generated by the parent randomized treatment group (see Table 8). All treatment-emergent AEs as defined above will be listed plus any ongoing AEs that started before the first belimumab dose (for subjects randomised to placebo in the parent study) that were not considered treatment-emergent. AEs that started in each parent study will be flagged.
- The hierarchical relationship between MedDRA SOCs, PTs and verbatim text will be displayed as a listing for all AEs.
- Adverse events in BEL114333 will be coded to the current MedDRA dictionary version at the time of study reporting (version 22.0).

  NOTE: the same version of the MedDRA dictionary which was used at the time of reporting the parent studies will be used for this current reporting (BEL113750, version 21.1; BEL112341, version 18.0). Any major coding discrepancies between different versions of MedDRA can be addressed in a CSR appendix, if necessary.

7.2.2. Adverse Event Summaries

- An overall summary of AEs will be presented showing the number (%) of subjects with at least one of the following: AE, related AEs, SAE, severe AE, AE resulting in study treatment discontinuation, and deaths.
- The number of events and the number (%) of subjects who had at least one treatment-emergent AE will be summarized for each category of AE listed in Table 9.

Table 9 Adverse Events Categories

AE's	Summary Category

	By SOC	By SOC & PT	By PT
All	YES	YES	YES
Serious	YES	YES	YES
Study Drug Related	YES	YES	YES
Severe	YES	YES	YES
Leading to permanent discontinuation of study	YES	YES	YES
Non-Serious Drug Related		YES	
Serious Drug Related Adverse Events		YES	

SOC = System Organ Class, PT = Preferred Term

- The table for AEs by SOC and PT will be repeated for subgroups. See Appendix 8: Examination of Covariates, Subgroups & Other Strata for more details.
- The tables for AEs by SOC will also be reported for event rates (see below for derivation).
- Summaries of AE incidence, by SOC and maximum severity will also be provided. For these displays, the number (%) 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. AEs that have missing severity will be excluded from the summaries.
- A Kaplan-Meier figure of cumulative incidence (at least one) of treatment-emergent AE by category (all, related, serious, severe) will be created relative to the first dose of belimumab and censored at the last visit date/contact.
- Listings of AEs will be presented (see Table 8). A listing of AEs in the Infections and Infestations SOC for those subjects with a Grade 3 or Grade 4 IgG toxicity at baseline and/or at any time post-baseline, will also be produced.

Adverse Event Rates

- The event rate will be calculated as the number of events per 100 person-years. The last contact date for AE reporting is the date of the latest scheduled visit where AE/SAE were assessed, as appropriate, up to the 16 week FU visit.

Event Rate = 100* Number of Events / Subject Years	
Overall Subject Years	$\frac{\sum_{\text{All Subjects in Population}} [(\text{Last Contact Date} - \text{1st Belimumab Treatment Date} + 1)]}{365}$ NOTE: This will be the denominator for the “Any Time Post Baseline” column.
Subject Years in Year k	$\frac{\sum_{\text{All Subjects in Population}} (\text{End of Interval Day} - \text{Start of Interval Day} + 1)}{365}$

7.3. Overview of Planned Adverse Events of Special Interest

Table 10 provides an overview of the planned Adverse Event analyses, with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 10 Overview of Planned Adverse Events of Special Interest

Endpoint	Absolute	
	Summary	Individual
	T	L
Adverse Events of Special Interest (AESI)		
Overall AESI by Category	Y	Y [1]
Malignant Neoplasm AESI by Category & PT	Y	
Post-Infusion Systemic Reaction AESI by Category & PT	Y	
Serious Post-Infusion Systemic Reaction AESI by Category & PT	Y	
Infection AESI by Category & PT	Y	
Serious Infection AESI by Category & PT	Y	
Infection AESI Leading to PD Discontinuation of Study Drug or WD from Study by Category & PT	Y	
Depression/Suicide/Self-injury AESI by Category & PT	Y	
Deaths by Category & PT	Y	
Adverse Events of Special Interest (AESI) Rates		
Overall AESI Rates by Category	Y	
Malignant Neoplasm AESI Rates by Category & PT	Y	
Post-Infusion Systemic Reaction AESI Rates by Category & PT	Y	
Serious Post-Infusion Systemic Reaction AESI Rates by Category & PT	Y	
Infection AESI Rates by Category & PT	Y	
Serious Infection AESI Rates by Category & PT	Y	
Infection AESI Leading to PD Discontinuation of Study Drug or WD from Study Rates by Category & PT	Y	
Depression/Suicide/Self-injury AESI Rates by Category & PT	Y	

NOTES:

- T = Table, L = Listing, Y = Yes display generated, (xN) = Number of separate displays generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Listing generated by AESI Category, SOC, PT and Verbatim Term.

7.3.1. Adverse Events of Special Interest

AESI have already been identified by the GSK Safety Review Team (SRT). This information will be provided for analysis purposes via an adjudication spreadsheet, and therefore, does not need to be re-derived from the raw data. For a broader description, see Appendix 10: PSAP Sections for AESI Reporting.

The reporting of AESIs is defined below.

An overall summary of the incidence of AESI will be tabulated, and presented by study year and "any time post-baseline". Rate of events per 100 person-years will also be reported. Further summaries of the preferred terms assigned to each AE special interest category will be provided.

A listing of all AESIs will be produced.

The categorizations for the adverse events of special interest groups are:

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
    - 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 (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*/suicide/self-injury (All and Serious, separately)

- Depression* (excluding suicide and self-injury)
- Suicide/self-injury
- Serious suicide/self-injury per GSK adjudication
    - Suicidal Behaviour
        - Completed Suicide
    - Suicidal Ideation

- Self-injurious Behaviour without Suicidal Intent

* Including mood disorders and anxiety.

Deaths

7.4. Overview of Planned Laboratory, Immunogenicity and Vital Signs Summaries

Table 11 provides an overview of the planned Laboratory, Immunogenicity, Immunoglobulins and Vital Signs summaries by parent randomised treatment group, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 11 Overview of Planned Laboratory, Immunogenicity and Vital Signs

	Summary		Individual
	T	F	L
Laboratory Parameters (by Visit)			
Lab Parameters Visit Values	Y (x5) [1] [2]	Y (x5) [1]	Y (x6) [3]
Lab Parameter Change from BL	Y (x5) [1] [2]	Y (x5) [1]	
Worst Laboratory Toxicity Grade (by Year Interval)			
Worst Lab Toxicity Grade	Y (x6) [3]		
Worst Lab Toxicity Grade by At least 2 Grades from BL	Y (x6) [3]		
Grade 3 & 4 Lab Toxicity Results			Y (x6) [3]
Laboratory Reference Range Shifts			
Lab Reference Shifts from BL	Y (x6) [3]		
Hepatobiliary (Liver)			
Liver Events			Y (x3) [4]
Immunogenicity			
Immunogenicity Response by Visit	Y		Y
Immunogenicity Response by Year Interval	Y		
Vital Signs			
Vital Signs Visit Values	Y		Y
Pregnancies			
On-study Pregnancies per End of Treatment CRF			Y

NOTES:

- BL = Baseline, T = Table, F = Figure, L = Listing, Y = Yes display generated, (xN) = Number of separate displays generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Separate displays generated for [A] Haematology, [B] Liver Function, [C] Electrolytes, [D] Other Chemistries, [E] Immunoglobulins.

[2] A combined display will be generated for Absolute and Change from baseline for each laboratory parameter.

[3] Separate displays generated for [A] Haematology, [B] Liver Function, [C] Electrolytes, [D] Other Chemistries, [E] Urinalysis, [F] Immunoglobulins. Note: immunoglobulin data will be summarised separately by parent study. See Section 5.1.

[4] Separate displays generated for [A] Liver Assessment, [B] Liver Biopsy Details, [C] Liver Imaging.

7.4.1. Clinical Laboratory Evaluations

- 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.
- Analyses will be performed based on the observed data. Only central laboratory data will be summarized.
- Refer to Appendix 5: Derived and Transformed Data for handling of laboratory values that are above or below the lower limit of quantification.
- Listings will be generated for all laboratory results, and additionally for Grade 3 or Grade 4 laboratory toxicity results.
- Baseline is defined as described in Section 11.4.2 and a list of laboratory parameters collected and definition of the toxicity grades provided in Appendix 9: Laboratory Parameters & Adverse Events Grading Tables.
    - Note: UREA is collected in BEL114333/BEL113750 and BUN is collected in BEL112341. "Urea (mmol/L) & BUN (mmol/L)" will be displayed as a single parameter in tabular summaries of laboratory parameters and a footnote added to highlight that different tests were performed in the different studies.
    - Note: Bilirubin direct data were not collected during the parent study for BEL112341 subjects; thus, because of missing data at baseline and post-baseline visits for the first 6 months of belimumab treatment (and data for the subsequent 12 months is limited to the placebo group), these subjects will be excluded from this summary.
- Toxicities will be reported as derived by the GSK EDU, as protocol toxicity grading was applied (or as assigned programmatically in the ADaM dataset creation, for lymphocytes, spot urine protein creatinine ratio and urine RBC). Note: toxicity data for partial thromboplastin time and prothrombin time will not be summarised because the data were only collected in the parent study. However, PT/PTT at baseline will be displayed in tabular summaries of laboratory parameters (see Section 7.4.2).

  Additionally, for potassium, glucose, calcium and sodium, toxicities are bi-directional (i.e. high or low directions) and both will be summarised 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 as

    - RESULT < (LLN+ULN)/2 = "Hypo" toxicity
    - RESULT > (LLN+ULN)/2 = "Hyper" toxicity.

7.4.2. Laboratory Parameters by Visit

- Summaries will be presented by parent randomized treatment group, and total Safety population.
    - Note: immunoglobulin data will be summarized for subjects from each parent study separately.
- The absolute values and the change from baseline for each analyte will be summarized using descriptive statistics, at each belimumab visit.
- Line graphs will display the time course for each analyte, separately for the absolute value and the change from baseline.

7.4.3. Worst laboratory toxicity grade post-baseline

- Toxicity grading for each analyte will be summarized. This reflects the worst grade for each analyte across all subjects and all assessments for each year interval and at any time post-baseline. The display will summarize the number (%) of subjects for each of the toxicity grades.

7.4.4. Shift in Laboratory toxicity grade post-baseline

- Toxicity grade shifts from baseline of ≥ 2 grades for each analyte will be summarized for each year interval and at any time post-baseline. The display will summarize the number (%) of subjects with at least one ≥ 2 grade shift as well as the specific shift categories: Grade 0 to 2, Grade 0 to 3, Grade 0 to 4, Grade 1 to 3, Grade 1 to 4, and Grade 2 to 4.
- See Appendix 2: Assessment Windows for handling of the post-last dose 16 Week follow-up visit.

7.4.5. Laboratory Reference Range Shifts

- Summaries will be presented by parent randomized treatment group, and total Safety population.
- Laboratory reference range shifts will be summarized only for laboratory tests without toxicity grades.
- A laboratory value that is outside of normal range will be considered abnormal (above or below).
- Shifts relative to the normal range will be summarized for each analyte, at each belimumab visit, as follows:
    - ‘n’ represents the number (%) of subjects with a low, high or normal value at the specified visit.
    - For subjects with a low value at the specified visit, the shift categories relative to baseline are shown as either remained low, or normal/high to low.
    - For subjects with a high value at the specified visit, the shift categories relative to baseline are shown as either remained high, or normal/low to high.

- For subjects with a normal value at the specified visit, the shift categories relative to baseline are shown as either remained normal, or high to normal, or low to normal.

7.4.6. Immunogenicity

- Serum samples for anti-belimumab anti-body measurements were obtained from subjects per the protocol.
    - Immunogenicity testing in BEL114333 subjects used a tiered approach. The binding assay (to detect the presence of anti-drug antibodies) consisted of 3-testing steps: screening, confirmation and titer. At each scheduled visit, the screening assessment was performed resulting in a positive (above screening cut point) or negative (below screening cut point) result. Samples testing potentially positive in the screening assay were then tested in the confirmation assay. Samples then testing positive in the confirmation assay (above confirmation cut point) were considered confirmed and reported as positive; samples with a result below the confirmation cut point were reported as negative for the binding assay. Samples with a confirmed positive result were also run in the titration assay, and a titer value reported. In addition, samples testing positive for the binding assay were also tested in the neutralization assay (to determine if ADA were neutralizing), which also produced a result of positive or negative.
    - Binding confirmatory assay results will be categorized for analysis as
        - negative,
        - persistent positive (defined as a positive immunogenic response on at least 2 consecutive assessments post-first dose of belimumab or a single positive result at the final assessment), or
        - transient positive (defined as a single post-first dose of belimumab positive immunogenic response that does not occur at the final assessment)

    Note: For the placebo cohort who proceeded to the open-label and received belimumab, the baseline result for the open-label analysis is defined as the last assessment prior to the start of belimumab treatment. The baseline result was assessed from the sample collected prior to the first dose of belimumab. The first positive post-dose assessment would be a transient positive, and if followed by a positive result in the next assessed sample, the result is considered persistent.
- Immunogenicity response (negative, persistent positive, transient positive) will be summarized by the parent randomized treatment group, and total Safety population, for each belimumab visit (including Week 16 FU and Month 6 FU visits). Note, collection of samples for immunogenicity testing at the Month 6 FU visit is reserved for subjects with a prior positive immunogenicity result such as from the Week 16 FU visit. Any Month 6 FU visit result for subjects having had a prior positive result will be summarized.

  Additionally, the immunogenicity response will be summarized for any time post baseline in which a subject will be counted once only, based on the highest binding

confirmatory assay result (lowest to highest result: Negative, Transient Positive, Persistent Positive).

- Immunogenicity response post-first dose will also be summarized by year interval in which the latest value in the year interval will be reported (usually Week 48 visit, but when not available, Week 24 or Exit visit value will be used).
- A summary of all (including baseline) immunogenicity results based on the highest binding confirmatory assay result will be produced by parent randomized treatment group, and the total Safety population. If a subject had Negative and Positive confirmatory results during the entire study period, they will be included in the Positive category.
- A quartile assessment of the titer value will not be performed due to the low number of positive results.

8. EFFICACY ANALYSES

The efficacy analyses will be based on the Safety population, unless otherwise specified. Further details of efficacy endpoints are provided in Appendix 5: Derived and Transformed Data.

8.1. Overview of SRI and Secondary Efficacy Endpoints

Table 12 provides an overview of the planned analyses for the SRI and secondary efficacy endpoints, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 12 Overview of Planned Efficacy Analyses

Endpoint	Summary		Individual
	T	F	L
SRI Response			
SRI Response	Y	Y	Y
SELENA SLEDAI [1]			
SELENA SLEDAI ≥ 4 Point Reduction from BL	Y	Y	Y
PGA [1]			
PGA No Worsening (Increase of < 0.30 points from BL)	Y	Y	Y
BILAG [1]			
BILAG No New 1A/2B Organ Domain Scores	Y	Y	Y
Prednisone			
Number of days of daily prednisone ≤ 7.5 mg/day and/or reduced by 50% from BL	Y		Y
SFI Flare			
Time to First Severe SFI Flare	Y	Y	Y

NOTES:

- BL = Baseline, T = Table, F = Figure, L = Listing, Y = Yes display generated, (xN) = Number of separate displays generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Component endpoints of the composite SRI response.

8.1.1. SRI Response Rate

The proportion of subjects achieving an SRI response will be summarised by parent randomised treatment group, and the total Safety population, for each belimumab visit (every Week 24 and Week 48 visit). Total Safety population data will be displayed graphically using a line graph.

The SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score, **AND**
- No worsening (increase of < 0.30 points from baseline) in Physician's Global Assessment (PGA), **AND**

- No new British Isles Lupus Assessment Group of SLE Clinics (BILAG) A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment.

  Note: This third bullet is more clearly written as, "No new British Isles Lupus Assessment Group of SLE Clinics (BILAG) A organ domain score **and at most 1** new BILAG B organ domain score compared with baseline at the time of assessment."

8.1.2. SELENA SLEDAI ≥ 4 Point Reduction from Baseline

The proportion of subjects with a reduction from baseline of ≥ 4 points in SELENA SLEDAI score will be summarised by parent randomised treatment group, and the total Safety population, for each belimumab visit (every Week 24 and Week 48 visit). Total Safety population data will be displayed graphically using a line graph.

8.1.3. PGA No Worsening

Scoring of the PGA scale ranges from 0-3, where 0 indicates no disease activity.

The proportion of subjects with no worsening in PGA (defined as an increase < 0.30 points from baseline, using the re-scaled score 0-3 scale) will be summarised by parent randomised treatment group, and the total Safety population, for each belimumab visit (every Week 24 and Week 48 visit). Total Safety population data will be displayed graphically using a line graph.

8.1.4. BILAG No New 1A/2B Organ Domain Scores

The proportion of subjects with no new BILAG A **and at most 1** new BILAG B organ domain scores (No New 1A/2B) compared to baseline at the time of the assessment, will be summarised by parent randomised treatment group, and the total Safety population, for each belimumab visit (every Week 24 and Week 48 visit). Total Safety population data will be displayed graphically using a line graph.

8.1.5. Number of Days of Daily Prednisone ≤ 7.5 mg/day and/or Reduced by 50% from Baseline

The number of days of daily prednisone dose ≤ 7.5 mg/day and/or reduced by 50% from baseline will be summarised at each Week 24 and 48 belimumab visit (in every year) and at any time post-baseline. Only subjects receiving a prednisone dose > 7.5 mg/day at the baseline visit will be included.

For subjects who have attended Week 24 and 48 belimumab visits (in every year), the number of days from first day of belimumab (given on the baseline visit) of daily prednisone dose ≤ 7.5 mg/day and/or reduced by 50% compared to the baseline visit will be summarised, using descriptive statistics.

8.1.6. Time to First Severe SFI Flare

SFI flare data are collected at scheduled visits where only one flare may be recorded. The frequency of these flare assessments vary and will be collected in accordance to their respective timings (Section 11.1). Additional flares occurring between scheduled assessments during study BEL114333 were collected using an additional SLE flare log. (Note: only the flare data were collected but no visit information) and flares will be assigned to the next scheduled visit for flares.

Time to the first severe SFI flare during belimumab treatment will be summarised by the parent randomised treatment group, and the total Safety population.

Note, for this study, analyses of SFI flares will be conducted based on the modified SLE flare index (modified excludes severe flares from the SELENA SLEDAI assessment that were triggered only by an increase in SELENA SLEDAI score to > 12, see Section 11.5.4.5).

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

Time to the first severe SFI flare is calculated as the number of days from the first dose of belimumab treatment up to the first severe flare event (event date – first dose date of belimumab + 1). The disposition of subjects is defined as follows:

Subject Disposition	Event Met	Event Date
Subject has a severe SFI flare		
Subject has a severe SFI flare during the study	Yes	Date of first severe SFI flare
Subject does not have a severe SFI flare		
Subject withdraws from the study	No	Censored at last available date where flare is assessed
Subject dies during the study	No	Censored at date of death.
Subject who completes the study *	No	Censored at last available date where flare is assessed

* As per the protocol. Includes subjects who transferred to study BEL116027, or who were still participating in the study at the time of the sponsor decision to close the study.

The display will summarise the number and percentage of subjects with a severe SFI flare as well as the Kaplan-Meier estimate of the median, 25th and 75th percentiles of days to first severe SFI flare. For subjects who experienced a severe SFI flare, the display will summarise the median, 25th and 75th percentiles, minimum and maximum time to the first severe SFI flare from baseline, by parent randomised treatment group, and the total Safety population.

A cumulative incidence curve for time to first severe SFI flare will be produced for the total Safety population, using Kaplan-Meier methods. The time of the first severe SFI

flare from baseline through to each belimumab visit at Week 24 and Week 48 of each year will be summarised.

8.2. Overview of Other Efficacy Endpoints

Table 13 provides an overview of the planned analyses of other efficacy endpoints, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 13 Overview of Planned Other Efficacy Analyses

Endpoint	Summary		Individual
	T	F	L
Disease Activity			
SELENA SLEDAI Change from BL	Y [1]	Y	
SELENA SLEDAI % Change from BL	Y [1]	Y	
SLICC/ACR Damage Index Observed and Change from BL	Y [1] [2]		Y
SLICC/ACR Damage Index Worsening	Y [2]		
PGA % Change from BL	Y [1]	Y	
Flares			
Time to First SFI Flare	Y	Y	
Number of Severe SFI Flares (and rate per 100 PY)	Y		
Number of SFI Flares (and rate per 100 PY)	Y		
Time to First 1A/2B BILAG Flare	Y	Y	
Time to First BILAG A Flare	Y	Y	
Organ-Specific Measures			
Time to First Renal Flare	Y	Y	
Proteinuria % Change from BL (among subjects with BL proteinuria)	Y [1]	Y	
Proteinuria Shifts from BL	Y		
Prednisone			
Prednisone % Change from BL	Y [1]	Y	
Prednisone Dose Reduced to ≤ 7.5 mg/day (among subjects with BL dose > 7.5 mg/day)	Y	Y	

NOTES:

- BL = Baseline, T = Table, F = Figure, L = Listing, Y = Yes display generated, (xN) = Number of separate displays generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] A combined display will be generated for Absolute and Change from baseline for each laboratory parameter.

[2] Data summarised separately by parent study. See Section 5.1.

8.2.1. SELENA SLEDAI Change from Baseline

The absolute values, the change, and the percent change from baseline in SELENA SLEDAI scores will be summarised using descriptive statistics, and presented by parent randomised treatment group and the total Safety population, for each belimumab visit

(every Week 24 and Week 48 visit). In summaries, decreases will reflect improvement in the assessment.

Data will be displayed graphically over time using a line graph for the total Safety population. Separate plots will be produced for the mean change from baseline (± SE) and mean percent change from baseline in SELENA SLEDAI score.

8.2.2. SLICC/ACR Damage Index

- The absolute values and change from baseline in SLICC/ACR Damage Index will be summarised using descriptive statistics, and presented by the parent randomised treatment group, for each belimumab visit. This data will be presented separately for subjects from each parent study.
- The SLICC/ACR Damage Index increases over time, and once an item is scored it continues to be scored at all subsequent assessments, even if the subject subsequently recovers.
    - Due to incorrect scoring, the database contains a small number of subjects who have at least one decrease in SLICC/ACR Damage Index since baseline.
    - Where the error occurred at closed sites, data management were unable to query and correct the error.
    - Due to these incorrect assessments, a worst score observation carried forward (WOCF) approach will be used at the item level for the SLICC/ACR Damage Index items. These WOCF values will then be used to calculate the total score which will be the value summarized and displayed for reporting.
- The number and percentage of subjects with a worsening in their SLICC/ACR Damage Index score compared with baseline (change score > 0) will be summarized.

See Appendix 5: Derived and Transformed Data for the derivation of SLICC/ACR Damage Index score including Worst Observation Carried Forward (WOCF).

8.2.3. Physician's Global Assessment Change from Baseline

The absolute values and percent change from baseline in PGA will be summarised using descriptive statistics, and presented by the parent randomised treatment group and total Safety population, for each belimumab visit (every Week 24 and Week 48 visit). Total Safety population data will be displayed graphically using a line graph. The plot will show the mean change from baseline (± SE) over time.

See Appendix 5: Derived and Transformed Data for the derivation.

8.2.4. Time to First SFI Flare

A SFI flare is defined as a mild/moderate or severe flare per the modified SELENA SLEDAI SLE Flare Index. Analyses of the first SFI flare will use the same methodology as for severe SFI flares (see Section 8.1.6).

8.2.5. Number of SFI Flares and Rates

The number of SFI flares (each for severe flares and any flares) will be summarised at any time post-baseline, and presented by the parent randomised treatment group and the total Safety population. Rates of flares per 100 person-years will also be reported.

The table will display the total number of SFI flares (each for severe flares and any flares), total person-years of follow-up for SFI flare assessments, and the rate of flare events per 100 person-years. See Section 11.5.4.5 for the derivation of the SFI flare rate.

8.2.6. Time to First 1A/2B BILAG Flare

A 1A/2B BILAG flare is defined as at least 1 new BILAG A or 2 or more new BILAG B organ domain scores compared to baseline. Note, a BILAG assessment needs to be performed to determine if there is a change in organ domains. Every 6 month BILAG assessments in BEL114333 will not allow the same reporting as in the parent study (every 4 weeks).

Time to first 1A/2B BILAG flare is calculated as the number of days from first dose of belimumab treatment up to the first BILAG flare event (event date – first belimumab dose date + 1). The event date is defined by the BILAG assessment date. The disposition of subjects is defined as follows:

Subject Disposition	Event Met	Event Date
Subject has a 1A/2B BILAG flare		
Subject has a BILAG flare during the study	Yes	Date of first BILAG flare
Subject does not have a 1A/2B BILAG flare		
Subject withdraws from the study	No	Censored at last available BILAG assessment
Subject dies during the study	No	Censored at date of death.
Subject completes the study *	No	Censored at last available BILAG assessment

* As per the protocol. Includes subjects who transferred to study BEL116027, or who were still participating in the study at the time of the sponsor decision to close/terminate the study

Analyses for the first 1A/2B BILAG flare will use the same methodology as for severe SFI flares (see Section 8.1.6).

8.2.7. Time to First BILAG A Flare

A BILAG A flare is defined as at least 1 new BILAG A organ domain score compared to baseline. Time to the first BILAG A flare will be summarised as per the BILAG 1A/2B flare endpoint (see Section 8.2.6).

8.2.8. Time to First Renal Flare

Only time to first renal flare will be analysed. Although a renal flare rate was of interest at the time of the protocol design writing, renal flare rates have been relatively

uncommon, and do not provide much clinical value at this current time. Focus will be placed upon providing a summary of the first renal flare event.

Assessments every 6 months during BEL114333 will not allow the use of the same definition of renal flares as in the parent studies, which requires assessments to be performed at two or more consecutive monthly visits. Thus, a renal flare is defined as the occurrence of one or more of the following criteria at a single (belimumab) visit at every Week 24 and Week 48, timepoints at which both protein creatinine ratio and lab assessments are scheduled in the protocol. Note, when identifying renal flares, data within the visit window at Week 24 and Week 48 visits will be considered.

1. An increase in 24-hour urine protein equivalent levels to
    a. > 1 g if the baseline value was < 0.2 g,
    b. > 2 g if the baseline value was 0.2 to 1 g, or
    c. More than twice the value at the baseline if the baseline value is > 1 g.

2. An increase in serum creatinine of >20 % or an increase of at least 0.3 mg/dL, accompanied by at least one of proteinuria (>1 g/24 hour equivalent), hematuria (≥ 4 red blood cells [RBCs]/high-power field [hpf]), cellular (RBC or WBC) casts. The inclusion of 'at least one of' and 'RBC or WBC' casts is an addition to the protocol specified definition. This addition has been included in the parent study BEL113750 RAP.

3. Treatment-emergent, hematuria (≥ 11 to 20 RBCs/hpf) or an increase in hematuria by 2 grade compared with baseline, associated with > 25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 0.8 g increase in 24-hour urinary protein levels (equivalent) or new RBC casts [Alarcón-Segovia, 2003].

To clarify criterion 2, [an increase in serum creatinine of > 20% OR an increase of at least 0.3 mg/dL], AND [proteinuria (> 1 g/24-hour equivalent) OR hematuria (≥ 4 red blood cells {RBCs}/high-power field {hpf}) OR cellular (RBC or WBC) casts].

To clarify criterion 3, [treatment-emergent, hematuria (≥ 11 to 20 RBCs/ hpf) OR (an increase in hematuria by 2 grades compared with baseline AND > 25% dysmorphic RBCs, glomerular in origin, exclusive of menses)], AND [0.8 g increase in 24-hour urinary protein levels (equivalent) OR new RBC casts].

Time to first renal flare is calculated as the number of days from first dose of belimumab treatment up to the first renal flare event (event date – first belimumab dose date + 1). The event date is defined by the scheduled laboratory assessment date. The disposition of subjects is defined as follows:

Subject Disposition	Event Met	Event Date
Subject has a renal flare		
Subject has a renal flare during the study	Yes	Date of first renal flare

Subject does not have a renal flare		
Subject withdraws from the study	No	Censored at last available date where all relevant parameters were assessed.
Subject dies during the study	No	Censored at date of death.
Subject completes the study *	No	Censored at last available date where all relevant parameters were assessed.

* As per the protocol. Includes subjects who transferred to study BEL116027, or who were still participating in the study at the time of the sponsor decision to close/terminate the study

Analyses for the first renal flare will use the same methodology as for severe SFI flares (see Section 8.1.6).

8.2.9. Proteinuria Percent Change from Baseline

Because no subjects had an actual 24 hour urine collection to assess proteinuria, the definition of proteinuria can be simplified to just using the spot urine PC ratio to assess the degree of proteinuria present at Week 24 and Week 48 (in every year). Proteinuria will be defined as a urine PC ratio > 0.5 mg/mg. Note, the PC ratio reported in mg/mg is the 24 hour gram equivalent.

For subjects with proteinuria at baseline, the absolute value and percent change from baseline in urine PC ratio will be summarised using descriptive statistics, and presented by the parent randomised treatment group and overall, for each belimumab visit.

For this group of subjects having proteinuria at baseline, the data will be displayed graphically using a line graph. The plot will show the mean percent change from baseline (± SE) over time.

See Section 11.5.4.6 for the conversion of urine PC ratio from SI units to mg/mg.

8.2.10. Proteinuria shifts

Proteinuria shifts as measured by spot urine PC ratio.

Urine PC ratio values will be summarised according to the following categories at baseline: normal (≤ 0.5 mg/mg) or high (> 0.5 mg/mg).

For each Week 24 and Week 48 belimumab visit (in every year), the data will be summarised by baseline status defined as normal or high.

- For subject with a normal value at baseline, the shift categories at the specified visit are shown as either ‘No change’ or ‘Normal to High’.
- For subjects with a high value at baseline, the shift categories at the specified visit are shown as either ‘No Change’ or ‘High to Normal’.

Additionally, the spot urine PC ratio values will be summarised based on shifts occurring any time while on treatment.

- For subject with a normal value at baseline, the number (%) of subjects with at least one high post-baseline value will be presented as 'Normal to High'; otherwise as 'No Change'.
- For subjects with a high value at baseline, the number (%) of subjects with at least one normal post-baseline value will be presented as 'High to Normal'; otherwise as 'No Change'.

8.2.11. Prednisone Percent Change from Baseline

The observed values and percent change from baseline in average daily prednisone dose will be summarised using descriptive statistics, and presented by the parent randomised treatment group and the total Safety population, for each Week 24 and 48 belimumab visit (in every year).

The derivation of average daily prednisone dose and conversion to the prednisone-equivalent dose are provided in Section 11.5.3

Total Safety population data will be displayed graphically using a line graph. The plot will show the mean percent change from baseline (± SE) over time.

8.2.12. Prednisone Dose ≤ 7.5 mg/day for Subjects with an Average Daily Dose > 7.5 mg/day at Baseline

For subjects with an average daily prednisone dose > 7.5 mg/day at baseline, the proportion of subjects with an average daily prednisone dose reduced to ≤ 7.5 mg/day will be summarised, and presented by the parent randomised treatment group, and overall, for each Week 24 and Week 48 belimumab visit (in every year).

For this group of subjects having an average daily prednisone dose > 7.5 mg/day at baseline, the data showing reduction to ≤ 7.5 mg/day will be displayed graphically using a line graph. The plot will show the proportion of subjects with this reduction (± SE) over time.

8.2.13. Prednisone Dose > 7.5 mg/day for Subjects with an Average Daily Dose ≤ 7.5 mg/day at Baseline

For subjects with an average daily dose ≤ 7.5 mg/day at baseline, the proportion of subjects with an average daily prednisone dose increased to > 7.5 mg/day, will be summarised, and presented by the parent randomised treatment group, and the overall, for each Week 24 and Week 48 belimumab visit (in every year).

For this group of subjects having an average daily prednisone dose ≤ 7.5 mg/day at baseline, the data showing elevation to > 7.5 mg/day will be displayed graphically using a line graph. The plot will show the proportion of subjects with this increase (± SE) over time.

9. BIOMARKER ANALYSES

The biomarker parameters will be based on the Safety population, unless otherwise specified.

9.1. Overview of Planned Biomarker Analyses

Table 14 provides an overview of the planned biomarker analyses, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 14 Overview of Planned Biomarker Analyses

Endpoint	Summary		Individual
	T	F	L
Serum Immunoglobulin (IgG, IgM & IgA)			
Lab Parameter Visit Values	Y [1] [4]		
Lab Parameter % Change from BL	Y [1] [4]	Y	
IgA, IgG, IgM below LLN by Visit	Y [4]		
IgA, IgG, IgM below LLN by Year Interval	Y		
Autoantibodies (anti-dsDNA)			
Lab Parameter Visit Values	Y [1]		Y [2]
Lab Parameter % Change from BL	Y [1]	Y	
Lab Parameter Visit Values for Subjects Positive at BL	Y [1]		
Lab Parameter % Change from BL for Subjects Positive at BL	Y [1]	Y	
Complement (C3, C4) Levels			
Lab Parameter Visit Values	Y [1]		Y [2]
Lab Parameter % Change from BL	Y [1]	Y	
Lab Parameter Visit Values for Subjects with Low Complement at BL	Y [1]		
Lab Parameter % Change from BL for Subjects with Low Complement at BL	Y [1]	Y	
B Cell Subsets [3]			
Lab Parameter Visit Values	Y [1] [4]		Y
Lab Parameter % Change from BL	Y [1] [4]	Y	

NOTES:

- BL = Baseline, T = Table, F = Figure, L = Listing, Y = Yes display generated, (xN) = Number of separate displays generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] A combined display will be generated for observed and change from baseline for each parameter.
[2] Combined into a single display.
[3] B cell data are collected only at 'selected sites' in which the selected sites were all Japan sites. See Section 11.5.5.1 for additional information.
[4] Data summarised separately by parent study. See Section 5.1.

9.1.1. Percent change from baseline

The absolute values and percent change from baseline in immunoglobulins, autoantibodies (anti-dsDNA), complement levels (C3 and C4), and B cell subsets (see Section 11.5.5.1) will be summarised using descriptive statistics, and presented by the parent randomised treatment group and the total Safety population. The frequency of these lab specimens vary and thus will be shown in accordance their respective timings (see Section 11.1).

Total Safety population data will be displayed graphically using a line graph. The plot will show the median percent change from baseline (interquartile range bars) over time.

Note: For immunoglobulins and B cell subsets, the data will be presented separately for subjects from each parent study.

Additionally, for anti-dsDNA, analyses will be performed among subjects who were positive at baseline; for complement levels, analyses will be performed among subjects with low values at baseline. See Section 11.5.5 for baseline classifications.

9.1.2. Immunoglobulin (IgG, IgA and IgM) below LLN

The number (%) of subjects with immunoglobulin (IgG, IgA and IgM) values below the lower limit of normal (LLN) will be summarised by the parent randomised treatment group, for each belimumab visit. This data will be presented separately for subjects from each parent study. See Section 11.5.5 for LLN classifications.

Additionally, the immunoglobulin data for all subjects will be shown by year interval and at “any time post-baseline”. See Section 11.5.5 for LLN classifications.

10. REFERENCES

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11. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
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Section 11.3	Appendix 3: Adverse Event Collapsing Rules and Assignment of Adverse Events to Study Year
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Section 11.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Biomarkers
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11.1. Appendix 1: Time & Events

11.1.1. BEL114333 Protocol Defined Time & Events

11.1.1.1. Open-label Year 1

Study Visit	Wk 48 of BEL 113750/ On/before Day 168 of C1115[1]	Wk 0 (Wk 52 of BEL113750/Day 168 of C1115) +1 week[1]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[2]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
Study Day		Day 0	28 ±7d	56 ±7d	84 ±7d	112 ± 7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d			
Written Informed Consent	X																
Inclusion/Exclusion Criteria		X*															
Efficacy Assessments																	
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG and PGA[3]		X						X						X	X		
SLICC/ACR Damage Index		X												X	X		
Safety Assessments																	
Symptom-driven Physical Exam		X						X						X	X	X	
Record Concurrent Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess/Record Adverse Events[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [5, 11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Visit	Wk 48 of BEL 113750/ On/before Day 168 of C1115[1]	Wk 0 (Wk 52 of BEL113750/Day 168 of C1115) +1 week[1]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[2]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
Study Day		Day 0	28 ±7d	56 ±7d	84 ±7d	112 ± 7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d			
Laboratory Assessments																	
Labs: Haematology & Modified Chem 20 (non fasting)[5]		X	X		X			X			X			X	X	X	
Urinalysis[5]		X	X		X			X			X			X	X	X	
Spot urine (protein to creatinine ratio)[5, 6]		X						X						X	X		
Urine Pregnancy Test [5,7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C3, C4, Anti-ds DNA Autoantibodies[5]		X						X						X	X		
IgG [5, 8]		X			X			X						X	X	X	
IgA & IgM [5, 8]		X												X	X		
PT/ PTT		X*															
Exploratory Lab Assessments																	
Immunogenicity [9]		X						X						X	X	X	X[9A]
B cell Markers [10]		X												X	X		X
Investigational Product																	
Belimumab Administration [11, 12]		X*	X	X	X	X	X	X	X	X	X	X	X	X			

Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study. During the first 48 weeks, the 1st visit is Baseline/Day 0. For all subsequent 48 week calendar years, the 1st visit will be Week 4. Note: BEL112341 is referred to as 'C1115' in this time and events table.
*****See footnote 1.

1. **For subjects from BEL113750**: The Week 52 visit in the parent study Protocol BEL113750 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Week 52 procedures in BEL113750 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Protocol, Section 6.1. At Week 48 of BEL113750, a subject should sign the informed consent for the BEL114333 study. In addition to the Week 52 procedures for BEL113750, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive belimumab (those procedures marked with an asterisk). Subjects must be able to receive the 1st dose of belimumab (Day 0) for BEL114333 four weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750.
   For subjects from C1115: The Day 168 (Week 24) visit in the open-label extension phase of C1115 serves as the Day 0 visit for the Protocol BEL114333. Performance of all the Day 168 procedures in C1115 will cover nearly all the procedures that are required for Day 0 of this protocol. Procedures necessary for both this protocol and the prior Phase III protocol need only be performed once and shall be recorded to CRFs as described in Protocol, Section 6.1. On or before the Day 168 visit, a subject should sign the informed consent for the BEL114333 study. In addition to the Day 168 procedures for C1115, a subject should be reassessed for inclusion/exclusion criteria of the BEL114333 study and receive IV belimumab. The target for starting IV belimumab (Day 0) for BEL114333 is 1 week after the last dose of SC belimumab (scheduled for Week 23 in the open-label extension). The EXIT visit of the C1115 study (Week 24) serves as the Day 0 visit for the Protocol BEL114333, and will have a +1 week visit window.
2. The Exit visit will occur approximately 4 weeks after the last dose of belimumab. Belimumab should not be administered, and all Exit visit assessments must be completed.
3. Refer to Protocol, Section 6.2.2.3 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
4. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 have to be transferred and followed up in BEL114333.
5. Samples should be obtained prior to dosing.
6. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
7. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See 'Critical Baseline Assessments', Protocol, Section 6.1 for definition of those exempted from subsequent pregnancy testing.
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.
   [9A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.
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). Note: B-cell subsets to be drawn at selected sites only.
11. It is recommended the patient be weighed at each visit prior to dosing. If weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose. Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured (see Protocol, Section 6.3.11).
12. Subjects will remain under clinical supervision for 3 hours after completion of the first 2 infusions. See Protocol, Section 5 and Protocol, Section 6.3.9.

11.1.1.2. Open-Label Additional Years

Study Visit	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[1]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
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, BILAG and PGA [2]						X						X	X		
SLICC/ACR Damage Index												X	X		
Safety Assessments															
Symptom-driven Physical Exam						X						X	X	X	
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess/Record Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [4, 10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments															
Labs: Haematology & Modified Chem 20 (non fasting) [4, 11]						X						X	X	X	
Urinalysis [5, 11]						X						X	X	X	
Spot urine (protein to creatinine ratio) [4, 5, 11]						X						X	X		
Urine Pregnancy Test [6, 11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C3, C4, Anti-dsDNA Autoantibodies [4, 11]						X						X	X		
IgG [4, 7, 11]												X	X	X	
IgA & IgM [4, 7, 11]												X	X		

Study Visit	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	EXIT[1]	16 wk FU ± 7d post infusion	6 month FU ± 7d post infusion
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			
Exploratory Lab Assessments															
Immunogenicity[8]						X						X	X	X	X[8A]
B cell Markers[9]												X	X		X
Investigational Product															
Belimumab Administration[10]	X	X	X	X	X	X	X	X	X	X	X	X			

Calendar represents a yearly (48-week) ongoing visit schedule until the subject is terminated from the study. Note: BEL112341 is referred to as 'C1115' in this time and events table.

1. The Exit visit will occur approximately 4 weeks after the last dose of belimumab. Study agent should not be administered, and all Exit visit assessments must be completed.
2. Refer to Protocol, Section 6.2.2.3 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
3. AE reports should be updated or completed prior to dosing. Ongoing Adverse events of BEL113750 or C1115 have to be transferred and followed up in BEL114333.
4. Samples should be obtained prior to dosing.
5. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
6. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See 'Critical Baseline Assessments', Protocol, Section 6.1 for definition of those exempted from subsequent pregnancy testing.
7. Serum immunoglobulin isotypes: IgG, IgM, IgA.
8. Immunogenicity testing includes quantifying the amount of belimumab present in the samples using the belimumab PK assay.
   [8A]For any subject who had an anti-belimumab antibody response at the 16-week follow-up visit (or last study visit at which immunogenicity was assessed if the 16-week follow-up immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent.
9. 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). Note: B-cell subsets to be drawn at selected sites only.
10. It is recommended the patient be weighed at each visit prior to dosing. If weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose. Systolic and diastolic blood pressure (sitting), heart rate, and oral temperature will be measured (see Protocol, Section 6.3.11).
11. During "Additional years", investigators can obtain any of the same laboratory assessments that are mentioned for Year 1 (hematology, 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.

11.1.2. Parent Study Protocol Defined Time & Events

11.1.2.1. BEL113750 - Double-Blind Phase

Procedures	Screen	Random-isation	Treatment in the Blinded Period													End of Therapy	8 Week FU	16 Week FU	6 Month FU
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Study Day	Up to -35d	0	14± 3d	28± 3d	56± 7d	84± 7d	112 ±7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d	364 OR EXIT (4-wks post dose) [1] ± 7d	8-wk Follow-up [2] ± 7d	16-wk Follow-up [16]± 7d	6 Month Follow-up
Study Week	Wk -5	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 64	6 month
Written Informed Consent	X																		
Subject Demography	X																		
Medical History	X																		
SLE History	X																		
Therapy History	X																		
Physical Examination	X																		
Inclusion/Exclusion Criteria	X	X																	
Efficacy Assessments																			
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG and PGA [3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
SLICC/ACR Damage Index		X														X			
Safety Assessments																			
Vital Signs [4, 5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight, height [5, 6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-lead ECG [5]	X								X							X			

Procedures	Screen	Random-isation	Treatment in the Blinded Period													End of Therapy	8 Week FU	16 Week FU	6 Month FU
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Study Day	Up to -35d	0	14± 3d	28± 3d	56± 7d	84± 7d	112 ±7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d	364 OR EXIT (4-wks post dose) [1] ± 7d	8-wk Follow-up [2] ± 7d	16-wk Follow-up [16]± 7d	6 Month Follow-up
Study Week	Wk -5	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 64	6 month
C-SSRS [5] See Protocol, Appendix 9 Baseline/ Screening. NOTE: "Baseline" does not refer to randomisation visit.	X																		
C-SSRS [5] Since Last Visit. See Protocol, Appendix 10		X	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	X		
Assess/Record Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments																			
Labs: HIV, Hepatitis B, C, and HBV DNA [7]	X																		
Labs: Haematology & Modified Chem 20 (non-fasting)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis [8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Spot urine (protein to creatinine ratio) [9]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
ALT, AST, Total bilirubin																		X [16]	

Procedures	Screen	Random-isation	Treatment in the Blinded Period													End of Therapy	8 Week FU	16 Week FU	6 Month FU
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Study Day	Up to -35d	0	14± 3d	28± 3d	56± 7d	84± 7d	112 ±7d	140 ±7d	168 ±7d	196 ±7d	224 ±7d	252 ±7d	280 ±7d	308 ±7d	336 ±7d	364 OR EXIT (4-wks post dose) [1] ± 7d	8-wk Follow-up [2] ± 7d	16-wk Follow-up [16]± 7d	6 Month Follow-up
Study Week	Wk -5	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 64	6 month
Pregnancy Test [5, 10]	S	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U[16]	
Pharmacogenetic Sampling[11]			X																
aCL Autoantibody		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 [12]	X	X			X				X				X			X			
IgA & IgM [12]	X	X														X			
PT/ PTT	X																		
Exploratory Lab Assessments																			
Pharmacokinetic Sampling [13]		X	X		X				X							X	X		
Immunogenicity [5, 14]		X			X				X							X	X		X
BLyS Protein [5]		X																	
B cell Markers [15]		X		X	X	X						X				X	X		
Investigational Product																			
Investigational product Administration[17]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
See Footnotes on next page																			

1. The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of investigational product. For subjects completing all 48 weeks of treatment in the blinded period and continuing into the open-label period, this visit will also serve as their 1st (i.e., Day 0 OL [Open-Label]) visit of the open-label period and 1st dose of investigational product for the open-label period will be administered. Dosing information will be recorded in the Day 0 OL CRF of the open-label period.
2. The 8-week follow-up visit is to occur approximately 8 weeks after last dose of investigational product, only if the subject does not enter the open-label period.
3. Refer to Protocol, Section 6.2.2.3 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
4. Vital signs include temperature, sitting blood pressure and heart rate.
5. Complete prior to dosing.
6. If the subject's weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose to be administered. Height measured only at screening.
7. HIV, Hepatitis B surface antigen, anti-HBc, anti-HBs, HBV DNA, and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot or PCR assay should be reflexively performed on the same sample to confirm the results). Note: For China subjects, if HBc result is reactive, the sample drawn for HBV DNA will be tested for viral DNA; otherwise, the sample will be destroyed). Subjects in China with positive hepatitis C screening results will be excluded without confirmatory hepatitis C testing; see Protocol, Appendix 2.
8. Urinalysis at screening will include drug screen.
9. A 24-hour urine may be done as an additional assessment if clinically indicated (e.g., renal flare).
10. Serum pregnancy test (S) required at screening. Results of urine pregnancy test (U) at subsequent visits, if required, must be available prior to dose. See 'Critical Baseline Assessments', Protocol, Section 6.1 for definition of those exempted from subsequent pregnancy testing.
11. PGx sampling: PGx informed consent must be obtained prior to any blood being taken for PGx research. Samples should be drawn prior to dosing.
12. Serum immunoglobulin isotypes: IgG, IgM, IgA.
13. Pharmacokinetic sampling: Before the start of infusion on Days 0, 56, and 364 (only if entering the open-label period and at a selected China site); immediately after the end of infusion on Days 14 and 168; at any time during the visit at Day 364 (if not entering the open-label period at selected China sites) or during the 8-week follow-up visit.
14. All subjects withdrawing early or who do not enter the open-label period will have a blood sample taken at least 6 months after the final dose of investigational product.
15. 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).
16. This '16-week' follow up visit is to occur approximately16 weeks after the last dose of investigational product. ALT, AST, Total bilirubin, and urine pregnancy tests (for female subjects) will be drawn for all subjects who exit the blinded period prior to completion, and only for subjects who complete the blinded period, but who do not enter the open-label period.
17. Subjects will remain under clinical supervision for 3 hours after completion of the first 2 infusions. See Protocol, Section 5.1 and Protocol, Section 6.3.11.

11.1.2.2. BEL112341 (HGS1006-C1115)

11.1.2.2.1. BEL112341 - Double-blind Phase

Procedures	52-week Treatment Period Days 0 – 364 (Weeks 0 – 52)																Post-Treatment Follow-up Period [B]	
	Day 0 Visit	Day 28 Visit ± 7 day	Day 56 Visit ± 7 day	Day 84 Visit ± 7 day	Day 112 Visit ± 7 day	Day 140 Visit ± 7 day	Day 168 Visit ± 7 day	Day 196 Visit ± 7 day	Day 224 Visit ± 7 day	Day 252 Visit ± 7 day	Day 280 Visit ± 7 day	Day 308 Visit ± 7 day	Day 336 Visit ± 7 day	Day 364/Exit Visit subjects moving to OL phase [A]	Day 364/Exit Visit early termination or subjects not moving	Day 364 for non-completers [F] ± 7 days	8 wk Follow-up Visit (8-wks post last dose) ± 7 day [B]	Unscheduled Visit [C]
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	1-4 wks after last SC dose	Wk 52		
SC administration of study agent*	X	Weekly (±1 day) with final dose at Week 51																
Clinical Assessments:																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom-driven PE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
C-SSRS Baseline/Screening	At Screening visit only (See Protocol, Section 6.1, Appendix 11, and Section 7.5)																	
C-SSRS Since Last Visit [M]	X	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		X	X
Collect self-injection logs; record dosing in CRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Record All Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
SLE Disease Activity Scales [D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SLICC/ACR Damage Index	X													X	X			
FACIT-Fatigue Scale [E]	X	X	X	X			X			X				X	X			

Procedures	52-week Treatment Period Days 0 – 364 (Weeks 0 – 52)																Post-Treatment Follow-up Period [B]	
	Day 0 Visit	Day 28 Visit ± 7 day	Day 56 Visit ± 7 day	Day 84 Visit ± 7 day	Day 112 Visit ± 7 day	Day 140 Visit ± 7 day	Day 168 Visit ± 7 day	Day 196 Visit ± 7 day	Day 224 Visit ± 7 day	Day 252 Visit ± 7 day	Day 280 Visit ± 7 day	Day 308 Visit ± 7 day	Day 336 Visit ± 7 day	Day 364/Exit Visit subjects moving to OL phase [A]	Day 364/Exit Visit early termination or subjects not moving	Day 364 for non-completers [F] ± 7 days	8 wk Follow-up Visit (8-wks post last dose) ± 7 day [B]	Unscheduled Visit [C]
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	1-4 wks after last SC dose	Wk 52		
Survival assessment [F]																X		
Laboratory Assessments:																		
Pregnancy Test [G]	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	X
Spot Urine Protein Creatinine Ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PT/PTT	X		X				X							X	X			
Hematology & Modified Chem 20 (non fasting) [H]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Complement (C3/C4) and anti-dsDNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pharmacokinetics [I]	X	X	X		X		X							X	X		X	X
Immunogenicity [J]	X		X				X							X	X		X	X
B cells	X		X				X							X	X			
ANA	X																	
Extractable nuclear antigens (ENAs) [K]	X		X				X							X	X			
Antiphospholipid antibodies (aCL, lupus anticoagulant, +/- beta-2-glycoprotein-1)	X		X				X							X	X		X	
Serum Immunoglobulin (IgA, IgM, IgG)	X		X		X		X		X		X			X	X		X	

Procedures	52-week Treatment Period Days 0 – 364 (Weeks 0 – 52)																Post-Treatment Follow-up Period [B]	
	Day 0 Visit	Day 28 Visit ± 7 day	Day 56 Visit ± 7 day	Day 84 Visit ± 7 day	Day 112 Visit ± 7 day	Day 140 Visit ± 7 day	Day 168 Visit ± 7 day	Day 196 Visit ± 7 day	Day 224 Visit ± 7 day	Day 252 Visit ± 7 day	Day 280 Visit ± 7 day	Day 308 Visit ± 7 day	Day 336 Visit ± 7 day	Day 364/Exit Visit subjects moving to OL phase [A]	Day 364/Exit Visit early termination or subjects not moving	Day 364 for non-completers [F] ± 7 days	8 wk Follow-up Visit (8-wks post last dose) ± 7 day [B]	Unscheduled Visit [C]
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	1-4 wks after last SC dose	Wk 52		
BLyS Protein	X																	
Pharmacogenetic Sampling [L]	X																	

* The 1st (Day 0) and 2nd (Day 7 ± 1) day administration will be under supervision at the study site.

A This is Day 0 for subjects entering the open-label (OL) extension phase of the protocol. The visit window is ± 1 day

B Subjects must complete an exit visit 1-4 weeks after their last dose of study agent and a follow-up visit 8 weeks after their last dose of study agent. Subjects who enter the open-label (OL) extension phase will complete the 8-week follow-up visit after their last dose of study agent in the open-label phase. Subjects who enroll in the continuation protocol do not need to complete the 8-week follow-up visit.

C Perform other assessments as clinically indicated.

D SLE Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG, PGA.

E Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

F Assessed only for subjects who withdraw from treatment prior to Week 52. Attempt should be made to follow subjects who have lost to follow-up.

G Serum pregnancy test is required at screening. Urine pregnancy tests are performed during the remainder of the study. See Protocol, Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing.

H Refer to Protocol, Appendix 8 for a listing of laboratory assessments to be completed. PT/PTT will be assessed according to the separate line item for PT/PTT in this table.

I Pharmacokinetic sampling: prior to the injection on Day 0, and at any time at Weeks 4, 8, 16, 24 and 52 and anytime during the 8-week follow-up and unscheduled visit.

J For subjects not entering the open-label extension portion of the study who had a positive anti-belimumab antibody response at the 8 week follow-up visit (or last study visit at which immunogenicity was assessed if 8 week follow-up visit immunogenicity sample is not available), an attempt will be made to obtain an additional serum sample for anti-belimumab antibodies (see Protocol, Section 6.8).

K Will be measured in all subjects at Day 0 and samples will be collected at the time points specified; however, the assay will be run only on subjects with elevated titers of these autoantibodies at Day 0.

[L] Pharmacogenetic sampling informed consent must be obtained prior to any blood being taken for PGx research. Sample should be drawn prior to dosing, or the sample may be taken at any time while the subject is participating in the clinical study

[M] C-SSRS Since Last Visit (see Protocol, Appendix 12) will be used at Day 0 and all subsequent visits. The C-SSRS Baseline/Screening form (see Protocol, Appendix 11) is only used at Screening.

11.1.2.2.2. BEL112341 - Open-Label Phase

	Day 0 [A] (± 1 day)	Day 28 Visit ± 7 day	Day 84 Visit ± 7 day	Day 168 Visit ± 7 days	Exit visit for non-completers[B]	8-wk Follow-up Visit [H] (8 wks post last dose) ± 7 days
		Wk 4	**Wk 12**	**Wk 24**		
SC administration of belimumab	X[B]	Weekly (+/- 1 day) with final dose at Week 23				
Clinical Assessments:						
Adverse Events	See Day 364/Exit Visit in 52-Wk Treatment Period	X	X	X	X	X
Collect self-injection logs; record dosing in CRF		X	X	X	X	
Record All Concurrent Medications		X	X	X	X	X
Weight				X	X	
Symptom-driven PE				X	X	
SLE Disease Activity Scales [C]				X	X	
SLICC/ACR Damage Index				X	X	
FACIT-Fatigue Scale[D]				X	X	
Laboratory Assessments:						
Urine Pregnancy Test [E]		X	X	X	X	X
Urinalysis				X	X	X
Spot Urine Protein Creatinine Ratio				X	X	
PT/PTT				X		
Hematology & Modified Chem 20 (non fasting) [F]				X	X	X
Complement (C3/C4) and anti-dsDNA				X	X	
Serum Immunoglobulin (IgA, IgM, IgG)			X	X	X	
B-Cells				X	X	
Immunogenicity [G]				X		X
See Footnotes on next page						

[A] Day 0 of the extension portion of the trial is the Week 52 study visit of the double-blind phase, and represents the first belimumab administration in the open-label phase for those subjects continuing on the 6-month open-label study (see Protocol, Table 6.1). The visit schedule is based on the schedule for the 52-week double-blind phase. The visit window is ± 1 day.

[B] The exit visit is scheduled for Week 24, one week after the last dose of study agent. Subjects who discontinue study agent before Week 23 must complete an exit visit 1-4 weeks after the last dose of study agent

[C] SLE Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG, PGA.

[D] Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

[E] Home urine pregnancy test is performed by the subject every 4 weeks and results are called-in to the site except during scheduled visits, when urine pregnancy test is performed at the site.

[F] Refer to Protocol, Appendix 8 for a listing of laboratory assessments to be completed. PT/PTT will be assessed according to the separate line item for PT/PTT in this table.

[G] For subjects who had a positive anti-belimumab antibody response at the 8 week follow-up visit (or last study visit at which immunogenicity was assessed if 8 week follow-up visit immunogenicity sample is not available), an attempt will be made to obtain an additional serum sample for anti-belimumab antibodies (see Protocol, Section 6.8).

[H] 8-Week Follow-up visit is not required in subjects entering the separate continuation protocol.

11.2. Appendix 2: Assessment Windows

As baseline is defined as the last available value prior to the initiation of treatment with belimumab, windowing of the safety endpoints will be employed to align years of belimumab exposure between those who were originally randomized to belimumab and those originally randomized to placebo.

11.2.1. Year Intervals

- To report subject disposition and AE assessments with similar durations of exposure to active belimumab treatment, assessments will be slotted into year intervals using a 365-day calendar year.
- Few subjects are expected to have > 6 years exposure and therefore "Year 6+" will be extended to the last available visit.
- For subjects who withdraw during an interval, the end date of their final interval will be set to their exit visit date.
- For summaries, the "Any Time Post-Baseline" includes the follow-up visits, where follow-up visits are excluded from the "Year 6+" year interval.
- For laboratory assessments, the worst value/highest toxicity reported over the year interval will be used in the analyses. Concomitant medications will be reported by what medications a subject is taking during the interval. In addition, AEs will be reported by start date. Subject disposition, worst value/highest toxicity laboratory assessments, concomitant medications, and AEs will be summarized according to the following year categories.

Study Year	Belimumab Study Days	
	Start Day	End Day
Year 0-1	**Day 1[1] First Treatment Date**	Day 365
Year 1-2	Day 366	Day 730
Year 2-3	Day 731	Day 1095
Year 3-4	Day 1096	Day 1460
Year 4-5	Day 1461	Day 1825
Year 5-6	Day 1826	Day 2190
Year 6+	Day 2191	Maximum Study Day [2]

NOTES:

[1] Protocols specify Day 0 as First Treatment, but due to CDISC standard implementation first treatment date will appear as Day 1 in the analyses. Also, first treatment date refers to first belimumab treatment, regardless of originally randomized treatment.

[2] Last visit date will be defined as the exit visit date where applicable. Subjects who do not have an exit visit date and only a follow up date, the date of the follow up will be used. See Section 11.5.1 for more details.

11.2.2. Belimumab Visits

- For summaries performed by belimumab visit, placebo subjects are aligned based on start of exposure to belimumab.
- Baseline for both belimumab and placebo randomized subjects will be the last non-missing value prior to or on the first treatment date, except for corticosteroid use, which is the last 7 days prior to treatment start date.
- Visits will be aligned so that each visit represents equivalent exposure time to belimumab, regardless of parent study treatment, and will be mapped accordingly based on the endpoint and scheduled visits collected.

Belimumab Visit Name	BEL113750 Parent Randomized Study Treatment		BEL112341 Parent Randomized Study Treatment	
	Belimumab	**Placebo**	**Belimumab**	**Placebo**
Year 1 Day 0	**PS Week 0**	**PS Week 52/ OL Year 1 Week 0**	**Day 0**	**Day 364/Exit**
Year 1 Week 4	PS Week 4	OL Year 1 Week 4	PS Day 28	PS Day 28 OLE
Year 1 Week 8	PS Week 8	OL Year 1 Week 8	PS Day 56	
Year 1 Week 12	PS Week 12	OL Year 1 Week 12	PS Day 84	PS Day 84 OLE
Year 1 Week 16	PS Week 16	OL Year 1 Week 16	PS Day 112	
Year 1 Week 20	PS Week 20	OL Year 1 Week 20	PS Day 140	
Year 1 Week 24	PS Week 24	OL Year 1 Week 24	PS Day 168	PS Day 168 OLE/ OL Year 1 Week 0
Year 1 Week 28	PS Week 28	OL Year 1 Week 28	PS Day 196	OL Year 1 Week 4
Year 1 Week 32	PS Week 32	OL Year 1 Week 32	PS Day 224	OL Year 1 Week 8
Year 1 Week 36	PS Week 36	OL Year 1 Week 36	PS Day 252	OL Year 1 Week 12
Year 1 Week 40	PS Week 40	OL Year 1 Week 40	PS Day 280	OL Year 1 Week 16
Year 1 Week 44	PS Week 44	OL Year 1 Week 44	PS Day 308	OL Year 1 Week 20
Year 1 Week 48	PS Week 52/OL Year 1 Week 0	OL Year 1 Week 48	PS Day 364/Exit	OL Year 1 Week 24
NOTE: PS Week 48 is not mapped to a belimumab visit due to issues within visit alignment for other visits and reporting of data but is used for any derivations. See Section 5.1 for more details.				
Year 2 Week 4	OL Year 1 Week 4	OL Year 2 Week 4	PS Day 28 OLE	OL Year 1 Week 28
Year 2 Week 8	OL Year 1 Week 8	OL Year 2 Week 8		OL Year 1 Week 32
Year 2 Week 12	OL Year 1 Week 12	OL Year 2 Week 12	PS Day 84 OLE	OL Year 1 Week 36
Year 2 Week 16	OL Year 1 Week 16	OL Year 2 Week 16		OL Year 1 Week 40
Year 2 Week 20	OL Year 1 Week 20	OL Year 2 Week 20		OL Year 1 Week 44
Year 2 Week 24	OL Year 1 Week 24	OL Year 2 Week 24	PS Day 168 OLE/ OL Year 1 Week 0	OL Year 1 Week 48
Year 2 Week 28	OL Year 1 Week 28	OL Year 2 Week 28	OL Year 1 Week 4	OL Year 2 Week 4
Year 2 Week 32	OL Year 1 Week 32	OL Year 2 Week 32	OL Year 1 Week 8	OL Year 2 Week 8
Year 2 Week 36	OL Year 1 Week 36	OL Year 2 Week 36	OL Year 1 Week 12	OL Year 2 Week 12
Year 2 Week 40	OL Year 1 Week 40	OL Year 2 Week 40	OL Year 1 Week 16	OL Year 2 Week 16
Year 2 Week 44	OL Year 1 Week 44	OL Year 2 Week 44	OL Year 1 Week 20	OL Year 2 Week 20
Year 2 Week 48	OL Year 1 Week 48	OL Year 2 Week 48	OL Year 1 Week 24	OL Year 2 Week 24

Year 3 Week 4	OL Year 2 Week 4	OL Year 3 Week 4	OL Year 1 Week 28	OL Year 2 Week 28
Year 3 Week 8	OL Year 2 Week 8	OL Year 3 Week 8	OL Year 1 Week 32	OL Year 2 Week 32
Year 3 Week 12	OL Year 2 Week 12	OL Year 3 Week 12	OL Year 1 Week 36	OL Year 2 Week 36
Year 3 Week 16	OL Year 2 Week 16	OL Year 3 Week 16	OL Year 1 Week 40	OL Year 2 Week 40
Year 3 Week 20	OL Year 2 Week 20	OL Year 3 Week 20	OL Year 1 Week 44	OL Year 2 Week 44
Year 3 Week 24	OL Year 2 Week 24	OL Year 3 Week 24	OL Year 1 Week 48	OL Year 2 Week 48
Year 3 Week 28	OL Year 2 Week 28	OL Year 3 Week 28	OL Year 2 Week 4	OL Year 3 Week 4
Year 3 Week 32	OL Year 2 Week 32	OL Year 3 Week 32	OL Year 2 Week 8	OL Year 3 Week 8
Year 3 Week 36	OL Year 2 Week 36	OL Year 3 Week 36	OL Year 2 Week 12	OL Year 3 Week 12
Year 3 Week 40	OL Year 2 Week 40	OL Year 3 Week 40	OL Year 2 Week 16	OL Year 3 Week 16
Year 3 Week 44	OL Year 2 Week 44	OL Year 3 Week 44	OL Year 2 Week 20	OL Year 3 Week 20
Year 3 Week 48	OL Year 2 Week 48	OL Year 3 Week 48	OL Year 2 Week 24	OL Year 3 Week 24
Year 4 Week 4	OL Year 3 Week 4	OL Year 4 Week 4	OL Year 2 Week 28	OL Year 3 Week 28
Year 4 Week 8	OL Year 3 Week 8	OL Year 4 Week 8	OL Year 2 Week 32	OL Year 3 Week 32
Year 4 Week 12	OL Year 3 Week 12	OL Year 4 Week 12	OL Year 2 Week 36	OL Year 3 Week 36
Year 4 Week 16	OL Year 3 Week 16	OL Year 4 Week 16	OL Year 2 Week 40	OL Year 3 Week 40
Year 4 Week 20	OL Year 3 Week 20	OL Year 4 Week 20	OL Year 2 Week 44	OL Year 3 Week 44
Year 4 Week 24	OL Year 3 Week 24	OL Year 4 Week 24	OL Year 2 Week 48	OL Year 3 Week 48
Year 4 Week 28	OL Year 3 Week 28	OL Year 4 Week 28	OL Year 3 Week 4	OL Year 4 Week 4
Year 4 Week 32	OL Year 3 Week 32	OL Year 4 Week 32	OL Year 3 Week 8	OL Year 4 Week 8
Year 4 Week 36	OL Year 3 Week 36	OL Year 4 Week 36	OL Year 3 Week 12	OL Year 4 Week 12
Year 4 Week 40	OL Year 3 Week 40	OL Year 4 Week 40	OL Year 3 Week 16	OL Year 4 Week 16
Year 4 Week 44	OL Year 3 Week 44	OL Year 4 Week 44	OL Year 3 Week 20	OL Year 4 Week 20
Year 4 Week 48	OL Year 3 Week 48	OL Year 4 Week 48	OL Year 3 Week 24	OL Year 4 Week 24
Year 5 Week 4	OL Year 4 Week 4	OL Year 5 Week 4	OL Year 3 Week 28	OL Year 4 Week 28
Year 5 Week 8	OL Year 4 Week 8	OL Year 5 Week 8	OL Year 3 Week 32	OL Year 4 Week 32
Year 5 Week 12	OL Year 4 Week 12	OL Year 5 Week 12	OL Year 3 Week 36	
Year 5 Week 16	OL Year 4 Week 16	OL Year 5 Week 16	OL Year 3 Week 40	
Year 5 Week 20	OL Year 4 Week 20	OL Year 5 Week 20	OL Year 3 Week 44	
Year 5 Week 24	OL Year 4 Week 24	OL Year 5 Week 24	OL Year 3 Week 48	
Year 5 Week 28	OL Year 4 Week 28	OL Year 5 Week 28	OL Year 4 Week 4	
Year 5 Week 32	OL Year 4 Week 32	OL Year 5 Week 32	OL Year 4 Week 8	
Year 5 Week 36	OL Year 4 Week 36	OL Year 5 Week 36	OL Year 4 Week 12	
Year 5 Week 40	OL Year 4 Week 40	OL Year 5 Week 40	OL Year 4 Week 16	
Year 5 Week 44	OL Year 4 Week 44	OL Year 5 Week 44	OL Year 4 Week 20	
Year 5 Week 48	OL Year 4 Week 48	OL Year 5 Week 48	OL Year 4 Week 24	
Year 6 Week 4	OL Year 5 Week 4	OL Year 6 Week 4		
Year 6 Week 8	OL Year 5 Week 8	OL Year 6 Week 8		
Year 6 Week 12	OL Year 5 Week 12	OL Year 6 Week 12		
Year 6 Week 16	OL Year 5 Week 16	OL Year 6 Week 16		
Year 6 Week 20	OL Year 5 Week 20	OL Year 6 Week 20		
Year 6 Week 24	OL Year 5 Week 24	OL Year 6 Week 24		
Year 6 Week 28	OL Year 5 Week 28	OL Year 6 Week 28		

Year 6 Week 32	OL Year 5 Week 32	OL Year 6 Week 32		
Year 6 Week 36	OL Year 5 Week 36	OL Year 6 Week 36		
Year 6 Week 40	OL Year 5 Week 40	OL Year 6 Week 40		
Year 6 Week 44	OL Year 5 Week 44	OL Year 6 Week 44		
Year 6 Week 48	OL Year 5 Week 48	OL Year 6 Week 48		
Year 7 Week 4	OL Year 6 Week 4	OL Year 7 Week 4		
Year 7 Week 8	OL Year 6 Week 8			
Year 7 Week 12	OL Year 6 Week 12			
Year 7 Week 16	OL Year 6 Week 16			
Year 7 Week 20	OL Year 6 Week 20			
Year 7 Week 24	OL Year 6 Week 24			
Year 7 Week 28	OL Year 6 Week 28			
Year 7 Week 32	OL Year 6 Week 32			
Year 7 Week 36	OL Year 6 Week 36			
Year 7 Week 40	OL Year 6 Week 40			
Year 7 Week 44	OL Year 6 Week 44			
Year 7 Week 48	OL Year 6 Week 48			
Year 8 Week 4	OL Year 7 Week 4			

PS = Parent Study, OLE = Open-label extension of BEL112341, OL = Open-label study BEL114333

11.3. Appendix 3: Adverse Event Collapsing Rules and Assignment of Adverse Events to Study Year

11.3.1. Adverse Event Collapsing

- Adverse events were collected in both the parent studies and study BEL114333.
- Due to the ongoing nature of some AEs at the end of the parent study, some AEs originate in the parent study and continue into the BEL114333 study; however, such events will be counted once only.
- The following table shows where AEs reside by their relationship to the parent study exit date or Year 1 Day 0 visit of the BEL114333 study.

AE Occurrence	Database
AE starts and ends on/before parent study Exit Visit.	Parent study only.
AE starts on/before Exit Visit in the parent study and ends either on/after Year 1 Day 0 of BEL114333, or after the Exit Visit but before Year 1 Day 0 of BEL114333 (where there is a gap between these visits). [1]	Parent study and BEL114333 [2]
AE starts after Exit Visit of the parent study and ends before Year 1 Day 0 of the BEL114333 study (where there is a gap between these visits).	BEL114333 only
AE starts after Exit Visit of the parent study and ends on/after Year 1 Day 0 of the BEL114333 study (where there is a gap between these visits).	BEL114333 only
AE starts and ends on/after Year 1 Day 0 of the BEL114333 study.	BEL114333 only

[1] Records to be collapsed.

[2] Ongoing AEs in the parent study BEL112341 were entered by site in the BEL114333 eCRF. Ongoing AEs in the parent study BEL113750 were programmatically added to the BEL114333 data transfer.

- AEs that occur in both the parent study and study BEL114333 will be collapsed based on the following dataset attributes: MedDRA lower level term, AE start date, and action taken with Investigational Product (IP).
    - AEs in both the parent study and BEL114333 should be considered one event if they match on the attributes noted above. Severity, Seriousness and Relationship to IP should reflect worst case between the two collapsed records. Outcome and end date should reflect the final outcome in BEL114333.

- Values from BEL112341 may be mapped as appropriate. Note: AE Start Time was collected in BEL114333 but not in BEL112341, so the date part will be used for AE collapsing.

11.3.2. Assigning Adverse Events to Study Year

The following rules will be used for allocating AEs to study year:

- Each AE will be reported in the year it started.
- AEs continuing for more than one treatment year will only be reported in the year they first occurred.
- If distinct episodes (start and stop date) of an AE are reported in multiple years, the AE will be reported once in each study year in which the unique event began.
  - AEs with partial start and/stop dates will be assumed to have occurred on treatment unless there is evidence through comparison of partial dates to suggest otherwise.
  - Where possible the non-missing information will be used to assign the AE to a study year, if the non-missing information is insufficient to assign the AE to a study year then the AE will be assigned to the earliest plausible study year.
- If the AE onset date is missing assume the start date was in Year 0-1. The event will be reported in Year 1 and "Any Time Post-Baseline."
- If the AE end date is missing assume the AE continued until the end of study. The AE will be reported in year of onset and "Any Time Post-Baseline."
- AEs that begin and end on the first day of treatment will count in the Year 0-1 period and for "Any Time Post-Baseline."

Table 15 Example of Assigning AEs to Study Years

Scenario	Pre-Treatment	Year 0-1	Year 1-2	Year 2-3	Year 3-4	Year 4-5	After End of Treatment
A	←			→			
B		←				→	
C		←					→
D	←		→				

NOTE: Arrow indicates the start and stop date of a single AE.

Scenario	Assignment of AE to Study Year					
	Any Time Post-Baseline	Year 0-1	Year 1-2	Year 2-3	Year 3-4	Year 4-5
A	No	No	No	No	No	No
B	**Yes**	**Yes**	No	No	No	No
C	**Yes**	**Yes**	No	No	No	No
D	Yes	No	**Yes**	No	No	No

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions	
Parent Study	**Parent Study Display Group [1]**
Belimumab 10 mg/kg IV	Belimumab
Placebo IV	Placebo
Belimumab 200 mg SC	Belimumab
Placebo SC	Placebo

NOTES:

[1] The "Belimumab" group will consist of those on 10 mg/kg IV and 200 mg SC during the parent study PRIOR to joining BEL114333. The "Placebo" group will consist of those on IV and SC during the parent study PRIOR to joining BEL114333.

11.4.2. Baseline Definition

Belimumab baseline is defined as the last available value prior to the time of initiation of belimumab treatment. See Figure 1.

- For subjects who were randomised to receive belimumab treatment in the parent study, 'baseline' is the last value prior to the first dose of belimumab received in the parent study.
    - For most assessments, this will be the assessment conducted at the baseline visit, but it may be the screening visit if the baseline assessment is missing, or if the assessment was only scheduled to be performed at screening.
    - If the baseline values originally derived for the parent study analyses are found to be calculated from data occurring post treatment, those values will be re-derived or set to missing.
- For subjects who were randomised to placebo in the parent study, 'baseline' is the last available value prior to the first open-label belimumab dose i.e. either in BEL112341 open-label extension or BEL114333. For most assessments, this will be the assessment at the parent study DB Week 52 visit. For some assessments, not available or missing at Week 52, baseline will be the last available value prior to belimumab start date, whether in the parent study (back to the DB Week 48 visit) or either in BEL112341 open-label extension or BEL114333.
- Baseline demographic characteristics not captured at the beginning of BEL112341 open-label extension or BEL114333, will be pulled from the baseline of the parent study.

11.4.2.1. Baseline SLE Disease Duration

- Baseline SLE Disease Duration in years is calculated as follows:

$$\frac{\text{Date of First belimumab Treatment / Baseline Visit} - (\text{Date of SLE Diagnosis})+1}{365.25}$$

11.4.2.2. Total Number of ACR Criteria at Baseline

- ACR criteria were only collected at screening of the parent study, so all baseline values will be derived from parent study regardless of the randomized treatment group in the parent study.
- The total number of ACR criteria will be summed for a total possible score of 11.
- Subjects were required to have at least 4 to be eligible for the study.
- If sub-questions are present for a criterion, the sub-questions will be checked programmatically for the creation of the total score rather than the overall criterion score.

11.4.2.3. SLE Flares at Baseline

- Per the CRF page design, the assessment window for deriving categories at baseline of 'No flare', 'At least one flare', 'At least one severe flare' is the time interval between the last SLE assessment and 'baseline' (~4 weeks), defined as follows:
    - For subjects randomized to belimumab in the parent study, the time interval is from screening to baseline of the parent study.
    - For subjects randomized to placebo in the parent study BEL113750, the time interval is from Week 48 to Week 52 of the parent study.
    - For subjects randomized to placebo in the parent study BEL112341, the time interval is Week 48 to Week 52 of the DB phase of BEL112341.

11.4.2.4. 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]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.4.2 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 will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software 9.3 or higher will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Area	: arprod\gsk1550188\bel114333\final_01
QC Spreadsheet	: arprod\gsk1550188\bel114333\final_01\documents
Note: \data_look_01 will be used for the run dry.	
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for all tables in the final reporting delivery.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx) ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits

Reporting Standards	
• Unscheduled visits will be included in summary tables and/or figures in the 'Any Time Post baseline' time interval. Otherwise, unscheduled visits will not be displayed in by visit summaries or figures. • 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.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Subject Identifier, Breaks in Treatment and Date of Last Visit

Subject Identifier

- Subjects enrolled in BEL114333 from the parent study BEL113750 continued to use the same subject identifier as assigned in the parent study. Note: the site identifiers used in the parent study BEL113750 were changed in BEL114333 in order to retain the same subject identifier.
- Subjects enrolled in BEL114333 from the parent study BEL112341 were assigned subject identifiers ranging from 9001 to 9030.

Dose Interruption

- The first dose in the study BEL114333 must be given 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last IV dose for subjects enrolled from the parent study BEL113750.
- For subjects from the SC parent study BEL112341, the first IV dose in study BEL114333 is targeted for 1 week (+1 week window) after the last dose of SC belimumab (scheduled for Week 23 in the OL extension part of BEL112341).

Note: For the purposes of reporting, dose interruptions will be ignored and exposure will be treated as continuous.

Date of Last Visit

- Last visit date (in BEL114333) will be defined as the exit visit date, where available.
- For subjects who do not have an open-label exit visit date, and only have a follow up date, the following will be used to derive a last visit date in order of priority:
  1. Death Date if non-missing and prior to Disposition Date
  2. Disposition Date, if non-missing
  3. If last non-follow up visit is after last dose of belimumab, use the minimum of a) the last non-follow up visit date, or b) the last dose date + 28 days.
  4. If the last non-follow up visit is prior to the date of last dose, use the last dose date.

- Time to withdrawal (in days) will be calculated for each subject as
  - Time to Withdrawal = Date of Last Visit – First Dose Date of Belimumab + 1

Date of Last Contact

- Final contact (in BEL114333) will be defined as the latest visit, as appropriate, up to the 6 month FU visit (post-last dose of belimumab).

Multiple Measurements at One Time Point
• 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 first dose date of belimumab treatment: • Ref Date = Missing → Study Day = Missing • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

11.5.2. Study Population

Demographics
Age
• Full date of birth and age were collected at screening of the parent study, and will be available in the data transfer. • Analysis age in years will be derived from the full date of birth and the first dose date of belimumab treatment, and will be calculated in SAS as: **INTCK ('YEAR', date of birth, first dose date, 'C')** • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• BMI (kg/m^2) = weight (kg) / height (m)^2 will be derived from height at screening visit of the parent study, and weight measured at the belimumab baseline.

11.5.3. Safety

Adverse Events, Laboratory, SLE Medication, Average Daily Steroid Dose
Adverse Events of Special Interest (AESI)
• AESI have already been identified by the Safety Review Team (SRT) (via an enhanced MedDRA dataset) and any event specific updates will be applied via an adjudication spreadsheet.

Laboratory Parameters
• For laboratory values that are above or below the lower limit of quantification, having only character values starting with "<" or ">", numeric values will be derived using the following rules, where LRESSI in the character result in standard units, and LNRES is the numeric version of the result: If LRESSI = '> x' then LNRES = x + 1, where x is an integer ≥1. If LRESSI = '> x.y' then LNRES = x.y + 0.1, where x, y are integers. If LRESSI = '> x.yz' then LNRES = x.yz + 0.01, where x, y, z are integers. etc

Laboratory Parameters
If LRESSI = '< x' then LNRES = x - 1, where x is an integer ≥1. If LRESSI = '< x.y' then LNRES = x.y - 0.1, where x, y are integers. If LRESSI = '< x.yz' then LNRES = x.yz - 0.01, where x, y, z are integers. etc

SLE Medication Categories

- Concomitant medications will be reviewed and may be assigned to one of five categories based on their GSK Drug Dictionary preferred terms (using the current version of GSK Drug at the time of reporting) for summarisation throughout the course of the study: corticosteroid, anti-malarial, immunosuppressant, NSAID and Aspirin, and defined as:

Medication category	Definition
Corticosteroid	ATC code starts with "H02" and route of administration is intravenous, intramuscular, subcutaneous, intradermal, intra-articular or oral.
Anti-malarial	Preferred term includes QUINACRINE, QUININE, HYDROXYCHLOROQUINE, MEPACRINE or CHLOROQUINE. Meds with the following routes of administration will be **excluded**: topical, vaginal, conjunctival, intranasal, inhaled, intra-ocular, intratracheal, epidural, intra-articular or other.
Immunosuppressant	ATC code starts with "L04A" or preferred term contains CYCLOPHOSPHAMIDE, MERCATOPURINE or METOTREXATE. Meds with the following routes of administration will be **excluded**: topical or conjunctival.
NSAID	ATC code of "M01A". Meds with the following routes of administration will be **excluded**: topical or conjunctival.
Aspirin	Coded term contains ACETYLSALICYCLIC ACID or ACETYLSALICYLATE LYSINE. Meds with the following routes of administration will be **excluded**: topical or conjunctival.

Average Daily Steroid Dose

- Concomitant medications, including corticosteroids, were collected in both the parent studies and BEL114333. To determine average daily dose and for analysis of steroid use, all steroid dosages are converted to a prednisone equivalent dosage in milligrams.
- The average daily prednisone dose considers all steroids taken systemically intravenously (IV), intramuscularly (IM), SC, intradermally, and orally for both SLE and non-SLE reasons.
- At baseline, the average daily prednisone dose is the sum of all prednisone doses over 7 consecutive days up to, but not including Day 0, divided by 7.
- While on treatment, the average daily prednisone dose is the sum of all prednisone doses over 7 consecutive days, including the day of interest, divided by 7, unless otherwise specified.
- This average dose will be categorised as 0, >0 to ≤7.5, >7.5 to ≤40, and >40 mg/day. The average daily prednisone dose will be calculated for weeks 24 and 48 for each year.

Prednisone Equivalent Daily Dose Conversions

- At data base lock, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor exists for all terms with a systemic or intra-articular route of administration.
- Similarly, all routes of administration for preferred terms
- Reported dose of systemic steroid is converted to prednisone equivalent dose using a conversion factor for each medication (refer to online calculator http://www.globalrph.com/corticocalc.htm).
    - Prednisone equivalent dose (mg/day) =
      Collected dose (mg) x Conversion Factor x Frequency Factor

Preferred Term	Conversion Factor for Prednisone-Equivalent Dose (mg)
BETAMETHASONE	8.333
BETAMETHASONE DIPROPIONATE	8.333
BETAMETHASONE SODIUM PHOSPHATE	8.333
BUDESONIDE	No conversion applied – nasal spray taken by 1 subject in BEL113750
CELESTONA BIFAS	7.5
CORTISONE	0.2
CORTISONE ACETATE	0.2
DEFLAZACORT	5/6
DEPO-MEDROL MED LIDOKAIN	1.25
DEXAMETHASONE	6.667
DEXAMETHASONE ACETATE	6.667
DEXAMETHASONE SODIUM PHOSPHATE	6.667
FLUOCORTOLONE	3
HYDROCORTISONE	0.25
HYDROCORTISONE ACETATE	0.25
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	No conversion applied - conjunctival
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
QM	1/30
QOD	1/2
QPM	1
QW	1/7
QWK	1/7
TID	3
TIW	3/7
1 TIME PER WEEK	1/7
2 TIMES PER WEEK	2/7
3 TIMES PER WEEK	3/7

EVERY 2 WEEKS	1/14
EVERY 4 WEEKS	1/28
EVERY WEEK	1/7
UNKNOWN	null

11.5.4. Efficacy

11.5.4.1. SELENA SLEDAI Disease Assessment Scale

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.

[redacted]

11.5.4.2. BILAG

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.

	Domain									Endpoint		
	1	2	3	4	5	6	7	8				
Belimumab Visit	General	Mucocutaneous	Neurological	Musculoskeletal	Cardiovascular/ Respiratory	Vasculitis	Renal	Hematology	New A or New B Compared to Baseline	BILAG (SRI) component (No new A and at most 1 new B)	BILAG 1A/2B Flare (At least 1 new A and/or at least 2 new B)	BILAG 1A Flare (At least 1 new A)
Baseline	**A**	**B**	**E**	**E**	**D**	**E**	**D**	**E**	**1A, 1B**			
Year 1 Week 24	A	B	E	E	D	E	D	E	-	✓	×	×
Year 1 Week 48	B	B	E	E	D	E	D	E	-	✓	×	×
Year 2 Week 24	A	B	E	C	B	E	D	E	1 new B	✓	×	×
Year 2 Week 48	A	B	B	C	D	E	D	E	1 new B	✓	×	×
Year 3 Week 24	D	B	B	C	B	E	D	E	2 new B	×	✓ (1st event)	×
Year 3 Week 48	A	C	C	C	D	E	D	E	-	✓	×	×
Year 4 Week 24	B	B	B	C	B	E	D	E	2 new B	×	✓	×
Year 4 Week 48	A	A	C	C	D	E	D	E	1 new A	×	✓	✓ (1st event)
Year 5 Week 24	A	A	B	B	D	E	D	E	1 new A, 2 new B	×	✓	✓
Year 5 Week 48	D	A	A	C	B	E	D	E	2 new A, 1 new B	×	✓	✓
Year 6 Week 24	A	A	A	B	B	E	D	E	2 new A, 2 new B	×	✓	✓
Year 6 Week 48	A	A	B	B	B	E	D	E	1 new A, 3 new B	×	✓	✓

11.5.4.3. Physician's Global Assessment (PGA) Score

- The PGA is collected on a 10 cm 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. This re-scaling is applied in the eCRF data extraction.

11.5.4.4. SLICC/ACR Damage Index

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.

[redacted]

11.5.4.5. SLE Flare Index

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.

[redacted]

[redacted]

11.5.4.6. Spot Urine Protein Creatinine Ratio Conversion

Spot Urine Protein Creatinine Ratio
Conversion from mg/mmol to mg/mg (performed by central laboratory)
• For analysis, spot urine protein creatinine ratio (PCR) will be reported in mg/mg (or equivalently, g/24h). • The SI unit for PCR is mg/mmol (which is the same as g/mol as stored in the database). • To convert lab values reported as mg/mmol to mg/mg, divide the lab value by 113.12

Spot Urine Protein Creatinine Ratio
▪ Example: (20 g/mol) / 113.12 = 0.1768 mg/mg

11.5.5. Biomarkers

Biomarker Parameters
Anti-ds DNA
• Positive: ≥30 IU/mL • Negative: <30 IU/mL
Complement Level C3 [1]
• Low: <90 mg/dL • High: > 180 mg/dL
Complement Level C4 [1]
• 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
[1] The SI unit for C3, C4 is g/L. For analysis, complement levels will be reported in mg/dL. To convert lab values reported as g/L to mg/dL, multiply the lab value by 100.

11.5.5.1. B Cell Subsets

B cell specimens were collected at selected sites which were all Japan sites.

The B cell subsets (as specified in the protocol) include:

- CD20+
- Naïve CD20+/27–
- Memory CD20+/27+
- Activated CD20+/69+
- Plasmacytoid CD20+/138+

- SLE subset CD19+/27^{BRIGHT}/38^{BRIGHT}
- Plasma cells CD20-/138+

In addition, the following two B cell subsets have been added to the RAP:

- Concentration of CD19+
- Short-lived plasma subset $CD27+^{BRIGHT}$/CD20-

Note: the parent study BEL113750 included the analysis of these two additional B cell subsets. However, B cell samples were not analysed for the short-lived plasma subset in the parent study BEL112341; thus, because of missing data at baseline and post-baseline visits for the first 6 months of belimumab treatment (and data for the subsequent 12 months is limited to the placebo group), no summary will be produced for this B cell subset for BEL112341 subjects. However, available short-lived plasma B cell subset data will be listed.

Reporting of B Cells subsets

CD19+, CD20+, naïve and memory B Cell subsets (collectively known as "common B cell" subsets) are reported in counts per microliter (uL). Activated, plasmacytoid, SLE subset, plasma and short-lived plasma b cells (collectively known as "rare B cell" subsets) are reported in counts per millilitre (mL).

Table 16 includes the variables, labels and details of derivations to be used in the reporting of the B cell subsets.

Table 16 Variables, labels and details of derivations to be used in the reporting of the B cell subsets

Protocol specified B cell subset	B cell subset label for displays	ADaM Lab Test Code (LBTESTCD)	Derivation for Normalization and/or Conversion of B cell subsets SDTM Lab Test Code (LBTESTCD)	
			BEL114333 and BEL113750 [1]	BEL112341
Common B cells				
CD19+	CD19 (/uL)	CD19	CD19 requires conversion to /uL	CD19 reported as /uL
CD20+	CD20 (/uL)	CD20	CD20 requires conversion to /uL	CDZ037 reported as /uL
Naïve CD20+/27-	Naïve CD19+CD20+CD27- (/uL)	CDX136	CDX136 requires conversion to /uL	CDZ035 reported as /uL
Memory CD20+/27+	Memory CD19+CD20+CD27+ (/uL)	CDX137	CDZ137 requires conversion to /uL	CDZ034 reported as /uL
Rare B cells				
Activated CD20+/69+	Activated CD19+CD20+CD69+ Normalised (COUNT/mL)	CDX141N	CDX155E, CD19E from Plasma Panel and CD19 concentration from TBNK Panel	CDZ005EV, CD19EVC from Plasma Panel and CD19 concentration from TBNK Panel [1]
Plasma CD20-/138+	Plasma CD19+CD20-CD138+ Normalised (COUNT/mL)	CDX143N	CDX143E, CD19E from Plasma Panel and CD19 concentration from TBNK Panel	CDZ007EV, CD19EVC from Plasma Panel and CD19 concentration from TBNK Panel [1]
Plasmacytoid CD20+/138+	Plasmacytoid CD19+CD20+CD138+ Normalised (COUNT/mL)	CDX145N	CDX145E, CD19E from Plasma Panel and CD19 concentration from TBNK Panel	CDZ002EV, CD19EVC from Plasma Panel and CD19 concentration from TBNK Panel [1]
Short-lived Plasma CD27+^{BRIGHT}/CD20-	Short-lived Plasma CD19+CD20-CD27b+ Normalised (COUNT/mL)	CDX154N	CDX154E, CD19E from Plasma Panel and CD19 concentration from TBNK Panel	NA
SLE subset CD19+/27^{BRIGHT}/38^{BRIGHT}	SLE Subset CD19+CD38b+CD27b+Lymph Normalised (COUNT/mL)	CDX156N	CDX156E, CD19E from Plasma Panel and CD19 concentration from TBNK Panel	CDZ024EV, CD19EVC from Plasma Panel and CD19 concentration from TBNK Panel [1]

[1] The derivation for the normalisation of rare B cell subsets should use the CD19 Concentration from the TBNK flow panel. BEL113750 the TBNK method was used but the method was incorrectly reported as PLASMA by the central lab (and cannot be corrected as BEL113750 has met DBF). BEL112341 the method is not specified, but it is confirmed that TBNK was used.

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), multiple 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 millilitre (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 CD19+ B cell event count should be taken from the same flow panel as the B cell subset being converted in the derivation. The CD19+ concentration should be taken from the TBNK panel and converted to count/uL prior to the normalisation 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

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals and Completion

Element	Reporting Detail
General	• All subjects were indicated as withdrawn from study BEL114333 based on the design of the end of treatment CRF page. • Study completion (i.e. as specified in the protocol) is defined as ○ the subject was still participating in the study at the time belimumab became commercially available in Japan and Korea * or ○ the subject transferred to a different protocol (as indicated by a reason for withdrawal of Investigator Discretion), or ○ upon the decision by the sponsor to close/terminate the study (as indicated by a reason for withdrawal of Study/Closed Terminated). * the study is now being closed as PMDA approved Benlysta, and subjects have been transitioned from study supplied belimumab over to commercially available Benlysta. The KFDA approved Benlysta in 2015. • There will be no adjustments for missing results (i.e. LOCF) due to subject withdrawal prior to study termination. • All subjects are expected to return for an exit visit. Subjects no longer receiving belimumab after their exit visit are expected to return for follow up visits. See Section 2.3 for more details. • All available data will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data are 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 subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.

Element	Reporting Detail
SLE Duration	• If only year of SLE diagnosis is known, day and month will be set to 01 January. • If month and year are known, but not the day, the day will be set to 01.
Adverse Events	• The EDC does not allow partial dates to be entered for AE start and stop dates. • 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. • AEs with missing start dates will be considered as treatment-emergent.

Concomitant Medications	• The EDC allows partial dates to be entered for medication start dates (but the Year must be present). Partial dates cannot be entered for medication end dates.
	• For reporting, missing or partial start and/or end dates will remain missing, with no imputation applied.
	  ○ Medications with partial or missing start dates will be considered as 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 of belimumab, and if the month and year are the same or later, the medication will be considered concomitant.
	  ○ Medication with missing end dates will be considered 'ongoing'.

11.6.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
General	• The efficacy endpoints will be summarised using observed case data, for all subjects in the Safety population, unless otherwise stated. • Assessments not done will remain as missing.
SLICC/ACR Damage Index	• The Index is cumulative, once an item is scored it should continue to be scored for all subsequent assessments (see Section 11.5.4.4). • Where an assessment is completed (at least one item was marked or a total score of 0 was recorded), items left unchecked on the SLICC/ACR, and not previously checked, will be considered as "not present" (rather than missing), and assigned an item score of 0 in the analysis dataset (see Section 11.5.4.4).
SELENA SLEDAI	• Where an assessment is completed (at least one item was marked or a total score of 0 was recorded), items left unmarked on the SELENA SLEDAI will be considered as "not present" (rather than missing), and assigned an item score of 0 in the analysis dataset (see Section 11.5.4.1).
BILAG	• As OL BILAG assessments are every 6 months vs monthly for the DB part of the parent studies, items left unmarked on the questionnaire will not be imputed. See Section 11.5.4.2, for the derivation of organ domain scores with missing data.

11.7. Appendix 7: Methods for Handling Centres

11.7.1. Methods for Handling Centres

The data will be analysed on a combined-centre basis per the parent studies. No subjects transferred between centres in BEL114333.

11.8. Appendix 8: Examination of Covariates, Subgroups & Other Strata

11.8.1. Handling of Other Strata and Covariates

As all subjects, will receive IV belimumab treatment and there are no hypothesis tests, no additional strata or covariates will be employed in the analyses. Subgroups will be defined for further exploration of the data in a descriptive fashion.

11.8.2. Handling of Subgroups

The demographics, baseline disease characteristics, and AE endpoint summaries will also be performed within the following subgroups.

Category	Covariates and / or Subgroups
Age	< 65 years and ≥ 65 years
Gender	Male and Female
Baseline SELENA SLEDAI	≤ 9 and ≥ 10

NOTES :

- Age and baseline SELENA SLEDAI at first dose of belimumab treatment.

11.9. Appendix 9: Laboratory Parameters & Adverse Events Grading Tables

11.9.1. Laboratory Values

Hematology	Urinalysis	Modified Chem-20
Total white blood cell count (leukocytes) * Differential: • Absolute Neutrophils * ○ Segmented Neutrophils ○ Band Neutrophils ○ Myelocytes ○ Metamylocytes ○ Promyelocytes • Lymphocytes * • Monocytes • Eosinophils • Basophils Hemoglobin * Hematocrit Red blood cell count Platelet count * Prothrombin time * [1] Partial thromboplastin time * [1]	Protein * Glucose Ketones Occult blood Microscopic examination including: • WBC per hpf • RBC per hpf * • Dysmorphic RBC • Casts (specified by type eg, RBC, WBC) Spot Urine • Protein:creatinine ratio *	Electrolytes: • Sodium * • Potassium * • Magnesium * • Chloride • Carbon dioxide • Calcium adjusted for Albumin * • Inorganic Phosphate * Enzymes: • SGOT (AST) * • SGPT (ALT) * • Alkaline Phosphatase * • GGT * • LDH Other: • Creatinine * • Blood urea nitrogen [3] • BUN/creatinine ratio [3] • Bilirubin, direct [2] • Bilirubin, total * • Protein, total • Albumin * • Uric acid * • Glucose * • Estimated Creatinine Clearance/GFR (Cockroft-Gault)
Biological Markers	**Immunoglobulins**	**PK/Immunogenicity**
Serum Complement (C3 and C4) B cell subtypes Autoantibodies • Anti-dsDNA • ANA [1]	Serum immunoglobulin IgG *, IgM, IgA	Anti-belimumab antibodies

* Lab parameters with toxicity grading.

[1] Only collected in the parent study.

[2] Bilirubin, direct was not collected in the parent study BEL112341.

[3] Urea was collected in BEL114333/BEL113750 and BUN was collected in BEL112341. Display "Urea (mmol/L) & BUN (mmol/L)" as a single parameter and add a footnote to highlight that different tests were performed in the different studies.

11.9.2. 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)

*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

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CHEMISTRIES				
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 (nonfasting & no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
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)

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CHEMISTRIES (continued)				
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)

*(Goldfarb, 2001; Yamini, 2001; Eibl, 1995).

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)

RESPIRATORY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 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

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dipstick 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
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

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Modified from DMID Adult Toxicity Tables, 2001

11.10. Appendix 10: PSAP Sections for AESI Reporting

Section 15: Adverse Events of Special Interest

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 Section 17.

Section 15.1: 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 (Section 17.1). In addition, the following customizations have been made (generally since MedDRA v19.1).

The following terms have been added as hematological tumour types:

Marginal zone lymphoma recurrent

Epstein Barr virus positive mucocutaneous ulcer

Primary gastrointestinal follicular lymphoma

Transformation to acute myeloid leukaemia

FIP1L1/PDGFR alpha fusion kinase positive

Acute bilineal leukaemia

Primary breast lymphoma

The following terms have been added as a solid tumour type:

Malignant meningioma metastatic

Astroblastoma

Langerhans cell sarcoma

Nasopharyngeal cancer metastatic

Phosphaturic mesenchymal tumour

Squamous cell breast carcinoma

Gleason grading score

Oncotype test

Malignant urinary tract obstruction

Sarcomatoid carcinoma

Cystadenocarcinoma pancreas

Paracancerous pneumonia

Chromophobe renal cell carcinoma

Gastrointestinal adenocarcinoma

Pleuropulmonary blastoma

Primary pulmonary melanoma

Dysplastic naevus

ALK gene rearrangement positive

Breast tumour excision

NMP22 test abnormal

The following terms have been added as a skin tumour type:

Naevoid melanoma

Trichoblastic carcinoma

The following terms have been added as a tumour of unspecified malignancy:

Mismatch repair cancer syndrome

Skin neoplasm bleeding

Intestinal metastasis

Maternal cancer in pregnancy

Microsatellite instability cancer

Pulmonary tumour thrombotic microangiopathy

Tumour cavitation

Tumour hyperprogression

Paraneoplastic myelopathy

Carcinogenicity

BRAF V600E mutation positive

Paraneoplastic thrombosis

In addition, the preferred term “Malignant neoplasm progression” was moved from “Non-haematological Malignant Tumour” SMQ in MedDRA Version 20.1 to “Malignancy Related Conditions” SMQ in MedDRA Version 21.0, and was further customized to be a tumour of unspecified malignancy.

The following terms have been removed from the SMQ:

Paraneoplastic glomerulonephritis (as it is a complication of malignancy)

Lymphoma cutis

Mucinous cystadenocarcinoma of pancreas

Serous cystadenocarcinoma of pancreas

Secondary cerebellar degeneration

Bone marrow infiltration

Pseudoachalasia

Malignant exophthalmos

Tumour obstruction

Tumour psuedoprogression

Paraneoplastic arthritis

Tumour pruritus

Oncogenic osteomalacia

Neurogenic tumour

Non-melanoma skin cancer (NMSC) will be categorized using a CMQ developed by the Marketing Authorization Holder (MAH) (Section 17.1).

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.

Post-study malignancies 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. Post-study malignancies are not adjudicated by the SRT.

Additionally, for the BEL115467 “BASE” study, any malignancies that are reported annually (in the Year 2-5 post-treatment follow-up) via malignancy status updates in the CRF and not captured in ARGUS, will not be adjudicated by the SRT.

Section 15.2: Post-infusion/injection systemic reactions

Post-infusion/injection 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 terms: "Fixed eruption", "Drug eruption" and "Lipoedema".

GSK has also removed eight terms that are not relevant for an analysis of hypersensitivity reactions to belimumab ("Anaphylactic transfusion reaction", "Dialysis membrane reaction", "Cyanosis", "Nasal obstruction", "Ocular hyperaemia", "Tachypnoea", "Hereditary angioderma with C1 est" and "Acquired C1 inhibitor deficiency").

- Anaphylactic transfusion reaction is an adverse event associated with a blood transfusion, not related to study medication.

- Dialysis membrane reaction is associated with adverse events related to kidney transplants and dialysis, not related to study medication.

- Cyanosis, nasal obstruction, ocular hyperaemia, tachypnoea, hereditary angioderma with C1 est, acquired C1 inhibitor deficiency are adverse events generally not associated with post-infusion/injection systemic reactions.

The terms "Injection site urticaria", "Eye pruritis", and "Procedural shock" are part of the Anaphylactic Reaction SMQ but were inadvertently excluded (identified during PSAP Version 6 update). These terms will be included when the next MedDRA version i.e. MedDRA Version 21.1. is released.

Algorithmic Search Criteria

The post-infusion/injection 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.

GSK SRT will review all serious events identified via the broad search using a 21-day window from the start of an infusion/injection (see PSAP Section 8.3.2 for the definition of the assessment windows), and adjudicate these events as post-infusion/injection systemic reactions or hypersensitivity reactions per the criteria in Section 16.2. Therefore, the window for the narrow, broad and algorithmic searches of AE and SAE data from the clinical database for SRT reporting (PSAP Section 13.3) is 21 days to correspond to the window for adjudication. Adverse events with partial or missing start dates will be included unless there is evidence through comparison of partial dates to suggest otherwise.

Note, for CSR reporting, narrow, broad, and algorithmic searches of AE and SAE data will be run using a 3-day window from the start of an infusion/injection.

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 SRT 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 during the first 24 hours after the start of an infusion/injection.

b. Any AE or SAE in the “Gastrointestinal disorders” SOC that coincides with the event that meets the criterion in a) above.

c. Any anaphylaxis and hypersensitivity reactions per Anaphylactic Reaction SMQ algorithmic search SAE which occurs during the first 24 hours after the start of an infusion/injection.

Section 15.3: Infections

The infections of special interest are described below.

Section 15.3.1: Opportunistic Infections

Opportunistic infections will be identified using a broad CMQ developed by the MAH (Section 17.1). Any events falling under these preferred terms will be adjudicated by GSK to determine if criteria are met for an opportunistic infection, per the criteria in Section 16.3.

Section 15.3.2: Mycobacterium Tuberculosis

Tuberculosis events will be identified using a CMQ developed by the MAH (Section 17.1). Any events falling under these preferred terms will be adjudicated by GSK to determine if criteria are met for an opportunistic infection (Section 16.3).

Section 15.3.3: Herpes Zoster

Herpes Zoster events will be identified using a CMQ developed by the MAH (Section 17.1). Additional manual adjudication by GSK will identify events that are recurrent or disseminated (Section 16.3).

Section 15.3.4: Pneumonia

Pneumonia events will be identified using a CMQ developed by the MAH (Section 17.1). Pneumonia events will not be reported separately, but are being flagged in the event further evaluation is necessary.

Section 15.3.5: Sepsis

Sepsis events will be identified using a CMQ developed by the MAH (Section 17.1).

Section 15.4: Depression/suicide/self-injury

Section 15.4.1: 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 (20000167) plus additional terms added by the MAH (Section 17.1).

Section 15.4.2: Suicide and Self-Injury

Suicide and self-injury events will be identified using the SMQ (20000037) plus additional terms added by the MAH (Section 17.1).

Section 15.5: Fatalities

All fatalities that are reported while a subject is eligible for SAE reporting will be identified in the clinical database and subsequently adjudicated by the GSK SRT into a general category of death (Section 16.5).

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. Post-study fatalities are not adjudicated by the SRT.

Additionally, for the BEL115467 "BASE" study, any fatalities that are reported annually (in the Year 2-5 post-treatment follow-up) via survival status updates in the CRF and not captured in ARGUS, will not be adjudicated by the SRT.

Section 16: GSK SRT Adjudication of Adverse Events of Special Interest

Adverse events of special interest (AESI) are identified per the preferred terms(Section 17.1) and other criteria described in Section 15. The following AESI are adjudicated in-stream at the subject level by GSK during regular SRT meetings or during quarterly adjudication, and then prior to database release for CSR reporting purposes, per the criteria described below.

In-stream review/adjudication of AESI is conducted as follows:

- Review/Adjudication of AESI in ARGUS

  Safety Evaluation and Risk Management (SERM) lists all events in ARGUS each month for SRT to review. AESIs are adjudicated at SRT meetings and entered onto Excel spreadsheets maintained by SERM. These spreadsheets are cumulative and contain events for all belimumab studies (clinical trials, post-marketing studies and spontaneous reports). SERM refer to these as "Cumulative AESI spreadsheets". SERM use these spreadsheets to tabulate the numerators used for PBRER/DSUR rates (see PSAP Section 7.6). The numerators are typically updated shortly after the Data Lock Point, and updated numerators are then used for PBRER/DSUR updates. The numerators are tracked in spreadsheets referred to as "AESI numerator spreadsheets".

Review/Adjudication of AESI in the Clinical Database

The SRT central programming team sends spreadsheets of AESIs based upon the CRF (Clinical Database) to SERM for periodic in-stream review. These spreadsheets contain AEs and SAEs and are study specific. SERM enter adjudication based on the SRT adjudication ("Cumulative AESI spreadsheets") and checks for missing serious AESIs between ARGUS and the Clinical Database. SERM send the clinical data derived

spreadsheets to the study specific Medical Monitor, who adjudicates the non-serious events. Once updated, the spreadsheets are returned to the SRT central

- programming team and are used to create the SRT output for the next periodic in-stream review.

In addition, as part of individual study close-out procedures, the adjudications should be finalized as follows:

- Just preceding database freeze (DBF), allowing time to send queries or update the eCRF/database as necessary prior to DBF, and are used in the CSR.
- Between DBR and Source Database Lock (as required) 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 database freeze (DBF).

Note, at study close-out, the study programming team is responsible for generating spreadsheets of AESIs based upon the clinical data, in consult with the SRT central programming team, and liaising with SERM to finalise the adjudication. Refer to the SRT team site for more information: SRT/Team Documents/SRT documentation/ AESI/Belimumab_ADAE_AEANAL AESI Adjudication Variables Process.doc.

Section 16.1: Malignancies

All malignancies identified via the terms in Section 17.1 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 per the terms in Section 17.1, 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).

Section 16.2: Serious hypersensitivity and post-infusion/injection systemic reactions

GSK SRT will review all serious cases identified from the Broad Anaphylaxis SMQ as described in Section 15 and Section 17.1, applying clinical judgment to determine if the preferred terms are indicative of a hypersensitivity or post-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. The GSK SRT adjudicates serious hypersensitivity reactions into a category based primarily on time to onset: acute (onset < 24 hours), 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 studies where subjects are receiving weekly injections, any delayed, non-acute reactions will typically occur in the interval 4-7 days later, but may occur up to 21 days later following a missed injection or after the last injection.

In addition, possible cases of serious anaphylaxis per Sampson criteria will be identified per the criteria in Section 15. 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.

Section 16.3: Potential opportunistic infections

Opportunistic infections (OIs) will be identified using a list of preferred terms (Section 17.1), designed to cast a wide net for events potentially indicative of an opportunistic infection. Any identified events will be adjudicated by the GSK SRT 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
- Capnocytophaga infection
- 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 listed in Section 17.1, 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)
- Salmonella sepsis - there may be rare exceptions in which the presentation is atypical, which will be considered on a case-by-case basis by the SRT.
- Hepatitis B
- Hepatitis C

Herpes Zoster

Herpes Zoster events will be identified per terms in Section 17.1. 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 an 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.

Section 16.4: Suicide/self-injury

Suicide and self-injury SAEs will be identified using the preferred terms identified in Section 17.1 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 listed in Section 17.1, and utilizing the supplemental/narrative information, will adjudicate the SAEs as suicide/self-injury if warranted based on medical judgment.

Section 16.5: Fatalities

All fatalities that are reported while a subject is eligible for SAE reporting 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.

Section 17: AESI Preferred term definitions under current and prior versions of MedDRA

The AESI definitions under the current version of MedDRA are found via the IMMS pathname in Section 17.1. Prior AESI definitions under legacy versions of MedDRA are found in the subsequent sections.

Section 17.1: MedDRA v21

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_21.csv

Section 17.2: MedDRA v20.1

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_201.csv

Section 17.3: MedDRA v20.0

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_20.csv

Section 17.4: MedDRA v19.1

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_191.csv

Section 17.5: MedDRA v19.0

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_19.csv

Section 17.6: MedDRA v18.1

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_181.csv

Section 17.7: MedDRA v18.0

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_18.csv

Section 17.8: MedDRA v17.1

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_171.csv

Section 17.9: MedDRA v17.0

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_17.csv

Section 17.10: MedDRA v16.1

The AESI definitions were not updated for MedDRA v16.1.

Section 17.11: MedDRA v16.0

/Study File/GSK1550188/_Project/Meta Analysis/PSAP/AESI_16.csv

11.11. Appendix 11: Abbreviations & Trade Marks

11.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Anti-nuclear antibody
Anti-dsDNA	Anti-double-stranded DNA
ATC	Anatomical Therapeutic Chemical
BILAG	British Isles Lupus Assessment Group of SLE Clinics
BMI	Body Mass index
BUN	Blood Urea Nitrogen
C3 / C4	Complement 3 / Complement 4
CDISC	Clinical Data Interchange Standards Consortium
CNS	Central Nervous System
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Report Form
CSR	Clinical Study Report
DB	Double Blind
DP	Decimal Places
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
hpf	High-power Field
IDSL	Integrated Data Standards Library
IgA, IgG, IgM	Immunoglobulin A, G, M
IM	Intramuscular
IV	Intravenous
LLN	Lower Limit of Normal
LOC	Last Observation Carries Forward
LTC	Long Term Continuation (studies)
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non-melanoma skin cancer
OL	Open-Label
PDMP	Protocol Deviation Management Plan
PGA	Physician's Global Disease Assessment
PK	Pharmacokinetic
PSAP	Program Safety Analysis Plan
PT	Preferred Term
QC	Quality Control
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
SAC	Statistical Analysis Complete

Abbreviation	Description
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SELENA	Safety of Estrogen in Lupus National Assessment
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	System Organ Class
SOP	Standard Operation Procedure
SRI	SLE Response Index
SRT	Safety Review Team
TFL	Tables, Figures & Listings
ULN	Upper Limit of Normal
VAS	Visual Analogue
WOCF	Worst Observation Carried Forward
yrs	Years

11.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ADVAIR

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

11.12. Appendix 12: List of Data Displays

11.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.32	
Safety	2.1 to 2.86	2.1 to 2.14
Efficacy	3.1 to 3.29	3.1 to 3.16
Biomarker	5.1 to 5.11	5.1 to 5.8
Section	**Listings**	
ICH Listings (Safety)	1 to 56	
Other Listings		

11.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Section 11.13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Efficacy/Biomarker	EFF_Fn	EFF_Tn	EFF_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.12.3. Study Population Tables

Study Population : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
Subject Disposition					
1.1.	All Subjects	POP_T1	Subject Enrolment		
1.2.	Safety	POP_T2	Enrolment by Site		
1.3.	Safety	POP_T3	Belimumab Treated Person-Years on Study		
1.4.	All Enrolled Subjects	POP_T4	Subject Disposition Per End of Treatment CRF	Prioritise for SAC deliverable	
1.5.	Safety	POP_T5	Subject Completion Status Per Protocol		
1.6.	Safety	POP_T6	Subject Completion Status Per Protocol by Year Interval		
1.7.	Safety	POP_T7	Time to Withdrawal for Those Subjects Who Exited Prior to Study Closing		
Inclusion / Exclusion Criteria					
1.8.	All Enrolled Subjects	POP_T8	Summary of Inclusion/Exclusion Criteria Deviations		
Protocol Deviations					
1.9.	All Enrolled Subjects	POP_T9	Subjects with Important Protocol Deviations		
Demography & Baseline Characteristics					
1.10.	Safety	POP_T10	Demographic and Baseline Characteristics	Prioritise for SAC deliverable	
1.11.	Safety	POP_T10	Demographic and Baseline Characteristics by Age Group (< 65 years)		

Study Population : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
1.12.	Safety	POP_T10	Demographic and Baseline Characteristics by Age Group (>= 65 years)		
1.13.	Safety	POP_T10	Demographic and Baseline Characteristics by Gender (Male)		
1.14.	Safety	POP_T10	Demographic and Baseline Characteristics by Gender (Female)		
1.15.	Safety	POP_T10	Demographic and Baseline Characteristics by Baseline SELENA SLEDAI (<= 9)		
1.16.	Safety	POP_T10	Demographic and Baseline Characteristics by Baseline SELENA SLEDAI (>= 10)		
1.17.	All Enrolled Subjects	POP_T11	Summary of Age Ranges at Baseline	EudraCT	
1.18.	All Enrolled Subjects	POP_T12	Race and Racial Combination Details	Prioritise for SAC deliverable	
Baseline Disease Activity					
1.19.	Safety	POP_T13	Baseline Disease Activity		
1.20.	Safety	POP_T13	Baseline Disease Activity by Age Group (< 65 years)		
1.21.	Safety	POP_T13	Baseline Disease Activity by Age Group (>= 65 years)		
1.22.	Safety	POP_T13	Baseline Disease Activity by Gender (Male)		
1.23.	Safety	POP_T13	Baseline Disease Activity by Gender (Female)		
1.24.	Safety	POP_T13	Baseline Disease Activity by Baseline SELENA SLEDAI (<= 9)		
1.25.	Safety	POP_T13	Baseline Disease Activity by Baseline SELENA SLEDAI (>= 10)		
Other Baseline Data					
1.26.	Safety	POP_T14	Allowable SLE Medication Usage at Baseline		

Study Population : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
1.27.	Safety	POP_T15	ACR Classification Criteria at Parent Study Baseline	Data collected at DB parent study screening visit.	
1.28.	Safety	POP_T16	SELENA SLEDAI Organ and Item Involvement at Baseline		
1.29.	Safety	POP_T17	BILAG Grade by Organ Domain at Baseline		
1.30.	Safety	POP_T18	Complement Levels at Baseline	Parameters = C3, C4	
1.31.	Safety	POP_T19	Autoantibody Levels at Baseline	Parameters = anti-dsDNA, ANA	
1.32.	Safety	POP_T20	Immunoglobulin Levels at Baseline	Parameters = IgG, IgA, IgM	

11.12.4. Safety Tables

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
Medications					
2.1.	Safety	SAFE_T1	Concomitant Medications by ATC Level 1 and ATC Level 4 Term		
2.2.	Safety	SAFE_T1	Concomitant Medications by ATC Level 4 and Preferred Term		
2.3.	Safety	SAFE_T2	SLE Medication by Year Interval		
2.4.	Safety	SAFE_T3	Shifts from Baseline in Daily Prednisone Equivalent Steroid Dose by Belimumab Visit		
Exposure					
2.5.	Safety	SAFE_T4	Study Drug Exposure		
Adverse Events by SOC					
2.6.	Safety	SAFE_T5	Adverse Events Summary by Year Interval		
2.7.	Safety	SAFE_T6	Adverse Events by SOC		
2.8.	Safety	SAFE_T6	Serious Adverse Events by SOC		
2.9.	Safety	SAFE_T6	Severe Adverse Events by SOC		
2.10.	Safety	SAFE_T6	Study Drug Related Adverse Events by SOC		
2.11.	Safety	SAFE_T6	Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study by SOC		
Adverse Events Rates by SOC					
2.12.	Safety	SAFE_T7	Adverse Event Rates per 100 Person-Years by SOC		1
2.13.	Safety	SAFE_T7	Serious Adverse Event Rates per 100 Person-Years by SOC		1
2.14.	Safety	SAFE_T7	Severe Adverse Event Rates per 100 Person-Years by SOC		1

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.15.	Safety	SAFE_T7	Study Drug Related Adverse Event Rates per 100 Person-Years by SOC		
2.16.	Safety	SAFE_T7	Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study Rates per 100 Person-Years by SOC		
Adverse Events by SOC and PT					
2.17.	Safety	SAFE_T8	Adverse Events by SOC and PT	Prioritise for SAC deliverable	
2.18.	Safety	SAFE_T8	Serious Adverse Events by SOC and PT		
2.19.	Safety	SAFE_T8	Severe Adverse Events by SOC and PT		
2.20.	Safety	SAFE_T8	Study Drug Related Adverse Events by SOC and PT		
2.21.	Safety	SAFE_T8	Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study by SOC and PT		
Adverse Events by SOC and PT (Subgroups)					
2.22.	Safety	SAFE_T8	Adverse Events by Age Group (< 65 Years), SOC and PT		
2.23.	Safety	SAFE_T8	Adverse Events by Age Group (≥ 65 Years), SOC and PT		
2.24.	Safety	SAFE_T8	Adverse Events by Gender (Male), SOC and PT		
2.25.	Safety	SAFE_T8	Adverse Events by Gender (Female), SOC and PT		
2.26.	Safety	SAFE_T8	Adverse Events by Baseline SELENA SLEDAI (≤ 9), SOC and PT		
2.27.	Safety	SAFE_T8	Adverse Events by Baseline SELENA SLEDAI (≥ 10), SOC and PT		
Adverse Events: Non-Serious and Serious by SOC and PT (for Disclosure)					

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.28.	Safety	SAFE_T8	Most Common Non-Serious Drug Related Adverse Events (≥10% incidence in any interval) by SOC and PT	PLS	
2.29.	Safety	SAFE_T8	Most Common Serious Drug Related Adverse Events (≥2% incidence in any interval) by SOC and PT	PLS – 2% cut-off to be used for dry run, may revise for final	
2.30.	Safety	SAFE_T9	Most Common (≥ 5%) Non-Serious Adverse Events by SOC and PT (Number of Subjects and Occurrences)	FDAAA – prioritise for SAC deliverable	
2.31.	Safety	SAFE_T10	Serious Adverse Events by SOC and PT (Number of Subjects and Occurrences)	FDAAA – prioritise for SAC deliverable	
Adverse Events by PT					
2.32.	Safety	SAFE_T8	Adverse Events by PT		
2.33.	Safety	SAFE_T8	Serious Adverse Events by PT		
2.34.	Safety	SAFE_T8	Severe Adverse Events by PT		
2.35.	Safety	SAFE_T8	Study Drug Related Adverse Events by PT		
2.36.	Safety	SAFE_T8	Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study by PT		
Adverse Events by Maximum Intensity					
2.37.	Safety	SAFE_T11	Adverse Events by SOC and Maximum Severity		
2.38.	Safety	SAFE_T12	Adverse Events by SOC and PT and Maximum Severity		
Adverse Events of Special Interest					
2.39.	Safety	SAFE_T13	Adverse Events of Special Interest by Category		
2.40.	Safety	SAFE_T14	Malignant Neoplasm Adverse Events of Special Interest by Category and PT		

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.41.	Safety	SAFE_T14	Post-Infusion Systemic Reaction Adverse Events of Special Interest by Category and PT		
2.42.	Safety	SAFE_T14	Serious Post-Infusion Systemic Reaction Adverse Events of Special Interest by Category and PT		
2.43.	Safety	SAFE_T14	Infection Adverse Events of Special Interest by Category and PT		
2.44.	Safety	SAFE_T14	Serious Infection Adverse Events of Special Interest by Category and PT		
2.45.	Safety	SAFE_T14	Infection Adverse Events of Special Interest Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study by Category and PT		
2.46.	Safety	SAFE_T14	Depression/Suicide/Self-injury Adverse Events of Special Interest by Category and PT		
2.47.	Safety	SAFE_T14	Deaths by Category and PT		
Adverse Events of Special Interest Rates					
2.48.	Safety	SAFE_T15	Adverse Events of Special Interest Rates per 100 Person-Years by Category		
2.49.	Safety	SAFE_T16	Malignant Neoplasm Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		
2.50.	Safety	SAFE_T16	Post-Infusion Systemic Reaction Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		
2.51.	Safety	SAFE_T16	Serious Post-Infusion Systemic Reaction Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.52.	Safety	SAFE_T16	Infection Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		
2.53.	Safety	SAFE_T16	Serious Infection Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		
2.54.	Safety	SAFE_T16	Infection Adverse Events of Special Interest Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study Rates per 100 Person-Years by Category and PT		
2.55.	Safety	SAFE_T16	Depression/Suicide/Self-injury Adverse Events of Special Interest Rates per 100 Person-Years by Category and PT		
Laboratory					
2.56.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Hematology		
2.57.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Liver Function		
2.58.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Electrolytes		
2.59.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Other Chemistries		
2.60.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL113750)		
2.61.	Safety	SAFE_T17	Laboratory Results (Observed and Change from Baseline) by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL112341)		
Worst Laboratory Toxicity Grade (by Year Interval)					

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.62.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Hematology		
2.63.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Liver Function		
2.64.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Electrolytes		
2.65.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Other Chemistries		
2.66.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Urinalysis		
2.67.	Safety	SAFE_T18	Worst Laboratory Toxicity Grade by Year Interval: Immunoglobulins		
2.68.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Hematology		
2.69.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Liver Function		
2.70.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Electrolytes		
2.71.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Other Chemistries		
2.72.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Urinalysis		
2.73.	Safety	SAFE_T19	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline by Year Interval: Immunoglobulins		
Laboratory Reference Range Shifts (by Visit)					
2.74.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Hematology		

Safety : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.75.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Liver Function		
2.76.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Electrolytes		
2.77.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Other Chemistries		
2.78.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Urinalysis		
2.79.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL113750)		
2.80.	Safety	SAFE_T20	Laboratory Reference Range Shifts from Baseline by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL112341)		
Immunogenicity					
2.81.	Safety	SAFE_T21	Immunogenic Response by Belimumab Visit		
2.82.	Safety	SAFE_T22	Immunogenic Response by Year Interval		
2.83.	Safety	SAFE_T23	Immunogenic Summary	See 3750 DB, DS Table 3.73	
Vital Signs					
2.84.	Safety	SAFE_T24	Vital Signs by Belimumab Visit		
2.85.	Safety	SAFE_T24	Weight (kg) by Belimumab Visit (Subjects from Parent Study BEL113750)		
2.86.	Safety	SAFE_T24	Weight (kg) by Belimumab Visit (Subjects from Parent Study BEL112341)		

11.12.5. Safety Figures

Safety : Figures					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.1.	Safety	SAFE_F1	Time to Withdrawal for Subjects Who Exited Prior to Study Closing [1]		
2.2.	Safety	SAFE_F2	Cumulative Adverse Event Incidence Over Time		
Laboratory					
2.3.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Haematology		
2.4.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Liver Function		
2.5.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Electrolytes		
2.6.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Other Chemistries		
2.7.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL113750)		
2.8.	Safety	SAFE_F3	Laboratory Results by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL112341)		
2.9.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Hematology		
2.10.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Liver Function		
2.11.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Electrolytes		
2.12.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Other Chemistries		
2.13.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL113750)		

Safety : Figures					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
2.14.	Safety	SAFE_F3	Laboratory Results Change from Baseline by Belimumab Visit: Immunoglobulins (Subjects from Parent Study BEL112341)		

11.12.6. Efficacy Tables

Efficacy : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
SRI and Secondary Efficacy Endpoints					
3.1.	Safety	EFF_T1	SRI Response by Belimumab Visit		
3.2.	Safety	EFF_T1	SELENA SLEDAI (≥ 4 Point Reduction from Baseline) by Belimumab Visit		
3.3.	Safety	EFF_T1	PGA No Worsening (Increase of < 0.30 points from Baseline) by Belimumab Visit		
3.4.	Safety	EFF_T1	BILAG No New 1A/2B Organ Domain Scores Compared to Baseline by Belimumab Visit		
3.5.	Safety	EFF_T2	Number of Days of Daily Prednisone ≤ 7.5 mg/day and/or Reduced by 50% from Baseline, Among Subjects with Baseline Daily Prednisone Dose > 7.5 mg/day		
3.6.	Safety	EFF_T3	Time to First Severe SFI Flare		
3.7.	Safety	EFF_T4	Number of Subjects with At Least One Severe SFI Flare by Belimumab Visit		
Other Efficacy Endpoints: Disease Activity					
3.8.	Safety	EFF_T5	SELENA SLEDAI (Observed and Change from Baseline) by Belimumab Visit		
3.9.	Safety	EFF_T5	SELENA SLEDAI (Observed and Percent Change from Baseline) by Belimumab Visit		
3.10.	Safety	EFF_T5	SLICC/ACR Damage Index (Observed and Change from Baseline) by Belimumab Visit (Subjects from Parent Study BEL113750)		

Efficacy : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
3.11.	Safety	EFF_T5	SLICC/ACR Damage Index (Observed and Change from Baseline) by Belimumab Visit (Subjects from Parent Study BEL112341)		
3.12.	Safety	EFF_T1	SLICC/ACR Damage Worsening (Change > 0) from Baseline by Belimumab Visit (Subjects from Parent Study BEL113750)		
3.13.	Safety	EFF_T1	SLICC/ACR Damage Worsening (Change > 0) from Baseline by Belimumab Visit (Subjects from Parent Study BEL112341)		
3.14.	Safety	EFF_T5	PGA (Observed and Percent Change from Baseline) by Belimumab Visit		
Other Efficacy Endpoints: Flares					
3.15.	Safety	EFF_T3	Time to First SFI Flare		
3.16.	Safety	EFF_T4	Number of Subjects with At Least One SFI Flare by Belimumab Visit		
3.17.	Safety	EFF_T6	Total Number of Severe SFI Flares (Rate per 100 Person-Years)		
3.18.	Safety	EFF_T6	Total Number of SFI Flares (Rate per 100 Person-Years)		
3.19.	Safety	EFF_T3	Time to First 1A/2B BILAG Flare		
3.20.	Safety	EFF_T4	Number of Subjects with At Least One 1A/2B BILAG Flare by Belimumab Visit		
3.21.	Safety	EFF_T3	Time to First BILAG A Flare		
3.22.	Safety	EFF_T4	Number of Subjects with At Least One BILAG A Flare by Belimumab Visit		
Other Efficacy Endpoints: Organ-Specific Measures					
3.23.	Safety	EFF_T3	Time to First Renal Flare		

Efficacy : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
3.24.	Safety	EFF_T4	Number of Subjects with At Least One Renal Flare by Belimumab Visit		
3.25.	Safety	EFF_T5	Proteinuria (Observed and Percent Change from Baseline) by Belimumab Visit, Among Subjects with Baseline Proteinuria		
3.26.	Safety	EFF_T8	Proteinuria Shifts from Baseline by Belimumab Visit		
Other Efficacy Endpoints: Prednisone					
3.27.	Safety	EFF_T5	Prednisone (mg/day) (Observed and Percent Change from Baseline) by Belimumab Visit		
3.28.	Safety	EFF_T1	Daily Prednisone Dose Reduced to $\leq$ 7.5 mg/day by Belimumab Visit, Among Subjects with Baseline Prednisone Dose > 7.5 mg/day		
3.29.	Safety	EFF_T1	Daily Prednisone Dose Increased to > 7.5 mg/day by Belimumab Visit, Among Subjects with Baseline Prednisone Dose $\leq$ 7.5 mg/day		

11.12.7. Efficacy Figures

Efficacy : Figures					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
SRI and Secondary Efficacy Endpoints					
3.1.	Safety	EFF_F1	SRI Response by Belimumab Visit		
3.2.	Safety	EFF_F1	SELENA SLEDAI (≥ 4 Point Reduction from Baseline) by Belimumab Visit		
3.3.	Safety	EFF_F1	PGA No Worsening (Increase of < 0.30 points from Baseline) by Belimumab Visit		
3.4.	Safety	EFF_F1	BILAG No New 1A/2B Organ Domain Scores Compared to Baseline by Belimumab Visit		
3.5.	Safety	EFF_F2	Time to First Severe Flare		
Other Efficacy Endpoints: Disease Activity					
3.6.	Safety	EFF_F3	SELENA SLEDAI Percent Change from Baseline by Belimumab Visit		
3.7.	Safety	EFF_F3	SELENA SLEDAI Change from Baseline by Belimumab Visit		
3.8.	Safety	EFF_F3	PGA Percent Change from Baseline by Belimumab Visit		
Other Efficacy Endpoints: Flares					
3.9.	Safety	EFF_F2	Time to First SFI Flare		
3.10.	Safety	EFF_F2	Time to First 1A/2B BILAG Flare		
3.11.	Safety	EFF_F2	Time to First BILAG A Flare		
Other Efficacy Endpoints: Organ-Specific Measures					
3.12.	Safety	EFF_F2	Time to First Renal Flare		

Efficacy : Figures					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
3.13.	Safety	EFF_F3	Proteinuria Percent Change from Baseline by Belimumab Visit, Among Subjects with Baseline Proteinuria		
Other Efficacy Endpoints: Prednisone					
3.14.	Safety	EFF_F3	Prednisone Percent Change from Baseline by Belimumab Visit		
3.15.	Safety	EFF_F1	Daily Prednisone Dose Reduced to ≤ 7.5 mg/day by Belimumab Visit, Among Subjects with Baseline Prednisone Dose > 7.5 mg/day		
3.16.	Safety	EFF_F1	Daily Prednisone Dose Increased to > 7.5 mg/day by Belimumab Visit, Among Subjects with Baseline Prednisone Dose ≤ 7.5 mg/day		

11.12.8. Biomarker Tables

Biomarker : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
Immunoglobulin (IgG, IgA, IgM)					
5.1.	Safety	EFF_T5	Immunoglobulin (Observed and Percent Change from Baseline) by Belimumab Visit (Subjects from Parent Study BEL113750)		
5.2.	Safety	EFF_T5	Immunoglobulin (Observed and Percent Change from Baseline) by Belimumab Visit (Subjects from Parent Study BEL112341)		
5.3.	Safety	SAFE_T25	Immunoglobulin Levels below the Lower Limit of Normal (LLN) by Belimumab Visit (Subjects from Parent Study BEL113750)		
5.4.	Safety	SAFE_T25	Immunoglobulin Levels below the Lower Limit of Normal (LLN) by Belimumab Visit (Subjects from Parent Study BEL112341)		
5.5.	Safety	SAFE_T26	Immunoglobulin Levels below the Lower Limit of Normal (LLN) by Year Interval		
Autoantibodies (anti-dsDNA)					
5.6.	Safety	EFF_T5	Anti-dsDNA (IU/mL) (Observed and Percent Change from Baseline) by Belimumab Visit		
5.7.	Safety	EFF_T5	Anti-dsDNA (IU/mL) (Observed and Percent Change from Baseline) by Belimumab Visit, for Subjects Positive at Baseline		
Complement (C3, C4) Levels					
5.8.	Safety	EFF_T5	Complement Levels (Observed and Percent Change from Baseline) by Belimumab Visit		
5.9.	Safety	EFF_T5	Complement Levels (Observed and Percent Change from Baseline) by Belimumab Visit, for Subjects with Low Complement at Baseline		

Biomarker : Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
B Cell Subsets					
5.10.	Safety	EFF_T5	B Cell Subsets (Observed and Percent Change from Baseline) by Belimumab Visit (Japanese Subjects from Parent Study BEL113750)		
5.11.	Safety	EFF_T5	B Cell Subsets (Observed and Percent Change from Baseline) by Belimumab Visit (Japanese Subjects from Parent Study BEL112341)		

11.12.9. Biomarker Figures

Biomarker : Figures					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Priority]**
Immunoglobulin (IgG, IgA, IgM)					
5.1.	Safety	EFF_F3	Immunoglobulin Percent Change from Baseline by Belimumab Visit (Subjects from Parent Study BEL113750)		
5.2.	Safety	EFF_F3	Immunoglobulin Percent Change from Baseline by Belimumab Visit (Subjects from Parent Study BEL112341)		
Anti-dsDNA					
5.3.	Safety	EFF_F3	Anti-dsDNA Percent Change from Baseline by Belimumab Visit		
5.4.	Safety	EFF_F3	Anti-dsDNA Percent Change from Baseline by Belimumab Visit, for Subjects Positive at Baseline		
Complement (C3, C4) Levels					
5.5.	Safety	EFF_F3	Complement Levels Percent Change from Baseline by Belimumab Visit		
5.6.	Safety	EFF_F3	Complement Levels Percent Change from Baseline by Belimumab Visit, for Subjects with Low Complement at Baseline		
B Cell Subsets					
5.7.	Safety	EFF_F3	B Cell Subsets Percent Change from Baseline by Belimumab Visit (Japanese Subjects from Parent Study BEL113750)		
5.8.	Safety	EFF_F3	B Cell Subsets Percent Change from Baseline by Belimumab Visit (Japanese Subjects from Parent Study BEL112341)		

11.12.10. ICH Listings

ICH : Listings					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
Subject Disposition					
1.	All Screened Subjects	SAFE_L1	Subject Disposition		
2.	All Enrolled Subjects	SAFE_L2	Reasons for Study Withdrawal		
3.	All Screened Subjects	SAFE_L3	Reasons for Screen Failure		
Inclusion / Exclusion Criteria					
4.	All Enrolled Subjects	SAFE_L4	Inclusion or Exclusion Criteria Not Met		
Protocol Deviations					
5.	All Enrolled Subjects	SAFE_L5	Important Protocol Deviations		
Baseline Demographic Characteristics					
6.	Safety	SAFE_L6	Demographic Characteristics		
7.	All Enrolled Subjects	SAFE_L7	Race		
8.	Safety	SAFE_L8	Baseline Characteristics: Anti-dsDNA, ANA, Complement Levels and SLE Medication Use		
9.	Safety	SAFE_L9	Baseline Characteristics: Disease Duration, PGA, SLICC/ACR Damage Index and Proteinuria Results		
10.	Safety	SAFE_L10	Baseline Characteristics: SELENA SLEDAI		

ICH : Listings					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
11.	Safety	SAFE_L11	Baseline Characteristics: BILAG Index Results		
12.	Safety	SAFE_L12	Baseline Characteristics: SLE Flare Index		
Medical History					
13.	Safety	SAFE_L13	Medical History		
Medications					
14.	Safety	SAFE_L14	Concomitant Medications		
15.	Safety	SAFE_L15	Concomitant Procedures/Surgery		
16.	Safety	SAFE_L16	Daily Prednisone Equivalent Dose		
17.	Safety	SAFE_L17	Study Drug Exposure		
18.	Safety	SAFE_L18	Study Drug Administration		
Adverse Events					
19.	Safety	SAFE_L19	Subject Numbers for Individual Adverse Events		
20.	Safety	SAFE_L20	All Adverse Events		
21.	Safety	SAFE_L20	Serious Adverse Events		
22.	Safety	SAFE_L20	Fatal Serious Adverse Events		
23.	Safety	SAFE_L20	Non-Fatal Serious Adverse Events		
24.	Safety	SAFE_L20	Adverse Events Leading to Permanent Discontinuation of Study Drug		
25.	Safety	SAFE_L20	Infections and Infestations SOC Adverse Events for Subjects with a Grade 3 or Grade 4 IgG Toxicity		
26.	Safety	SAFE_L21	Adverse Events of Special Interest		

ICH : Listings					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
27.	Safety	SAFE_L22	Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		
28.	Safety	SAFE_L23	Reasons for Considering as a Serious Adverse Event		
Laboratory					
29.	Safety	SAFE_L24	Laboratory Results: Hematology		
30.	Safety	SAFE_L24	Laboratory Results: Liver Function		
31.	Safety	SAFE_L24	Laboratory Results: Electrolytes		
32.	Safety	SAFE_L24	Laboratory Results: Other Chemistries		
33.	Safety	SAFE_L24	Laboratory Results: Urinalysis		
34.	Safety	SAFE_L24	Laboratory Results: Immunoglobulins		
35.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Hematology		
36.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Liver Function		
37.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Electrolytes		
38.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Other Chemistries		
39.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Urinalysis		
40.	Safety	SAFE_L25	Grade 3 or Grade 4 Laboratory Toxicity Results: Immunoglobulins		
41.	Safety	SAFE_L26	Liver Assessment		
42.	Safety	SAFE_L27	Liver Biopsy Details		
43.	Safety	SAFE_L28	Liver Imaging		
Immunogenicity					

ICH : Listings					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
44.	Safety	SAFE_L29	Immunogenicity Results		
Vital Signs					
45.	Safety	SAFE_L30	Vital Signs		

11.12.11. ICH Listings (Efficacy/Biomarkers)

ICH : Listings					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Final Deliverable [Stage]**
Disease Activity					
46.	Safety	EFF_L1	SRI Results Relative to Baseline [1]		
47.	Safety	EFF_L2	SELENA SLEDAI Results		
48.	Safety	EFF_L3	Physician's Global Assessment (PGA) Results		
49.	Safety	EFF_L4	BILAG Results		
50.	Safety	EFF_L5	SLICC/ACR Damage Index Results		
51.	Safety	EFF_L6	SLE Flare Index Results		
Biomarkers					
52.	Safety	EFF_L7	Autoantibody and Complement Level Results		
53.	Safety	EFF_L7	B Cell Results		
Pregnancies					
54.	Safety	SAFE_L31	On-Study Pregnancies		
AE/Post 16 Week Follow-up Visit					
55.	Safety	SAFE_L14	Concomitant Medications Starting After the 16 Week Follow-up		
56.	Safety	SAFE_L20	Adverse Events Starting After the 16 Week Follow-up Visit		

11.13. Appendix 13: Example Mock Shells for Data Displays

Refer to the separate mock example shell document.