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Title:	Reporting and Analysis Plan (RAP) for BEL115467, A Randomized, Double-Blind, Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab

Compound Number: GSK1550188

Effective Date: 18-OCT-2018

Description: This is a global, multi-center, randomized, double-blind, placebo-controlled, 52-week study to assess mortality and adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving belimumab. Subjects will receive belimumab or placebo through Week 48 with a final visit conducted at Week 52 and standard therapy will be received throughout the study. Subjects will be assessed for malignancies including non-melanoma skin cancers (NMSC), serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, suicidality, and serious infusion and hypersensitivity reactions. All-cause mortality will be reported. All other serious adverse events regardless of causality will also be recorded. Efficacy endpoints are secondary in nature. Following the 52-week study, all subjects will be contacted annually through Year 5 to assess mortality and malignancy (including NMSC). This Reporting and Analysis Plan (RAP) prospectively describes the safety and efficacy analyses that will be performed through the Week 52 treatment period. Details of the planned summaries for the post-treatment follow-up for Years 2 to 5 will be described in a separate RAP.

Subject: Systemic Lupus Erythematosus, SLE, belimumab, GSK1550188, Benlysta, efficacy, safety, placebo, mortality, adverse events of special interest.

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ABBREVIATIONS

ACR	American College of Rheumatology
ADaM	Analysis Data Model
AE	Adverse Event
AESI	AEs of special interest
Anti-dsDNA	Anti-double-stranded DNA
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIL	Clinical investigative lead
CMQ	Customized MedDRA Query
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DBF	Database freeze
DBR	Database release
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IM	Intramuscular(ly)
IP	Investigational Product
ITT	Intention-to-treat
IV	Intravenous(ly)
IXRS	Interactive response system
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical monitor
NMSC	Non-melanoma skin cancer
NTM	Non-tuberculous mycobacterium
PSAP	Program Safety Analysis Plan
PSRQ	Possible Suicidality Related Questionnaire
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SD	Standard deviation
SDAC	Statistical Data Analysis Center
SDTM	Study Data Tabulation Models
SELENA	Safety of Estrogen in Lupus National Assessment
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
SRT	Safety Review Team
TB	Tuberculosis

TLFs	Tables, Listings and Figures
WOCF	Worst Observation Carried Forward

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1. INTRODUCTION

This reporting and analysis plan (RAP) documents the planned summaries through the Week 52 treatment period for the HGS1006-C1113 study. The study will be reported under its GSK study number BEL115467. A separate RAP will be produced to document the planned summaries of the post-treatment follow-up for Years 2 to 5.

This is a global, multi-center, randomized, double-blind, placebo-controlled, 52-week study to assess mortality and adverse events of special interest (AESI) in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) treated with belimumab plus standard therapy vs placebo plus standard therapy. Following the 52-week study, all subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including non-melanoma skin cancers [NMSC]).

This RAP is based upon the following study documents:

- Study Protocol Amendment 03 (May 22, 2017)
- Final Case Report Form (CRF) Version 6.4 (February 05, 2018)
- Program Safety Analysis Plan (PSAP) Version 6 (October 2, 2018).
  Note: for reporting purposes, the most current version of the PSAP at the time of database freeze (DBF) will be used. For reference, sections of the PSAP that are relevant to reporting are given in Appendix 6: PSAP Sections for AESI Reporting. The most current MedDRA version at the time of database freeze (DBF) will be used.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

To evaluate the following in adult SLE subjects receiving belimumab plus standard therapy versus subjects receiving placebo plus standard therapy:

- Mortality and adverse events of special interest (AESI) over 1 year (through 52 weeks).
- Corticosteroid reduction during Weeks 40-52.

2.2. Study Endpoints

2.2.1. Safety Endpoints

- All-cause mortality
- Serious infections (including serious opportunistic infections and any event of TB or TB reactivation)
  - See clarification in Section 2.2.3 (this endpoint will be referred to in the RAP as Serious Infections)

- Non-serious opportunistic infections and other infections of interest (protocol Appendix 2)
    - See clarification in Section 2.2.3 (this endpoint will be referred to in the RAP as Opportunistic Infections and Other Infections of Interest)
- Non-melanoma skin cancers (NMSC)
- Malignancies (excluding NMSC)
- Psychiatric events suggesting serious mood disorders and anxiety
- Suicidality (using C-SSRS; see protocol Appendix 4 and Appendix 5)
- Serious infusion and hypersensitivity reactions
- All serious adverse events (SAEs)

Section 9.5.12 provides definitions for all the protocol-defined AESIs. Section 2.2.3 provides the rationale for cases in which these may differ from the protocol.

2.2.2. Efficacy Endpoints

The major efficacy endpoint is:

- Percent of subjects whose average prednisone (or equivalent) dose has been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 in subjects receiving greater than 7.5 mg/day at baseline.

Other efficacy endpoints include:

- Use of immunomodulatory medications to treat SLE.
- Number of hospitalizations per patient.
- Percent of patients hospitalized.

Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index will be recorded at baseline and at Week 52 to permit assessment of accrual of damage in subjects who may be followed in a subsequent study.

Section 2.2.3 provides the rationale for cases in which these may differ from the protocol.

2.2.3. Changes to the Protocol Defined Statistical Analysis Plan

Changes/clarifications from the original planned summaries specified in the protocol are as follows:

- Whilst the protocol description of the AESI for serious infections was stated to include “any event of TB or TB reactivation”, this has been defined in the RAP as All Serious Infections from the MedDRA ‘Infections and Infestations’ System Organ Class (SOC) aligned with the focus on serious infections. Hence any non-serious events, including those of ‘TB or TB reactivation’, would not be included in the endpoint but will be summarized separately.

- Whilst the protocol description of the AESI "Non-serious opportunistic infections and other infections of interest" refers to only non-serious events, the main summary will be of overall incidence (i.e., serious and non-serious events) aligned with focusing on all events of opportunistic infections and other infections of interest. Supplemental summaries of study agent related non-serious events will be produced, which will include non-serious opportunistic infections and other infections of interest. The endpoint will be derived using the "All infections" definition from the PSAP, Section 16.3 (See Appendix 6: PSAP Sections for AESI Reporting). This definition encompasses all infections of interest as defined in protocol Appendix 2. See Section 9.5.12.
- For the mortality endpoint, the protocol specifies that a hazard ratio (and 95% confidence interval [CI]) for belimumab vs placebo will be estimated using a Cox Proportional Hazards model. However due to the small number of events and low incidence rate, estimation using a difference in rates (and 95% CI) is considered more informative and so this supplemental analysis will not be conducted. A Kaplan-Meier curve and cumulative mortality counts by visit will be generated to illustrate the time profile.
- For the major efficacy endpoint (steroid dose reduction), the protocol states that if a subject switches immunomodulatory medications for reasons other than toxicity or lack of availability they should be considered a non-responder. However, the eCRF has not been designed to collect data on reasons for switches and therefore all new immunomodulatory agents to treat SLE will render a subject a non-responder in the analysis. Hence, subjects who switch will be considered non-responders regardless of the reason for switching. Additionally prednisone analyses and summaries are based only on steroids used to treat SLE (see Section 9.5.16 and Section 12.1.1).
- "Immunomodulatory medications" will be identified as immunosuppressants (ATC code beginning "L04A") plus cyclophosphamide and mercaptopurine, per the definition used across the Benlysta program.
- The number of hospitalizations per patient and percent of patients hospitalized will be derived from the SAE data. See Section 9.3 for further detail.
- SLICC/ACR Damage Index is not explicitly stated as an endpoint in the protocol. However, this is an endpoint of interest and therefore analyses will be performed as described in Section 12.2.3.

2.3. Statistical Hypotheses

There are no formal statistical hypotheses for the primary safety endpoints in the study. The main purpose of this study is to provide an evaluation of the difference in the rates of all-cause mortality and all prespecified AESI between the belimumab and placebo groups with a 2-sided 95% CI. SAEs will be summarized descriptively only. See Section 11.1.2 for details of the protocol-defined AESIs.

3. STUDY DESIGN

This is a global, multi-center, randomized, double-blind, placebo-controlled, 52-week study to assess mortality and AESI in adults with active, autoantibody-positive SLE treated with belimumab plus standard therapy vs placebo plus standard therapy. Approximately 4,000 subjects will be randomized (1:1) to belimumab plus standard therapy or placebo plus standard therapy. Randomization will be stratified for region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia; see Appendix 1: Countries by Region for details of countries and regions), Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) score (≤9 vs ≥10), and steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent). There is no minimum score required for the SELENA SLEDAI to be eligible for this study.

Subjects will receive investigational product (IP) on Days 0, 14, 28, and every 28 days thereafter through Week 48 with a final in clinic visit conducted at Week 52. Subjects who discontinue treatment at any time during the study but do not withdraw from study visits will be followed at 28-day intervals through Week 52. If the subject withdraws from study visits prior to Week 52, an attempt will be made to assess mortality and occurrence of malignancy (including NMSC) at Week 52 and annually for Years 2 through 5. See protocol Section 3.1 for further details. If a subject is not contactable (withdrew consent or lost to follow-up), where allowed by individual subject's legal consent status and individual country regulations, sites may utilize other available records to perform a mortality assessment at Week 52 - this may include search of public records aided by an independent party.

An Independent Data Monitoring Committee (IDMC) will review unblinded safety data until the data are locked and analyzed. The IDMC will monitor all SAEs (including all-cause mortality), serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events, suicidality and serious infusion and hypersensitivity reactions. Details of the summaries provided to the IDMC by an Independent Statistical Data Analysis Center (SDAC) are described in the IDMC Charter and IDMC Report Template.

4. PLANNED ANALYSES

4.1. Interim Analyses

The EMA requested that an interim analysis be carried out for monitoring patients' safety.

An interim analysis was planned to be conducted when at least 2,000 randomized subjects had completed through Week 52. The database was released when individual subject records for all subject visits that occurred within the timeframe of the Week 52 visit of the 2,000th subject had been locked. Therefore, the interim analysis also included data for subjects who were randomized but had not yet completed Week 52.

The interim analysis was solely for monitoring patients' safety and reporting event rates to health authorities. It was descriptive in nature and no comparative statistical inferences for claims were to be made.

To minimize bias and maintain data integrity the interim analysis was performed by Statistics Collaborative Inc (SCI), an independent SDAC. They prepared the interim summaries and generated the interim report for IDMC review, producing the same summaries as those created for bi-annual IDMC reviews.

This interim analysis was conducted as planned and submitted to EMA in December 2016.

Following the final analysis of the treatment period through Week 52 as described in Section 4.2, interim summaries will be generated to report post-treatment follow-up mortality and malignancy rates at the end of Year 2, Year 3, and Year 4 for reporting to health authorities.

4.2. Final Analysis

There will be two database releases corresponding to the end of the following study periods as described in Section 9.1.1 and Section 9.1.2:

- Treatment Period (through Week 52)
- Post-Treatment Follow-Up (Years 2 to 5)

The first database release will occur after data through the Week 52 visit (occurring approximately 4 weeks after the last dose of study agent) for all subjects have been collected, verified and validated. Data for subjects who withdraw from IP but stay in the study through Week 52 will be included in this database release. This database will include Year 1 survival status and occurrence of malignancy for subjects who withdraw from the study prior to the Week 52 visit and have follow-up mortality and malignancy data at Week 52. Data for the Years 2 to 5 post-treatment follow-up that has been obtained to this point will be included in the first database release but these data will not be fully validated or locked and will not be reported unless otherwise specified.

The second database release will occur after data through the Year 5 survival status and occurrence of malignancy follow-up have been collected, verified and validated.

This RAP details the planned summaries through the Week 52 treatment period. All outputs required for the Treatment Period (through Week 52) will be listed in the Mock Tables, Listings and Figures (TLFs) Shells document. A separate RAP will be produced to document the planned summaries of the post-treatment follow-up for Years 2-5.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

It was originally planned that a target of 5,000 SLE subjects would be enrolled in this safety study. The sample size was based on the feasibility of enrolling a large number of SLE subjects in a global trial that would provide a reasonable estimate for mortality and other AESI rates. Assuming a common first year mortality rate of 0.68% for both treatment groups, the precision of the 95% CI for the difference between treatment groups is ±0.46%.

Following the completion of 2 additional placebo-controlled trials (BEL112341/C1115, BEL113750), revised mortality estimates based on data from all 5 of the completed studies were as follows: 0.504% (6/1,190 for the placebo group) and 0.564% (14/2,484 for the belimumab group) with a delta of 0.060%.

Using a conservative revised mortality rate of 0.564%, the 95% CI for a 4,000-subject sample size with 1:1 randomization was also ±0.46%. As a result, given the revised mortality estimate, a sample size of 4,000 subjects would not result in any loss of precision (i.e., the width of the 95% CI remains unchanged). Therefore, agreement was reached with regulatory authorities to reduce the sample size from 5,000 to 4,000 subjects.

All sample size calculations were performed using the Chi-Square Simple Asymptotic Pearson method in Power Analysis and Sample Size software (PASS 2012).

6. ANALYSIS POPULATIONS

Randomized

The Randomized population is defined as all subjects who are randomized. Summaries using the Randomized population will group subjects according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

Any subject assigned a treatment randomization number by the Interactive Response System (IXRS) system is considered to have been randomized.

One subject was randomized in the IXRS system but was not entered as a randomized subject into the eCRF, since the site had not administered study agent to the subject. It was not possible to subsequently update the randomization number into the eCRF because the site was closed. Therefore the subject cannot be included in the data displays as part of the randomized population. A footnote will be included on relevant tables to indicate this.

Intention-to-Treat (ITT)

The ITT population is defined as all subjects who are randomized and received at least one dose of study agent. The ITT analysis will be performed per the treatment that a

subject was randomized to receive, regardless of the actual treatment received. All efficacy endpoints will be analyzed using the ITT population unless otherwise specified.

As-Treated

The As-Treated population is defined as all subjects who are randomized and received at least one dose of study agent. The As-Treated population will group subjects according to the actual treatment administered to the subject based on the treatment that the subject received most of the time (>50% of the time). Therefore, if a subject received an incorrect treatment at more than half the visits, the As-Treated treatment group assignment will differ from the randomized treatment group assignment. Safety analysis will be performed on the As-Treated population.

Note: Two investigative sites (PPD and PPD) were investigated for potential GCP non-compliance. These sites were closed during the conduct of the study. The data from both these sites will be included in all analyses/summaries since the primary endpoint and several of the secondary endpoints relate to safety and there were no concerns noted with the AE data. Also, in view of the large total sample size, inclusion of data from these sites (N=14 and N=4 at PPD and PPD in the As Treated population, respectively) is not considered to impact the overall study conclusions.

6.1. Analysis Datasets

All safety summaries will use the observed data, which are the data collected or observed for the subject with no imputation for missing data. Summaries may also include data as adjudicated by the safety review team (SRT) and/or clinical team where specified (see Section 9.2 and Section 9.3 for detail). See Section 9.5.16 for imputation rules for steroid reduction.

7. TREATMENT COMPARISONS

The difference in the rates of all protocol-defined AESI and all-cause mortality, between the belimumab and the placebo groups will be evaluated with a 2-sided 95% CI.

7.1. Data Display Treatment and Other Subgroup Descriptors

The following treatment descriptors will be used on all data tabulations:

- Placebo
- Belimumab 10 mg/kg

For tables presenting baseline demographics and characteristics described in Section 10, the data will also be presented for all subjects using a Total column. Other subgroup descriptors will be described in more detail in Section 8.3.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

- All data summaries and analyses will be performed using the latest available version of SAS software (as available at GSK).
- Data displays will follow the shells outlined in the Mock TLFs document which will follow the Benlysta program standards and, as far as possible, follow the agreements proposed by the GSK Integrated Data Standards Library (IDSL).
- The most current version of MedDRA at the time of DBF will be used for reporting.
- The most current version of the Benlysta PSAP at the time of DBF will be used for reporting.
- Where SDTM terminology differs from the eCRF and/or mock shells, the SDTM terminology will be presented in displays unless otherwise specified.

Unless otherwise stated, the following will apply:

- Continuous variables will be summarized with the statistics mean, median, standard deviation (SD), 25th and 75th percentiles, minimum and maximum.
- Categorical variables will be summarized with frequency counts and percentages, or proportions where specified. A 'Missing' category will be added to frequency counts if there is at least one missing record.
- Percentages will be calculated using the number of subjects in the relevant population/treatment group (denoted by N) as the denominator, unless otherwise stated.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database.
- The mean, median, 25th percentile and 75th percentile will be reported to one more decimal place than the raw data recorded in the database.
- The SD will be reported to two more decimal places than the raw data recorded in the database.
- A maximum of four decimal places will be used.
- The same rules apply to scores calculated in the derived datasets.
- Percentages will be presented to one decimal place. Incidence rates and difference in incidence rates for the primary analyses will be presented to two decimal places.
- A count of zero will have no corresponding percentage.
- For statistical analyses, all tests will be two-sided and p-values will be presented to a maximum of 4 decimal places.
- Listings will be based on the Randomized population and generally be limited to those required by ICH guidelines and will be sorted by treatment group, investigator number, subject number and visit (where appropriate).

8.1. Multicenter Studies

This is a multicenter trial and subjects will be centrally randomized by region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia – See Appendix 1). There will be no analyses performed at the center level.

Note that in this study, no subjects from Israel were randomized.

8.2. Other Strata and Covariates

In addition to randomization by region, randomization will include stratification by subjects' screening SELENA SLEDAI score (≤9 vs. ≥10) and steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent). Any subgroup summaries (or analyses controlling for stratification factors as covariates, as applicable) will use data from the eCRF, not the strata variable from the randomization dataset.

Differences are anticipated between the randomization strata and the eCRF strata for baseline steroid dose. Sites were instructed to calculate the baseline dose for randomization using all steroids received for any indication (i.e. SLE and non-SLE). However, in the eCRF completion guidelines sites were instructed to record only steroids taken for SLE, pre-infusion (as prophylaxis against infusion reactions and hypersensitivity reaction), for AESI and SAEs in the eCRF. For subgroup summaries and for derivation as covariates (where used for analysis adjustment), only steroids received for SLE will be used to calculate baseline steroid dose. See Section 9.5.16 for details.

Other covariates of interest may include age, race, gender, complement levels and anti-dsDNA as defined in Section 8.3.

8.3. Examination of Subgroups

Since the reported incidence for primary safety endpoints is expected to be low, subgroup categories may be refined where necessary.

Mortality, AESIs and all AEs (i.e. AESI and SAEs) during the On-Treatment period will be summarized by the following subgroups:

- Age (<65 years vs. ≥65 years)
- Gender (Male vs. Female)
- Race Stratification (Black vs. Other). The Black category is defined as subjects who are in the race category "Black or African American". The race hierarchy rule (Section 9.5.10) will not apply and a subject will be categorized as Black if they have selected multiple race categories and any of them is "Black or African American".
- Randomization Stratification Factors (see Section 8.2, derived from eCRF data):
  - Region (US/Canada, Central America/South America/Mexico, Europe/Australia/Israel, Asia)
  - Screening SELENA SLEDAI (≤9, ≥10). Note: if any individual item is missing the total score cannot be calculated, however if the subject can be definitively

categorized as ≤9 or ≥10 regardless of the response to the missing item(s) then the appropriate subgroup will be assigned.

- Steroid dose (≤7.5 mg/day, >7.5 mg/day prednisone or equivalent) (baseline average daily dose, see Section 9.5.16.1). Note: Only systemic steroids given for SLE are included in the derivation.

- Screening Complement Levels and Anti-dsDNA (Low Complement and High Anti-dsDNA binding, Not (Low Complement and High Anti-dsDNA binding)), derived from the screening SELENA SLEDAI assessment. This subgroup is intended to be an indicator of high versus low disease activity. Note: If the evaluations to the SELENA SLEDAI assessment questions "Low Complement" and "Increased DNA Binding" are both missing, the subject will not be classified into one of the subgroup categories. If either item is marked "No", the subject will be classified into the Not (Low Complement and High Anti-dsDNA binding) group regardless of whether the other item is missing or "Yes".

Demographic and baseline characteristics and baseline disease activity will also be summarized by all subgroups except Screening Complement Levels and Anti-dsDNA.

8.4. Multiple Comparisons and Multiplicity

There is no statistical hypothesis to be tested (no formal statistical testing) for the primary safety analyses, and therefore no need to control for multiple comparisons. Analyses of the secondary efficacy endpoints will also not be subject to any multiple comparison procedure. All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

9. DATA HANDLING CONVENTIONS

This section describes data handling conventions including the study periods, handling of premature withdrawal and missing data and derived and transformed data.

9.1. Study Periods

The study has a Treatment Period (to Week 52) and a Post Treatment Follow-up (Years 2 through 5) as described below. Summaries of data collected during the latter will be defined in more detail in a separate RAP.

9.1.1. Treatment Period (to Week 52)

Subjects will receive IP through Week 48 with a final treatment period in clinic visit conducted at Week 52. Subjects who discontinue IP prior to Week 48 will have a follow-up in clinic visit performed approximately 4 weeks after the last dose of IP.

Per protocol, subjects may withdraw from IP during Year 1 and continue on study, or may withdraw from Year 1 study visits and reconsent to a Week 52 follow up. As a result, the time 'on treatment' versus the time 'on study' will differ for some subjects. Therefore, 2 analysis periods have been defined as the 'On-Treatment' and 'On-Study' periods. Further detail below.

The primary analysis summaries of Mortality, AESIs and SAEs will be performed using the 'On-Treatment' Period (defined in the table below).

Supportive summaries of the primary analysis will be performed using the 'On-Study' Period (includes on and off treatment data to Week 52).

For subjects who withdraw and reconsent for a Week 52 assessment only mortality and malignancy are assessed at Week 52, whereas all other endpoints will be assessed only up until the time of withdrawal. Therefore, in this case follow-up for mortality and malignancy will be longer than for other assessments.

Study Period	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Study to Week 52	***All data except Mortality and Malignancy events:*** Study Treatment Start Date ≤ Date ≤ minimum (Date of Death, maximum (Study Withdrawal or Completion Date (DSSTDT), Study Treatment Stop Date + 28 Days)) ***Mortality and all Malignancy events including NMSC (see Section 9.5.12 for definitions of mortality and malignancy events):*** • Alive or Lost to Follow Up at Week 52 Follow-Up: Study Treatment Start Date ≤ Date ≤ minimum (Last Known to be Alive Date, Study Treatment Start date + 371) • Dead at Week 52 Follow-Up: Study Treatment Start Date ≤ Date ≤ Date of Death • Week 52 follow-up missing: Study Treatment Start Date ≤ Date ≤ minimum (Date of Death, maximum (Study Withdrawal or Completion Date (DSSTDT), Study Treatment Stop Date + 28 Days)) Note: If the derived on-treatment period (i.e. study treatment stop date + 28 days) ends later than the derived on-study to Week 52 period, the derived on-study period will be updated such that it ends in line with the derived on-treatment period.
On-Treatment	***All data:*** • Study Treatment Start Date ≤ Date ≤ minimum (Date of Death, Study Treatment Stop Date + 28 days)

Note: After study withdrawal or last exposure plus 28 days (whichever occurs later) if AESIs and SAEs are recorded, other than mortality and malignancy, these will not be included in the on-study period. See Section 11.2.1 for further detail on how these events will be handled.
Note: For mortality, date of death will be derived as the end date of the SAE with fatal outcome.
Note: Each study treatment infusion should have a start date and end date recorded, but in some cases only one variable is completed. The study treatment stop date is the date of the final study treatment infusion (taken as the first non-missing date of the final study treatment infusion start or end date).
Note: Only dates will be used to identify start and end of treatment (times will not be considered).

9.1.2. Post-Treatment Follow-Up

After the Treatment Period (to Week 52) all subjects will be contacted annually through Year 5 (Week 260) to assess mortality and malignancy (including NMSC). Annual follow-up also applies to subjects who discontinue IP before Week 48 and have remained in monthly follow-up and to subjects who withdraw consent from the study prior to Week 52 but re-consent for this annual follow-up.

9.2. GSK Adjudication of Death Categories and AESI

See Appendix 6: PSAP Sections for AESI Reporting for sections of the PSAP relating to death categories and AESI adjudication.

All fatalities (reported during the Week 52 study period) will be identified in the clinical database and subsequently adjudicated by the GSK SRT into a general category of death.

AESI are identified per the preferred terms and other criteria described in Appendix 6: PSAP Sections for AESI Reporting. Malignancies, serious post-infusion systemic reactions, potential opportunistic infections, suicidality and fatalities are adjudicated at the subject level by the GSK SRT. The adjudication occurs prior to database release and is performed for reporting purposes. Final confirmation of adjudications is required before database freeze (DBF).

9.3. Hospitalizations Review

A specific subject hospitalization form was not generated in the eCRF system for this study. Therefore, to measure all hospitalizations in this study, a manual clinical review process to identify the number of hospitalization events through review of all the SAEs has been implemented. The basis of this approach is that any event resulting in hospitalization mandates reporting as a SAE (refer to protocol Section 7.1).

Main review

The spreadsheet containing hospitalization data will be reviewed and updated in-stream and will be available for reporting. The summary of the process is presented below:

1. Clinical Programming will extract all SAEs from the eCRF into a spreadsheet listing for clinical review. Updates of SAE data will be extracted into the spreadsheet approximately every 4-6 weeks.
2. SAEs are reviewed by the study clinical investigation lead (CIL) and medical monitor (MM), or their equivalent designees. The reviewer determines the number of hospitalizations, and then assigns a hospitalization code for each hospitalization identified. The code consists of a combination of the Subject ID number and the hospitalization number for that subject (e.g., hospitalization code PPD = Subject ID P and hospitalization PP).
3. In the absence of a 'reason for hospitalization' data field in the eCRF, to avoid the potential bias and/or influence of the Sponsor (GSK) in the determination of reason for hospitalization in any way, the SAE source verbatim term will be reported in the

listing of hospitalizations and indicated as 'SAE(s) contributing to Hospitalization'. If more than one SAE is reported within the same hospitalization, all SAE source verbatim terms will be reported on the listing.

4. Once there are no outstanding issues after review of each SAE case (either after initial review, or after resolution of any queries), the review is then documented in the spreadsheet as completed with an initial and date by the reviewer. The spreadsheet is then reflected back into the ADaM datasets by Clinical Programming for reporting.

At any time, any SAEs from individual reviewers can be flagged for further team discussion / review to occur during ad hoc roundtable SAE review meetings, or by consult with the MM.

Independent secondary review

In addition, a second independent review of the SAEs for the hospitalization events will be performed by an independent medical reviewer. The reviewer will be provided with the guidelines for review based on the protocol and following the same convention of the main review described above.

Once the review is completed, a comparison between the main review and the independent secondary review spreadsheets will be performed for the number of hospitalization and the assigned hospitalization code where applicable. Identified discrepancies will be discussed and reconciled at a round table meeting between the GSK clinical representatives (MM and study CIL or designee) and the independent medical reviewer. The reconciled records will be reflected on the main spreadsheet following the round table review meeting.

Full details of the hospitalizations review process will be documented as part of the Study Data Quality Plan and associated documents.

9.4. Premature Withdrawal and Missing Data

9.4.1. Premature Withdrawal from 'IP only' Prior to Week 52

Subjects who discontinue IP but do not withdraw from the study will continue the visit schedule through Week 52 and will be contacted annually for Years 2 through 5 to assess mortality and malignancy.

- All data collected through Week 52 post withdrawal from IP will be included in summaries unless otherwise specified.
- Annual assessment of mortality and malignancy will be included in the summaries of Year 2 to 5 (to be detailed in a separate RAP).

9.4.2. Withdrawal from Study Prior to Week 52

For subjects who withdraw from the study prior to Week 52, an attempt will be made to assess mortality and occurrence of malignancy (including NMSC) at Week 52 and annually for Years 2-5.

- For subjects who withdraw from the study, all data reported on the database will be used in the summaries through Week 52 unless otherwise specified.
- For subjects that withdraw early from Year 1 of the study, Week 52 mortality information will be collected if allowed by individual subject's legal consent status. This includes the potential use of a third party to aid sites in identifying information available from public sources.

9.4.3. Missing Data

Adverse Events (AESIs, Serious Adverse Events) and Concomitant Medications

Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listings.
Concomitant Medications	• Where medication start date (CMSTDT) is completely missing but medication end date (CMENDT) is on or after Day 1, the medication start date (CMSTDT) will be imputed as study treatment start date (TRTSDT). • Where medication start date (CMSTDT) is completely missing and medication end date (CMENDT) is missing and the medication is ongoing (CMONGO = "Y"), the medication start date (CMSTDT) will be imputed as study treatment start date (TRTSDT) and the medication will be considered as ongoing. <u>Medication End Date (CMENDT)</u> Missing end dates for concomitant medications will not be imputed, and the medication will be considered ongoing. For corticosteroids, the medication end date will be imputed as study completion or withdrawal date during the ADPRED dataset creation in order for those medications to be included in prednisone summaries. However, if the start date of the medication is greater than the study completion or withdrawal date, the end date will not be imputed.
Adverse Events	The eCRF does not allow for the possibility of missing or partial AE dates (except for missing AE end dates which are allowed if the AE is ongoing).

See Section 9.5.13 for further details on whether AE is considered as treatment-emergent.

Other than described above, missing data will not be imputed unless stated otherwise for an individual endpoint.

A missing category will be added to frequency counts if there is at least one missing record.

Partial Dates

Element	Reporting Detail
Date of Birth	• Only year of birth is collected on the eCRF. • Day will be set to 30 and month will be set to JUNE for all subjects.

Concomitant Medications	<u>Medication Start Date (CMSTDT)</u>
	Medication start date (CMSTDT) is imputed as study treatment start date (TRTSDT) *unless*:
	• CMENDT is < TRTSDT, whether CMENDT is complete (DD/MM/YY) or partial (some combination of CMENDT day, month or year imputed) OR
	• The month or month and year of the partial CMSTDT are different from the month and/or year of TRTSDT OR
	• "Taken prior to study?" is checked.
	If any of the above conditions are met then medication start date (CMSTDT) is imputed with JAN for missing month and 01 for missing day, whatever is applicable.
	
	<u>Medication End Date (CMENDT)</u>
	• If month and year are present, then:
	  • If the medication started on or after study withdrawal or completion then set to the last day of that month.
	  • If the medication started prior to study withdrawal or completion set to the last day of that month, unless the end month and year are the same as the month and year of the study withdrawal or completion date, in which case set to the study withdrawal or completion. date.
	• If only year present, then:
	  • if the medication started on or after study withdrawal or completion then set to 31DEC.
	  • if the medication started prior to study withdrawal or completion then set to 31DEC, unless the end year is the same as the year of the study withdrawal or completion date, in which case set to the study withdrawal or completion date.

Date of SLE diagnosis	• For records where month and day are missing for diagnosis date, impute with 01 for day and January for month to assume that the duration was the longest possible duration. • For records where the day only is missing for start date, impute with 01 for day to assume that the duration was the longest possible duration.

Element	Reporting Detail
Last known to be alive date	• For records where month and day are missing for last known to be alive date, impute 01 for day and January for month. • For records where the day only is missing, impute 01 for day.

9.5. Derived and Transformed Data

9.5.1. Baseline

The protocol specifies Day 0 as Baseline/Treatment Start date, but the CDISC standard is to refer to the Baseline/Treatment Start date as Day 1; therefore Baseline/Treatment Start date will be referenced as Day 1 in this document. A table indicating the target study day for each planned visit is in Section 9.5.3.

The baseline value of a variable is defined as the last available value measured prior to dosing on or before the date of first dose (Day 1), unless otherwise specified.

If the last available value occurs on Day 1 but the time of the assessment is not collected, then the assessment will be assumed to be prior to dosing. Noted exceptions to this rule are concomitant medications and AEs; these will be considered as being concomitant and treatment-emergent, respectively, if the start date occurs on the first day of dosing. However, if time is available for an AE or concomitant medication and the end time is earlier than the start time of first dose of IP, the AE or concomitant medication will not be considered as treatment-emergent or concomitant, respectively.

9.5.2. Study Day

Study Day is the number of days from the treatment start date to a study date of interest (e.g. event start date) and is calculated as follows:

If condition is…	Then Study Day is…
study date <treatment start date	study date – treatment start date
study date is ≥treatment start date	study date – treatment start date +1

Note: Study Day cannot be zero. If either date is missing, then Study Day is missing.

9.5.3. Analysis Visit and Analysis Visit Number

Where applicable, the data are summarized per the planned visit assignment in the data. The visit windows below will be used to assign events to scheduled visits for tabular summaries of time to withdrawal from study, time to premature withdrawal from IP by clinical visit, cumulative time to mortality (On-Treatment Period) and cumulative time to mortality (On-Study Period).

Analysis Visit	Analysis Visit Number	Target Study Day[1]	Interval Start Day	Interval End Day
Screening	10	-30	Na	Na
Treatment Period visits:				
Baseline	25	1	Na	Na
Week 2	30	15	1	15
Week 4	40	29	16	29
Week 8	50	57	30	57
Week 12	60	85	58	85
Week 16	70	113	86	113
Week 20	80	141	114	141
Week 24	90	169	142	169
Week 28	100	197	170	197
Week 32	110	225	198	225
Week 36	120	253	226	253
Week 40	130	281	254	281
Week 44	140	309	282	309
Week 48	150	337	310	337
Week 52	160	365	338	[2]

[1]Study Day with Baseline/Treatment Start Date as Day 1.
[2] Any events on or after Day 338 will be assigned to Week 52

9.5.4. Subject Years of Follow-Up to Week 52

Start and end dates for study periods are defined in Section 9.1. For calculation of exposure adjusted incidence rates (during the on-treatment period) and study follow-up adjusted incidence rates (during the on-study period), the following will be derived (in years) for each subject. Additionally, for summaries of subject follow-up time, the off-treatment, missing and total possible follow-up will be derived in years.

Note: The On-Study (to Week 52) terminology reflects the intended duration of follow-up for mortality and AESIs during the main study (i.e. 52 weeks). Some subjects will have less than 52 weeks of follow-up (e.g. where the subject has died or withdrawn from the study). The terminology 'follow-up' has been used to describe the time periods during which subjects are followed up for event assessment during the main 1-year study and does not refer to the post-treatment follow-up period in Years 2-5 (described in Section 9.1.2).

On-Treatment Follow-Up: Mortality and Malignancy and Other Data

[(End Date for On-Treatment Period – Study Treatment Start Date) + 1]/365.25

On-Study Follow-Up (to Week 52): Mortality and Malignancy

[(End Date of On-Study Period for Assessment of Mortality and Malignancy (to Week 52) – Study Treatment Start Date) + 1]/365.25

On-Study Follow-Up (to Week 52): Other Data

[(End Date of Study Period for assessment of all data excluding mortality and malignancy (to Week 52) – Study Treatment Start Date) + 1]/365.25

Off-Treatment Follow-Up Time: Mortality and Malignancy

[(End Date for On-Study Period for Assessment of Mortality and Malignancy – [End Date for On-Treatment Period + 1]) + 1]/365.25

Off-Treatment Follow-Up Time: Other Data

[(End Date for On-Study Period for assessment of all data excluding mortality and malignancy – [End Date for On-Treatment Period + 1]) + 1]/365.25

Total Possible Follow-Up Time: Mortality and Malignancy

[(Possible Follow-Up Date – Study Treatment Start Date) + 1]/365.25

For subjects whose end of on-study period for mortality and malignancy is on or after Study Day 358 (lower allowable visit window for Week 52 assessment) the possible follow-up date will be assigned as the end date for the on-study period for assessment of mortality and malignancy.

For subjects whose end of on-study period for mortality and malignancy is before Study Day 358 (lower allowable visit window for Week 52 assessment) the possible follow-up date will be assigned as the minimum of Study Day 365 and date of death.

Total Possible Follow-Up Time: Other Data

[(Possible Follow-Up Date – Study Treatment Start Date) + 1]/365.25

For subjects whose end of on-study period for all data excluding mortality and malignancy is on or after Study Day 358 (lower allowable visit window for Week 52 assessment) the possible follow-up date will be assigned as the end date for the on-study period for assessment of all data excluding mortality and malignancy.

For subjects whose end of on-study period for all data excluding mortality and malignancy is before Study Day 358 (lower allowable visit window for Week 52 assessment) the possible follow-up date will be assigned as the minimum of Study Day 365 and date of death.

Missing Follow-Up Time (Years): Mortality and Malignancy / Other Data

Total possible follow-up time – (on-treatment follow-up + off-treatment follow-up)

9.5.5. Change from Baseline

Change from baseline will be calculated as:

Visit value – baseline value.

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

9.5.6. Percent Change from Baseline

Percent change from baseline will be calculated as

$$\frac{\textit{Visit Value - Baseline Value}}{\textit{Baseline Value}} \textit{ X 100.}$$

If the baseline value is zero or missing, then the percent change should be set to missing.

9.5.7. Treatment Completer

A “treatment completer” is defined as a subject who does not discontinue study agent prematurely. Treatment completion date or treatment discontinuation date is defined using the date from SDTM.DS where DSSCAT=’STUDY TREATMENT’. Treatment completion date is assigned for subjects who completed study treatment (DSDECOD='COMPLETED') and study treatment discontinuation date is assigned for subjects who did not complete study treatment (DSDECOD not missing and not equal 'COMPLETED').

9.5.8. Study Completer

A “study completer” is defined as a subject who does not withdraw from the study prior to Week 52. Data for ‘study completers’ can include off-treatment data for subjects who discontinue study agent but continue on the visit calendar for study assessments.

Note: Each subject should have a date of study withdrawal or completion. Study withdrawal or completion date is defined using the date from SDTM.DS where DSSCAT=’STUDY CONCLUSION’. Study completion date is assigned for subjects who completed the study (DSDECOD='COMPLETED') and study discontinuation date is assigned for subjects who did not complete the study (DSDECOD not missing and not equal 'COMPLETED').

9.5.9. Analysis Age

Analysis age is derived in years relative to the treatment start date for randomized subjects, and is calculated in SAS as follows:

INTCK (‘YEAR’, Date of birth, Date of treatment start date, ’C’).

For subjects who are randomized but do not receive study agent and therefore have no treatment start date, randomization date will be used instead.

9.5.10. Race Hierarchical Rule

If multiple race categories are checked on the eCRF, the subject will be assigned to a unique race group based on which of the races checked appears first in the list below:

- Native Hawaiian or Other Pacific Islander
- American Indian or Alaska Native
- Asian
- Black or African American
- White

For example, if Black or African American and Asian are both checked, then the subject will be assigned as Asian since it appears highest in the list. In the race and racial combination details table, subjects with multiple race categories checked will be reported in the race per the hierarchical rule as well as in the multiracial category. Subjects who select more than one Asian category and no other non-Asian categories will be represented in the Mixed Asian Race category as well as the Asian category. Similarly, subjects who select both white categories and no non-white categories will be represented in the Mixed White Race category as well as the White/Caucasian category. The Mixed Asian Race and Mixed White Race categories will only appear in the table if a subject selects multiple Asian or multiple white categories, respectively.

For the Race subgroup, if a subject selects multiple races they will be assigned "Black" if any of the races is "Black or African American", i.e., the hierarchical rule will not apply in this instance (see Section 8.3).

9.5.11. SLE Disease Duration

SLE Disease Duration is defined as

$$\frac{\textit{Treatment Start date - SLE diagnosis date + 1}}{\textit{365.25}}$$

If either date is missing, then SLE Disease Duration will be missing. Partial dates for SLE diagnosis date will be imputed as described in Section 9.4.3.

9.5.12. Mortality and Protocol-Defined AESI

Mortality status will be derived from the SAE data, where outcome is fatal.

The derivation for the protocol-defined AESIs are provided in the table below. Treatment emergent AESIs (see Section 9.5.13 and Section 9.5.15) only will be summarized.

Where the protocol defined AESI utilize definitions from the PSAP, the detailed derivations from the PSAP are provided in Appendix 6: PSAP Sections for AESI Reporting. AESI are identified per the preferred terms and other criteria described in the PSAP.

Protocol-Defined AESI (see Section 2.2.1 and Section 2.2.3 for clarification)	Definition	Programming Derivation (Protocol Definition)
Serious infections	SAEs within Infections and Infestations SOC.	SOC=Infections and Infestations & AESER = 'Y'
Opportunistic infections and other infections of interest	"All Infections" per PSAP definition to cover all OI and infections of interest.	CQ06NAM ne '' or CQ07NAM ne '' or CQ08NAM ne ''
Non-melanoma skin cancers (NMSC)	NMSC per PSAP definition.	CQ00MLFL = 'Y' and CQ03NAM ne '' and CQ03NMFL = 'Y'
Malignancies (excluding NMSC)	PSAP defined, "all malignancies excluding NMSC".	[CQ00MLFL = 'Y' and (CQ01NAM ne '' or CQ02NAM ne '' or (CQ03NAM ne '' and CQ03NMFL ne 'Y'))] Or (CQ04NAM ne '' and CQ04NPFL = 'Y')
Psychiatric events suggesting serious mood disorders and anxiety	Serious events from the depression CMQ (PSAP defined – depression including mood disorders and anxiety).	CQ09NAM ne '' and AESER = "Y"
Suicidality (C-SSRS)	Any treatment-emergent C-SSRS suicidal ideation (1-5) or suicidal behavior (6-10) (defined in Section 9.5.15) – i.e. maximum ideation score worsens relative to pre-treatment or maximum behavior score worsens relative to pre-treatment	C-SSRS Ideation categories 1-5 and Behavior categories 6-10; any subject with ideation or behavior that is treatment-emergent (defined in Section 9.5.15).
Serious infusion and hypersensitivity reactions	Serious infusion and hypersensitivity reactions per the PSAP definition. Includes all SAEs from the anaphylactic reactions CMQ broad search (see Section 11.2.4, includes events on the day of the infusion or within 3 days after the infusion).	CQ05NAM ne '' and AESER='Y' and AEINF3FL='Y'

9.5.13. Treatment-Emergent AEs and AE Duration

Only treatment-emergent AESIs and SAEs, will be summarized, unless otherwise stated. A treatment-emergent AE is an AE that emerges on or after the first treatment dose, having been absent pre-treatment, or that worsens relative to the pre-treatment state.

The duration of the AE will be calculated as follows:

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

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

9.5.14. Incidence Rate

Event incidence rates and subject incidence rates will be calculated for Mortality and Malignancy and other AESIs during the on-treatment and on-study (to Week 52) periods as defined below. Note, for Mortality only subject incidence rates will be calculated. Subject incidence rates will also be calculated for SAEs during the on-treatment and on-study periods at the SOC level only.

Typically for subject incidence rates the subject years would be censored at the time of the event for subjects who experience the event i.e. the subject years contributed to the incidence rate calculation for a subject would be the total years from treatment start date to the event date. However, in consideration of the low number of events, this additional adjustment is not anticipated to have a significant impact. Therefore, the additional adjustment will not be used and the subject years contributed by a subject with an event will be the total years from treatment start date to the end of the treatment period of interest for all AESIs and mortality.

On-treatment

$$Subject\ Incidence\ Rate = 100\ X\ \frac{Number\ of\ Subjects\ with\ an\ Event}{Overall\ Subject\ Years\ On-Treatment}$$

$$Event\ Incidence\ Rate = 100\ X\ \frac{Number\ of\ Events}{Overall\ Subject\ Years\ On-Treatment}$$

Where overall subject years of on-treatment follow-up =

$\sum_{\text{all subjects in population}}$ [on-treatment follow-up in years]

See Section 9.5.4 for detail on the calculation of on-treatment follow-up.

On-study (to Week 52)

$$Subject\ Incidence\ Rate = 100\ X\ \frac{Number\ of\ Subjects\ with\ an\ Event}{Overall\ Subject\ Years\ On-Study}$$

$$Event\ Incidence\ Rate = 100\ X\ \frac{Number\ of\ Events}{Overall\ Subject\ Years\ On-Study}$$

Where overall subject years on-study =

$\sum_{\text{all subjects in population}}$ [on-study follow-up in years]

See Section 9.5.4 for detail on the calculation of on-study follow-up.

As described in Section 9.1.1, the on-study follow-up (to Week 52) will be different for Mortality and Malignancy compared with other AESIs. This is expected because subjects who withdraw from the study may reconsent to be followed up at Week 52 where only mortality and malignancy data are collected.

9.5.15. Treatment-Emergent C-SSRS

For suicidal ideation, the pre-treatment reference period is the lifetime history, current history and baseline (for further detail refer to the IDSL documentation). For suicidal behavior, the pre-treatment reference period is the lifetime history and baseline (note: suicidal behavior is not re-assessed for the current history time period).

Suicidal ideation and suicidal behavior will be considered as distinct categories and assessed independently of each other. Treatment emergence will be assessed for the on-treatment period and the on-study period.

Suicidal ideation will be assessed using responses to C-SSRS ideation questions (categories 1 to 5) only. Suicidal behavior will be assessed using responses to C-SSRS behavior questions (categories 6 to 10) only.

- **Treatment emergent suicidal ideation** will be assessed using the maximum ideation score pre-treatment, compared to the maximum ideation score post-treatment (on-treatment or on-study as appropriate). If the maximum ideation score worsens relative to the pre-treatment reference period then this will be considered a treatment emergent suicidal ideation. This is derived from responses to suicidal ideation questions (categories 1 to 5).
- **Treatment emergent suicidal behavior** will be assessed using the maximum behavior score pre-treatment, compared to the maximum behavior score post-treatment (on-treatment or on-study as appropriate). If the maximum behavior score worsens relative to the pre-treatment reference period then this will be considered a treatment emergent suicidal behavior. This is derived from responses to suicidal behavior questions (categories 6 to 10).
- **Treatment emergent suicidal ideation or behavior** will be defined as a subject having a treatment emergent suicidal ideation (as defined above) and/or a treatment emergent suicidal behavior (as defined above). This definition is used to assess the protocol defined AESI endpoint of ‘Suicidality (C-SSRS)’ (see Section 9.5.15).

Suicidal Ideation (categories):

1. Wish to be Dead
2. Non-Specific Active Suicidal Thoughts
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan
5. Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (categories):

6. Preparatory Acts or Behavior
7. Aborted Attempt
8. Interrupted Attempt
9. Non-Fatal Actual Suicide Attempt
10. Completed Suicide

A subject must have at least one pre-treatment C-SSRS assessment (screening and/or baseline) and at least one on-treatment C-SSRS assessment (post-baseline) to be included in any assessment of treatment emergent.

9.5.16. Prednisone

All prednisone analyses and summaries will consider SLE-related steroids only but data will also be derived for all indications steroids (SLE and non-SLE) for reference where indicated below.

The following will apply to all derivations in this section unless otherwise stated:

- For steroid use analyses, all steroid dosages are converted to a prednisone equivalent in milligrams; therefore, analyses refer to average daily prednisone dose instead of average daily steroid dose. See Appendix 4: Prednisone Equivalent Conversion for instructions on converting steroids to prednisone equivalents.
- This appendix will be updated throughout the course of the study to include all corticosteroids taken by subjects and will be finalized prior to the first database release and unblinding.
- For all derivations of the average daily prednisone equivalent dose including baseline, days on which a subject does not have prednisone use recorded will be considered as 0 mg for the day.
- Steroids taken intravenously (IV), intramuscularly (IM), subcutaneously (SC), intradermally, and orally are considered in prednisone dose derivations only.
- All steroids taken on any given day, including overlaps, will be accounted for in calculations of average daily prednisone dose. To achieve this programmatically, each entry is converted to the prednisone equivalent daily dose (see Appendix 4: Prednisone Equivalent Conversion) and the sum of the prednisone equivalent doses on Day X gives the total prednisone equivalent daily dose on Day X. For example, if two steroids are given on the same day they will be converted to a prednisone equivalent daily dose and then added together to achieve a total for that day.

Steroids used to treat SLE are those with medication type corticosteroid for SLE (SDTM.CM.CMCAT = ‘CORTICOSTEROID FOR SYSTEMIC LUPUS ERYTHEMATOSUS').

9.5.16.1. Average Daily Prednisone Equivalent

Prior to carrying out calculations, each steroid must be converted to its prednisone equivalent and then the daily dose calculated using the frequency factors provided in

Appendix 4: Prednisone Equivalent Conversion. Days on which the subject has no steroid use will be considered as 0mg.

Baseline

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

This will be derived for both steroids used to treat SLE and steroids used to treat all indications (SLE and non-SLE) separately. The baseline average daily prednisone dose for all indications will not be reported but will be used to carry out a cross-check against the randomization strata, which were determined by sites based on steroids received for any indication.

Treatment completion average dose

The average daily prednisone dose is the sum of all prednisone doses over 7 consecutive days up to and including the date of treatment completion, divided by 7.

This will be derived for steroids received for SLE only.

9.5.16.2. Average Daily Prednisone Dose during Weeks 40 to 52

The average daily prednisone dose during Weeks 40 to 52 is the sum of all prednisone doses from the day following the Week 40 visit date up to but not including the Week 52 study completion date divided by the number of days between Week 40 visit date and study completion date (study completion date – Week 40 visit date).

For subjects who withdraw from the study prior to the Week 40 visit date, the average daily prednisone dose during Weeks 40 to 52 will be missing.

For subjects who withdraw from the study after the Week 40 visit date, the average daily dose will be calculated as the sum of all prednisone doses from the day after the Week 40 visit date up to and including the date of withdrawal or death, whichever is earlier divided by the number of days between Week 40 visit date and the date of withdrawal or death, whichever is earlier (date of withdrawal or death – Week 40 visit date + 1). If the Week 40 visit is missing for any subject who has not withdrawn or died prior to Week 40, the Week 40 visit date will be imputed as treatment start date + 40 * 7 for this derivation.

This will be derived for steroids received for SLE only.

9.5.16.3. Cumulative Prednisone Dose

Cumulative SLE-related prednisone dose (area under the curve [AUC]) is defined as the sum of daily prednisone dose from Day 1 to the Week 52 study completion date, considering only corticosteroids used to treat SLE. Missing values will be imputed for each day following the last visit day up to the scheduled Week 52 visit date (treatment start date + 52 * 7) for subjects who die or withdraw. The daily prednisone dose up to Week 52 after the last visit day, if prior to Week 52 visit date (i.e. for subjects who withdraw from the study or die), will be imputed using the average of the last 28 daily

prednisone doses prior to the day of last visit. For subjects who withdraw from study or die before Day 27, the daily prednisone dose up to Week 52 after early withdrawal or death will be imputed using the average post-baseline daily doses available prior to withdrawal or death.

9.5.17. Immunomodulatory Medications

Immunomodulatory medications are identified as all immunosuppressants with ATC code beginning "L04A" plus cyclophosphamide and mercaptopurine. For further detail see Appendix 3: SLE Allowable Medication Categories.

Only immunomodulatory medication used to treat SLE will be included in summary tables of immunomodulatory medication usage (with the exception of the concomitant medication summaries which will include all medications). These are identified as those with a medication type of treatment for SLE (SDTM.CM.CMCAT = 'SYSTEMIC LUPUS ERYTHEMATOSUS').

It will be determined whether immunomodulatory agents are being received at any given reference date by using medication start and stop dates as follows:

- Start date and stop date are prior to reference date → subject is not on immunomodulatory agents
- Start date on or before date and stop date on or after reference date → subject is on immunomodulatory agents
- Start date on or before reference date, stop date is missing and medication is ongoing → subject is on immunomodulatory agents

Status of immunomodulatory medication is assessed at the following dates (i.e. these are the reference dates for the above derivation):

- Baseline
- Treatment completion date in treatment completers (Section 9.5.7)

It is also assessed for shift tables from baseline to:

- Treatment completion date (treatment completers)
- Study agent discontinuation date (subjects who prematurely discontinued study agent)

9.5.18. Baseline Allowable SLE Medications

It will be determined whether medications defined in Appendix 3: SLE Allowable Medication Categories, with the exception of steroids, are being received at baseline by using medication start and stop dates as follows:

- Start date and stop date are prior to Day 1 → medication not taken at baseline
- Start date on or before Day 1 and stop date on or after Day 1 → medication is taken at baseline

- Start date on or before Day 1, stop date is missing and medication is ongoing → medication is taken at baseline

For steroids, baseline medication will be identified as that taken in the 7 days up to but not including Day 1 as described in Section 9.5.16.1.

9.5.19. SLICC/ACR Scoring

- For a given SLICC assessment, if any item(s) is missing, the entire assessment is excluded from summaries and analyses. The only exception to this is if the missing item has previously been scored with damage, in which case damage will be carried forward as detailed below.
- The SLICC/ACR Damage Index (see Appendix 5: SLICC/ACR Damage Index) increases over time. Once a subject meets the criteria for positive scoring of an item, that item should always be marked as present, even if the subject subsequently recovered. This includes baseline assessment.
- In the event the SLICC/ACR Damage Index is scored inconsistently (a decrease at Week 52 relative to baseline has occurred) and the data are unable to be queried and/or corrected, the baseline will be carried forward at the item level for the SLICC/ACR Damage Index questions, i.e. worst observation carried forward (WOCF). These carried forward values will then be used to calculate the total score which will be the value summarized and displayed for reporting. Within the renal domain, damage scored on the first two items (estimated glomerular filtration rate <50%, proteinuria >3.5 gm/24hours) should only be carried forward to Week 52 if the third item (end stage renal disease) has not been scored at Week 52. The reason for this is that scores on the first two items can decrease but only if the third item is then scored.
- Worsening is defined as an increase from baseline in SLICC/ACR Damage Index score (post-baseline visit score – baseline score) >0.
  Note: SLICC/ACR is collected only at baseline and Week 52 (in subjects who do not withdraw from the study). It is not collected at the time of IP and or study withdrawal (where applicable) for potential imputation (i.e. carry forward) at Week 52 (see Section 12.2.3 for details).

10. STUDY POPULATION

The ITT population will be used to summarize the study population data and data will be presented by treatment and for all subjects combined, unless otherwise specified.

10.1. Disposition of Subjects

The number and percentage of subjects randomized by site will be grouped by country and summarized overall and by treatment group using the Randomized population.

Using the Randomized population, the number of subjects in each population (Randomized, ITT, As-Treated) will be summarized overall and by treatment group.

The database did not include all subjects screened for study participation or the number excluded before randomization. Therefore, screening data (including reason for screen failure) will not be summarized or included in the CSR submission datasets since it is not part of the database.

Using the ITT population, an overall summary of subject disposition will be presented with the following included:

- The number and percentage of subjects who completed IP.
  - The number and percentage of subjects who completed the study.
  - The number and percentage of subjects who withdrew from the study
- The number and percentage of subjects who withdrew early from IP.
  - The number and percentage of subjects who completed the study.
  - The number and percentage of subjects who withdrew from the study.
    - The number and percentage of subjects who withdrew from the study on the same date as study agent discontinuation.
    - The number and percentage of subjects who withdrew from the study at a later date than study agent discontinuation.

Further summaries of the ITT population will be produced of subject years' follow-up on-treatment, off-treatment and missing. This will also be given as a percentage of the total possible subject years. Summary statistics will be presented for each category of follow-up: total possible, on-treatment, off-treatment and missing. The summary will be provided for the mortality and malignancy data and all other data separately as the follow-up time differs (except for on-treatment follow-up time which is the same for mortality and malignancy and other data).

Using the ITT population, the subject's study completion status will be assessed to evaluate percentages of withdrawals from study by treatment group as well as the reasons for withdrawal from study. The number and percentage of subjects who completed through Week 52 and who withdrew, including reasons for withdrawal, will be displayed by treatment group and overall. Additionally, the cumulative number and percentage of subjects who withdrew by study visit, derived using visit windows defined in Section 9.5.3, will be displayed by treatment group and overall. A Kaplan-Meier plot of time to study withdrawal will be generated to evaluate the pattern of dropouts over time. Subjects who complete through Week 52 will be censored at the study completion date. The Kaplan-Meier plot will be truncated at Week 52.

Using the ITT population, the subject's IP completion status will be assessed to evaluate percentages of IP withdrawals by treatment group as well as the reasons for IP withdrawal. The number and percentage of subjects who completed IP through Week 48 and who withdrew, including reasons for IP withdrawal, will be displayed by treatment group and overall. Additionally, the cumulative number and percentage of subjects who withdrew from IP by study visit, derived using visit windows defined in Section 9.5.3, will be displayed by treatment group and overall. A Kaplan-Meier plot of time to study treatment withdrawal will be generated to evaluate the pattern of dropouts over time. Subjects who complete IP through Week 48 will be censored at the study treatment

completion date and for subjects who discontinue IP prematurely, the study treatment discontinuation date will be used as the discontinuation date. The Kaplan-Meier plot will be truncated at Week 52.

The number and percentage of subjects who deviated from the inclusion or exclusion criteria will be displayed by treatment group and overall. A listing of subjects who had a deviation from the inclusion or exclusion criteria will be provided.

A listing of subject disposition will be provided showing their completion status and whether they are included in each population. Subjects who are randomized but do not receive any study agent will be identified in this listing. A listing of subjects who withdrew from the study, including reason for and time to withdrawal will also be provided. An additional listing will be provided of subjects who withdrew from IP, including reason and time to withdrawal. Subjects for whom the treatment blind was broken during the study will be listed. A listing of planned and actual treatment arms will be provided. Subjects excluded from any population will be listed.

10.2. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [Version 8; 19JUL2018].

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorized on the protocol deviations dataset.
- This INFORM dataset (DV) will be the basis for the summaries and listings of protocol deviations.

The percent of subjects who experience an important protocol deviation will be presented by treatment arm for the treatment period. The table will display the number and percentage of subjects with any important protocol deviation and each deviation type. A listing of subjects with an important protocol deviation will be provided by treatment group.

10.3. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the continuous demographic and baseline characteristics of age (years) and weight (kg). Counts and percentages of the following categorical demographic and baseline characteristics will be presented: country region/country, gender, Hispanic or Latino origin, age group (≤45 years, >45 – <65 years and ≥65 years and then within this last group: ≥65 – <75 years and ≥75 years) and race (Black or Other; see Section 8.3).

The above summary of demographic and baseline characteristics will be repeated for the following subgroups, where the subgroup categories are defined in Section 8.3:

- Age
- Gender

- Race
- Region
- SELENA SLEDAI
- Baseline steroid dose (based on systemic steroids used to treat SLE)

The number and percentage of subjects reporting each race and racial combination will be summarized. For subjects who check more than one race category, the race hierarchy rule defined in Section 9.5.10 will apply for this summary. Note that this differs to the handling of the race subgroup which ignores the hierarchy rule.

A standard summary of the number and percentage of subjects by age ranges Adolescents (12-17 Years), Adult (18– 64 Years), from 65 – 84 Years and ≥85 Years will be provided for disclosure purposes.

A summary of the number and percentage of subjects reporting current medical conditions and a separate summary of number and percentage of subjects reporting past medical conditions will be provided. A summary of the history of tobacco usage will also be provided.

A summary of the randomization stratification factors [screening SELENA SLEDAI score (≤9 vs. ≥10), region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia), and steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent)] will be presented per the randomization and eCRF data.

A cross-tabulation of stratification factors will also be produced summarizing the categories of the randomization strata from IXRS to the eCRF strata for SELENA SLEDAI score (≤9 vs. ≥10), region (US/Canada vs Central America/South America/Mexico vs Europe/Australia/Israel vs Asia), and steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent).

Note that for stratification factors summaries, the steroid dose will be derived from the eCRF considering steroids received for SLE only, whereas the randomization strata were derived by sites considering all steroids.

Demographic and baseline characteristics (age, gender, ethnicity, weight, race [black vs. other]), as well as stratification factors per IXRS, will be listed by subject. Race as assigned using the hierarchy rule (Section 9.5.10) will be listed by subject. Current and past medical conditions and tobacco use history will be listed by subject.

A summary of baseline disease activity will be provided, including counts and percentages for screening SELENA SLEDAI category (≤9, ≥10), complement levels (Low, Not Low), anti-dsDNA (High, Not High), complement and anti-dsDNA (Low Complement and High Anti-dsDNA, Not (Low Complement and High Anti-dsDNA)). and univariate statistics for SLE disease duration (years), screening SELENA SLEDAI total score, and SLICC/ACR Damage Index. This summary will be repeated for the following subgroups, where the subgroup categories are defined in Section 8.3:

- Age
- Gender
- Race
- Region
- SELENA SLEDAI
- Baseline steroid dose (based on systemic steroids used to treat SLE)

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

- Screening SELENA SLEDAI category by organ domain and item (count and percentage with each item present)
- Baseline SLICC by organ domain and item (count and percentage with each item present)
- Allowable SLE medication usage (see Appendix 3: SLE Allowable Medication Categories) at baseline – counts and percentages by class (Steroids, Anti-Malarials, and Other Immunosuppressive/Immunomodulatory Agents, Aspirin and NSAIDs) and drug as well as summary statistics for average daily prednisone dose (mg/day) (see Section 9.5.16.1 for derivation of average daily prednisone equivalent dose) at baseline and counts and percentages for average daily prednisone dose (mg/day) at baseline (0, >0 - ≤7.5, >7.5). See Appendix 4: Prednisone Equivalent Conversion for instructions on converting steroids to prednisone equivalents. Only steroids with medication type corticosteroid for SLE will be included. Only immunomodulatory modulatory medications used to treat SLE will be included. For other medications, all medication types will be included.
- Steroid, Anti-malarial and Immunosuppressant use at Baseline – counts and percentages by class (No Steroid, Immunosuppressant or Anti-malarial use, Steroid Only, Immunosuppressant Only, Anti-malarial Only, Steroid and Immunosuppressant Only, Steroid and Anti-Malarial Only, Immunosuppressant and Anti-Malarial Only, Steroid and Immunosuppressant and Anti-malarial). Only steroids with medication type corticosteroid for SLE will be included. Only immunomodulatory modulatory medications used to treat SLE will be included. For other medications, all medication types will be included.

Screening Columbia Suicide Severity Rating Scale (C-SSRS) scores by behavior and ideation components for lifetime and current (counts and percentages) will be presented.

Day 1 C-SSRS components since last visit will be summarized using counts and percentages.

In the screening (lifetime/current) and Day 1 C-SSRS summaries, the number (%) of subjects reporting each individual suicidal ideation (1-5) or behavior (6-10) will be presented (as opposed to the maximum ideation/behavior score).

A listing of screening SELENA SLEDAI results will be provided, including result for individual items and total score.

10.4. Concomitant Medications

Concomitant medications will be coded per drug name as defined in the GSK Drug Dictionary, and classified per the GSK-Drug ATC classification level 1 and ATC level 4. Concomitant medications are defined as medications that start on or before the first dose date of study treatment, and end on or after the first dose date of study treatment, or medications that start after the first dose date of study treatment. Note that medications with partial or missing start and/or stop dates will be assumed to be concomitant unless there is evidence through comparison of partial dates to suggest otherwise, for example, if the day is missing, then the month and year will be compared to the month and year of the first dose date of study treatment and if the month and year are the same or later, then the medication will be considered concomitant. See Section 9.4.3 for handling of missing and partial dates. Medications in the database that are determined to not be concomitant will be excluded from table summaries but included in the listing.

A summary of the number and percentage of subjects with concomitant medications by ATC level 1 term and ATC level 4 term will be displayed for the On-Study period. A further summary of concomitant medications by ATC level 4 term and preferred term will be provided for the on-study period (to Week 52). A listing of all concomitant medication data will be displayed by treatment and subject.

Commercial Benlysta is prohibited during the 52-week treatment period of the study, however, if subjects withdraw from IP and begin receiving it they can continue monthly visits as per the study calendar. As such, a listing of subjects who receive commercial Benlysta during the 52-week treatment period will be reported (from both the concomitant medication and the Years 2 to 5 CRF follow-up forms) with the caveat that the Years 2 to 5 data will not be locked at the time of reporting.

10.5. Extent of Exposure

The extent of exposure to study treatment through Week 52 will be assessed by examining the duration of exposure to belimumab/placebo in days and the total number of infusions a subject receives. Note that receipt of commercial Benlysta will not be included in exposure calculations.

Duration of exposure in days will be calculated as:

Duration of exposure (days) = Last infusion date – First infusion date + 28.

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

If a subject has more than one infusion on any given day (i.e. infusion is stopped and then restarted), this will be counted as a single infusion in summaries but both infusions will be listed.

Where a partial infusion is received, this will be counted as one infusion in the calculation of number of infusions.

The duration of exposure and the total number of infusions will be summarized using descriptive statistics for the ITT population. The total number of infusions will also be summarized using counts and percentages using the following categories: 1 – 5 doses, 6 – 10 doses and, 11-14 doses.

Subject level exposure data will be listed for all subjects by treatment group and subjects using the Randomized population, flagging subjects whose treatment group differs from the As-Treated population. A listing of study agent administration, including whether total dose was administered and if not the reason why, will be provided. A listing of subjects for whom the blind was broken will also be provided.

11. PRIMARY AND OTHER SAFETY ANALYSES

AESI are defined endpoints in the protocol (and clarified in Section 2.2.3). There are also AESI defined in the Benlysta PSAP (Section 15 and Section 16; see Appendix 6: PSAP Sections for AESI Reporting), which overlap with the protocol-defined AESIs.

Analyses and summaries described in Section 11.1.2 will use the protocol-defined AESIs. All safety data from the AE dataset will be displayed in summaries described in Section 11.2.1. This is expected to cover protocol-defined AESIs and SAEs and additionally, though not anticipated, any non-serious AEs which were not in scope for collection in the protocol but remained on the database at database release. The required PSAP summaries for AESI are described in Section 11.2.4.

The primary study summaries will be of overall subject incidence rates of all-cause mortality and AESIs during the on-treatment period, with supportive summaries during the on-study period. SAEs will be descriptively summarized during the on-treatment and on-study periods.

Safety will also be reported using more detailed summaries of deaths, AESIs (per PSAP), and standard summaries of SAEs. Since there is targeted collection of AEs in the study i.e. AESIs and SAEs, this will be clarified where applicable.

To allow comparison with other studies in the Benlysta program, the format and content of the more detailed AESI summaries will be per PSAP standards. Therefore, data on the primary safety endpoints may be contained both at a high level within Section 11.1 and in more detail in Section 11.2.

Safety analysis will be performed on the As-Treated population.

The extent of missing follow-up data (i.e. for subjects who have withdrawn from the study prior to the Week 52 visit) and off-treatment data will be summarized by treatment group. Exploratory analyses may be performed to characterize the potential impact of off-treatment and missing data on the primary mortality endpoint results (see Appendix 7, Mortality Missing Data Exploratory Sensitivity Analyses).

11.1. Primary Analysis: All-Cause Mortality, AESI and SAEs

The primary analyses will be performed for both the on-treatment and on-study periods, as defined in Section 9.1. The primary interest is in the on-treatment period, with the on-study considered an important supportive analysis.

The primary analyses for the on-treatment period will be repeated for subgroups as defined in Section 8.3. Follow-up adjusted summaries (i.e. subject incidence rate/event incidence rate) will not be included in subgroup tables.

An overall Double Dotplot for the percentage of subjects with an event will be provided for mortality and other AESIs for the on-treatment period. This is a panel display with two associated dot-plots; the left-hand panel will show the percentage of subjects with an event in each arm. The right-hand panel will show the difference in percentages, with bars for the 95% confidence interval around the difference. All AESIs and mortality will be displayed on the same plot. Further detail on methodology is given in Section 11.1.1 and Section 11.1.2.

An overall Double Dotplot for exposure-adjusted subject incidence rate will be provided for mortality and other AESIs for the on-treatment period. This is a panel display with two associated dot-plots; the left-hand panel will show the exposure-adjusted subject incidence rate in each arm. The right-hand panel will show the difference in the exposure-adjusted subject incidence rate, with bars for the 95% confidence interval around the difference. All AESIs and mortality will be displayed on the same plot. Further detail on methodology is given in Section 11.1.1 and Section 11.1.2.

11.1.1. All-Cause Mortality

See Section 11.2.1 and Section 11.2.2 for further summaries and listings of deaths.

Percentages

A summary of the number and percentage of subjects who have died will be provided for belimumab and placebo as well as the difference in the percentage of subjects between the belimumab and placebo groups. The difference in percentages will be evaluated with a 2-sided 95% CI, using the simple asymptotic Chi-Square (Pearson) method [Newcombe, 1998]. This will be considered as the primary method of assessment of the treatment difference.

Subject Incidence Rate

Whilst a difference between belimumab and placebo groups in IP exposure and overall study duration (to Week 52) is not anticipated, to account for this, supplemental summaries using subject incidence rates will be provided.

The subject incidence rate of mortality per 100 subject years will be provided for belimumab and placebo as well as the difference between belimumab and placebo with 95% CIs. For within-group rates per 100 subject years, the 95% CI will be obtained via

on an exact Poisson method [Stokes, 2012]. For differences in rates between groups, the 95% CI will be constructed using a Normal approximation (Wald's method, [Liu, 2006]).

See Section 9.5.14 for further details on the calculation of incidence rates for the on-treatment and on-study periods.

Kaplan-Meier Figure

A plot of the Kaplan-Meier curve, including standard error bands, for all-cause mortality for belimumab and placebo will be provided to show the change in risk over time. The Kaplan-Meier estimates table will be outputted for quality control purposes but will not be used included in the tables or listings.

Time to Event is defined for the On-Treatment Period and On-Study Period as follows:

- For subjects who died during the evaluation period of interest (i.e. on-treatment or on-study): Time to event is the date of death - first exposure date +1.
- For subjects who did not die or died after the end of the evaluation period of interest (i.e. on-treatment or on-study): Time to event (censored) is the censoring date – first exposure date + 1.

Occurrence and date of death will be determined based on the AE dataset where outcome = fatal (date of death will be derived as the end date of the SAE with fatal outcome).

The censoring date will be assigned based on the evaluation period of interest as follows:

- **On-treatment**: end date for On-Treatment period (see Section 9.1.1)
- **On-study:** end date for On-Study period for mortality and malignancy events (see Section 9.1.1)

The time to event will be calculated in days, as described above. However, the x-axis of the KM plot will display time in weeks. The following conversion will be applied for time to event days to weeks, in order to display the correct week according to the scheduled visit plan (see Section 9.5.2). For example, Day 57 as Week 8, Day 113 as Week 16.

Time to event (weeks) = [Time to event (days) – 1] /7

The number of subjects at risk at certain timepoints [i.e. Week 8 (Day 57), Week 16 (Day 113), etc.] will be presented for each treatment group. The number of subjects at risk is defined as the number of subjects alive and uncensored at a time just prior to time t (e.g. for Week 8, this would be the number of subjects at risk at the start of Day 57). The Kaplan-Meier plot will be truncated at Week 52.

Cumulative Time to Mortality

The cumulative number and percentage of subjects who died by study visit, derived using visit windows defined in Section 9.5.3, will be displayed by treatment group for the On-Treatment Period and the On-Study Period.

11.1.2. Protocol-Defined AESI

Protocol-defined AESIs are defined in Section 9.5.12.

Note, for Suicidality (C-SSRS) only, a subject must have at least one pre-treatment C-SSRS assessment (screening and/or baseline) and at least one on-treatment C-SSRS assessment (post-baseline) to be included in the summaries.

Percentages

For each of the AESIs a summary of the number and percentage of subjects experiencing at least one event will be provided for belimumab and placebo as well as the difference in the percentage of subjects (and 95% CI) between the belimumab and placebo groups using the same methodology as for mortality.

Subject Incidence Rate

The incidence rate for each AESI per 100 subject years will be provided for belimumab and placebo groups as well as the difference between placebo and belimumab (and 95% CI) using the same methodology as for mortality.

Event Incidence Rate

The number of events and event rate for each AESI, except Suicidality (C-SSRS), per 100 subject years will be provided for belimumab and placebo groups.

11.1.3. SAEs

SAEs will be presented using descriptive statistics.

A summary of the number and percentage of subjects with SAEs reported during the on-treatment and on-study (to Week 52) periods will be provided along with the number of events. Subject incidence rates will also be provided at the SOC level only (see Section 9.5.14 for derivation) for on-treatment and on-study periods.

See Section 11.2.1 for further details of SAE summaries and Section 11.2.2 for a description of the SAE listings.

11.2. Other Safety Summaries

11.2.1. AESI and SAEs

This section describes additional summaries to be generated for all safety data in the AE dataset. These data will be referred to as AESIs and SAEs throughout this section but could include out of scope AEs if entered by sites. For the AESI analysis/groupings as per the Belimumab PSAP definitions, see Section 11.2.4 (and Section 9.2 for AESI adjudication details).

For the following summaries, only treatment-emergent AESIs and SAEs will be summarized, unless otherwise stated (see Section 9.5.13 for definitions of Treatment Emergent and derivation of AE duration).

All treatment-emergent AESIs and SAEs will be summarized for the On-Treatment and On-Study (to Week 52) periods, unless otherwise specified in the list of displays.

All AESIs and SAEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by SOC and preferred term (PT), unless otherwise stated.

The investigator will evaluate all AESIs and SAEs with respect to seriousness, severity, and causality. The severity of an AESI or SAE is to be evaluated according to the Adverse Event and Laboratory Value Severity Grade Tables in Protocol Appendix 8, if a grade is defined for the AE of interest.

An overall summary of AESIs and SAEs will be presented showing the number and percent of subjects with at least one: AESI or SAE, Study Agent related AESI or SAE, serious AE (SAE), severe AESI or SAE, AESI or SAE resulting in premature study agent discontinuation, AESI or SAE resulting in study withdrawal, AESI or SAE resulting in premature study agent discontinuation and/or study withdrawal, deaths (timing based on fatal SAE start date) and deaths (timing based on fatal SAE end date i.e. date of death). This summary will be presented for the On-Treatment and On-Study periods.

The number and percentage of subjects experiencing an AESI or SAE and the total number of AESIs and SAEs will be summarized for AE categories and treatment periods as shown in Table 1.

A listing of subject numbers for each AESI or SAE will also be produced. AESIs and SAEs will be grouped and sorted by SOC and PT. A listing of all AESIs and SAEs and study agent related AESIs and SAEs will be presented, including duration and study day of onset/resolution.

Table 1 AESIs and SAEs Displays

Category	On-Treatment Period	On-Study (to Week 52) Period
All AESIs and SAEs	by SOC by SOC and PT by PT only	by SOC and PT
AESIs and SAEs by Severity	by SOC and PT	
Serious AEs	by SOC by SOC and PT by PT	by SOC and PT
Study Agent Related AESIs and SAEs	by SOC by SOC and PT by PT only	
Study Agent Related AESIs and SAEs by Severity	by SOC and PT	

Category	On-Treatment Period	On-Study (to Week 52) Period
AESIs and SAEs Leading to Premature Discontinuation of Study Agent	by SOC and PT by PT	by SOC and PT
AESIs and SAEs Leading to Withdrawal from Study	by SOC and PT	by SOC and PT
Common Non-Serious AESI ≥1%	by SOC and PT	
Non-serious Study Agent Related AESI	by PT	
Study Agent Related SAEs	by SOC and PT by PT	
Fatal SAEs (assigned to period based on SAE start date)	by SOC and PT by PT	by SOC and PT
Study Agent Related Fatal SAEs (assigned to period based on SAE start date)	by SOC and PT	
AESIs and SAEs by Age group	by SOC and PT	
AESIs and SAEs by Gender	by SOC and PT	
AESIs and SAEs by Race	by SOC and PT	
AESIs and SAEs by Region	by SOC and PT	
AESIs and SAEs by Complement Levels and Anti-dsDNA	by SOC and PT	

The tabular summary for each category of AESIs and SAEs listed above will include the number of events, number of subjects who reported at least one event, and percentage of subjects who reported at least one AESI or SAE (incidence) by treatment group for each SOC (where applicable), each PT, and overall. By default, adverse events will be sorted by MedDRA SOCs, in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any adverse event within the class, to the SOC with the lowest total incidence. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. Only SOCs with observed AE PTs will be presented. Repeat sort order for MedDRA PTs within each SOC.

Common AESIs and SAEs will be defined as ≥1% in either treatment group.

For disclosure, an additional summary of SAEs by SOC and PT will be produced in the format required for the on-treatment period. The table will include the number and percentage of subjects with an SAE along with the number of SAEs, drug-related SAEs, fatal SAEs and drug-related fatal SAEs.

A summary of AESIs and SAEs by SOC, PT and severity will be provided by treatment group. For this display, the number and percentage of subjects will be summarized as mild, moderate or severe based on the maximum severity observed across all PTs within the SOC for a given subject.

The hierarchical relationship between MedDRA SOCs, PTs, and verbatim text will be listed for all AESIs and SAEs.

A listing that displays which subjects reported each AESI or SAE will also be produced. AESIs and SAEs will be grouped and sorted by SOC and PT.

A listing of all AESIs and SAEs and study agent related AESIs and SAEs will be presented, including duration and study day of onset/resolution.

A listing of SAEs and AESIs that are recorded between withdrawal of consent and Week 52 Follow-Up, excluding mortality and malignancy, will be produced. The intent is to capture events that were not included in summaries for the on-study period as the protocol did not specify to collect them.

11.2.2. Deaths and Serious Adverse Events

In addition to the tabular summaries of AESIs and SAEs described in Section 11.2.1, listings for all SAEs, all fatal SAEs (deaths) and all non-fatal SAEs will be produced. A listing of reasons for considering an AE as an SAE will be provided. The categorization of the cause of death will be adjudicated by GSK (see Section 9.2).

A summary of deaths (fatal SAEs) by category and preferred term will be produced based on the start date of the fatal SAE (to determine whether the event occurred during the relevant study period). A separate summary will be produced of deaths by category and preferred term based on end date of fatal SAE (i.e. using date of death to determine whether the event occurred during the relevant study period). Both summaries will be for the on-treatment period.

Survival status will also be summarized at Week 52, based on information collected on the Week 52 Survival form, for all subjects in the As-Treated population. The number and percentage of subjects will be summarized for each of the following categories:

- Alive
- All Deaths (based on date of death)
    - Deaths on Treatment (during the on-treatment period)
    - Deaths Post-Treatment (after the on-treatment period)
- Unknown
    - Lost to Follow-Up
    - Unattainable

A listing of survival status at Week 52 will also be presented.

11.2.3. AESIs and SAEs Leading to Discontinuation of Investigational Product or Withdrawal from Study

In addition to the tabular summaries described in Section 11.2.1, the following listings will also be produced:

- all AESIs and SAEs leading to premature discontinuation of study agent.
- all AESIs and SAEs leading to withdrawal from the study (i.e., withdrawal of consent).

Note that non-serious AEs leading to withdrawal that are not protocol-defined AESI are not collected in the database.

11.2.4. PSAP-Defined Adverse Events of Special Interest

The PSAP has been developed to include AESI summaries for consistent reporting across belimumab studies which will be included here in addition to the primary summary of overall AESI rates described in Section 11.1.2 of this RAP.

Categorizations for the AESIs from the PSAP are defined Appendix 6: PSAP Sections for AESI Reporting and reporting of AESIs for these analyses is defined below.

An overall summary of AESI will be presented. Selected categories of AESI will be presented separately by PT. Infection AESIs will also be presented by PT for infections leading to discontinuation of study agent. The number and percentage of subjects with at least one occurrence and the number of events of the following AESI will be provided.

- Malignant Neoplasms
  - Malignancies Excluding non-melanoma skin cancer (NMSC) [see Section 9.5.12, protocol defined AESI]
  - Malignancies Including NMSC
  - Solid Tumour
  - Hematologic
  - Skin (All)
    - NMSC [see Section 9.5.12, protocol defined AESI]
    - Excluding NMSC
  - Tumours of unspecified malignancy adjudicated as malignant per GSK adjudication

- Post-Infusion Systemic Reactions
    - Post-Infusion Systemic Reactions per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search (on the day of the infusion or within 3 days after the infusion)
      - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search (on the day of the infusion or within 3 days after the infusion)

  - Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion)
    - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion) [see Section 9.5.12, protocol defined AESI]
  - Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ algorithmic search (on the day of the infusion or within 3 days after the infusion)
    - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ algorithmic search (on the day of the infusion or within 3 days after the infusion)
  - Serious Anaphylaxis per Sampson Criteria
  - Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK adjudication
    - Serious Acute Post-Infusion Systemic Reactions 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 [see Section 9.5.12, protocol defined AESI]
  - Serious Infections of Special Interest
  - All opportunistic infections per GSK adjudication
    - Serious opportunistic infections per GSK adjudication
  - Opportunistic infections per GSK adjudication excluding Tuberculosis and Herpes Zoster
    - Serious opportunistic infections per GSK adjudication excluding Tuberculosis and Herpes Zoster
  - Active Tuberculosis
    - Non-Serious Active Tuberculosis
    - Serious Active Tuberculosis
    - Non-Opportunistic
      - Serious Non-Opportunistic
    - Opportunistic
      - Serious Opportunistic
  - Herpes Zoster
    - Serious Herpes Zoster
    - Non-Opportunistic
      - Serious Non-Opportunistic
    - Opportunistic
      - Serious Opportunistic
      - Recurrent

        - Serious Recurrent
    - Disseminated
        - Serious Disseminated
- Sepsis
    - Serious Sepsis

- Depression/suicide/self-injury
    - Depression (Inc. mood disorders and anxiety)
        - Serious Depression (Inc. mood disorders and anxiety) [see Section 9.5.12, protocol defined AESI]
        -
    - Suicide/self-injury
        - Serious Suicide/self-injury
    - Serious Suicide/Self-injury per GSK Adjudication
        - Suicidal behavior per GSK Adjudication
            - Completed Suicide per GSK Adjudication
        - Suicidal Ideation per GSK Adjudication
        - Self-injurious Behavior Without Suicidal Intent per GSK Adjudication

- Deaths (using start date of fatal SAE to determine whether event occurred during the relevant study period)
- Deaths (using end date of fatal SAE i.e. date of death to determine whether event occurred during the relevant study period)

A listing of all PSAP-defined AESIs will be produced.

11.2.4.1. Post-infusion Systemic Reactions

Summaries of post-infusion systemic reactions will be presented by the first six infusions and PT for the following categories:

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

11.2.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The definition of treatment-emergent with respect to C-SSRS (suicidal ideation and/or behavior) is given in Section 9.5.15.

Suicidality assessments are completed at every visit. Assessments are done using the C-SSRS. If a “yes” response is given to any suicidal behavior or a “yes” response to suicidal ideation questions with category 3, 4 or 5 on the C-SSRS, the investigator will be

prompted to complete the Possible Suicidality Related Questionnaire (PSRQ). A listing of the PSRQ will be presented.

Listings will be generated for the following:

- Suicidal ideation and behavior data for subjects who have any suicidal ideation or behavior recorded at any point on the study (including screening or baseline).
- Behavior details for subjects who have any suicidal behavior recorded at any point on the study (including screening or baseline)
- The most severe suicidal ideation details for subjects who have any suicidal ideation recorded at any point on the study (including screening or baseline).

11.2.5.1. C-SSRS Suicidal Ideation or Behavior

The number and percentage of subjects with suicidal ideation or behavior at any time during the on-treatment and on-study (to Week 52) periods will be presented. For suicidal ideation, the maximum ideation score (1-5) at any time during the relevant period will be presented. For suicidal behavior, all behaviors (6-10) present at any time during the relevant period will be presented. This will be regardless of whether the subject had pre-treatment history (up to and including baseline [see Section 9.5.1 for baseline definition]). The categories of suicidal ideation and behavior are presented in increasing order of severity from 1 to 5, and 6-10 respectively.

11.2.5.2. C-SSRS Suicidal Ideation or Behavior Relative to Pre-Treatment

The number and percentage of subjects with treatment-emergent suicidal ideation or behavior -post-baseline will be presented during the on-treatment and on-study (to Week 52) periods (see Section 9.5.15).

A subject must have at least one pre-treatment C-SSRS assessment (screening and/or baseline) and at least one on-treatment C-SSRS assessment (post-baseline) to be included in this display.

A subject may have treatment emergent suicidal ideation and/or behavior.

The following categories will be presented:

- The number (%) of subjects with any treatment emergent suicidal ideation (1-5)
    - The number (%) of subjects with any treatment emergent more severe suicidal ideation (4-5)
- The number (%) of subjects with any treatment emergent suicidal behavior (6-10)
- The number (%) of subjects with any treatment emergent suicidal ideation (1-5) or suicidal behavior (6-10)

Note: treatment emergent suicidality can only be assessed in subjects with a pre-treatment maximum ideation score of 4 or lower (as subjects with a pre-treatment ideation score of 5 have no potential to worsen on the 1-5 ideation scale)

In addition, a shift table showing the maximum pre-treatment ideation score versus the maximum post-treatment ideation score will be produced for the on-treatment and on-study periods. The maximum pre-treatment behavior score versus the maximum post-treatment behavior score will also be presented in the summary table. These summaries will be provided post Statistical Analysis Complete (SAC).

11.2.5.3. C-SSRS Shift Changes in Categories from Pre-Treatment to On-Treatment

A summary of the shift from maximum pre-treatment C-SSRS category to maximum on-treatment and on-study (to Week 52) category will be produced.

The pre-treatment period for ideation is based on the lifetime, current and baseline history. For behavior, it is based on the lifetime and baseline history. A subject must have at least one pre-treatment assessment and at least one on-study assessment to be included in this display.

The table will display the number and percentage of subjects within the specific shift categories: No suicidal ideation or behavior, suicidal ideation, and suicidal behavior.

Each subject will appear in the table only once. For the purposes of this table only, a subject with both suicidal ideation and suicidal behavior in any period (pre-treatment/on-treatment/on-study) will appear in the category of suicidal behavior only.

12. EFFICACY ANALYSES

The efficacy analyses will be performed for the ITT population as defined in Section 6 unless otherwise stated. The data will be presented by treatment group.

12.1. Major Efficacy Analyses

12.1.1. Percent of Subjects with Prednisone Reduction by ≥25% from baseline to ≤7.5 mg/day during Week 40 through Week 52

Primary Analysis

For this analysis, only steroids used to treat SLE will be included and only subjects with a baseline average daily prednisone dose >7.5mg/day will be included. See Section 9.5.16.1 for derivation of baseline prednisone dose and Section 9.5.16.2 for derivation of average prednisone use between Week 40 to Week 52.

The percent of subjects whose average prednisone dose has been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 will be compared between belimumab and placebo using a logistic regression model. Independent variables in the model will include treatment group, baseline prednisone dose, and the following

randomization stratification factors per the eCRF: screening SELENA SLEDAI score (≤9 vs. ≥10), and region. A responder is defined as having a prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52.

Any subject who withdraws from the study or adds new immunomodulatory agents used to treat SLE (note that this will include switches) prior to the Week 52 visit will be considered having no steroid reduction.

A summary of the number and percentage of subjects who are responders by treatment group, the treatment difference versus placebo, the odds ratio and 95% CI versus placebo, and a p-value for the odds ratio will also be provided.

Sensitivity Analysis

- To examine the robustness of the results, a sensitivity analysis of the SLE-related steroid reduction will be performed without considering any information related to the use of new immunomodulatory agents (note that this will include switches).

Additional Summaries of Prednisone

- A summary of the number and percentage of subjects with average SLE-related daily prednisone dose ≤7.5mg/day and >7.5 mg/day at baseline (Day 1) and treatment completion date will be presented for treatment completers.
- The cumulative SLE-related prednisone dose will be derived as described in Section 9.5.16.3. A table of descriptive statistics will be presented including the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum.
- A listing of cumulative SLE-related prednisone dose will be displayed by treatment and subject.

12.2. Other Efficacy Analyses

12.2.1. Immunomodulatory Agents to Treat SLE

The following summaries will present immunomodulatory agents used to treat SLE only, i.e. those with medication type 'SYSTEMIC LUPUS ERYTHEMATOSUS'.

- A summary of the number and percentage of subjects taking immunomodulatory agents to treat SLE by ATC level 4 term and preferred term will be displayed for the on-study period.
- A summary of the number and percentage of subjects on immunomodulatory agents to treat SLE at baseline (see Section 9.5.17 for derivation of baseline medication) and at the treatment completion date (in treatment completers as defined in Section 9.5.7 with a treatment completion date) will be presented.

A summary of the shift (on versus off immunomodulatory agents to treat SLE) from baseline category to treatment completion date (in subjects who completed IP as

scheduled) and at study agent discontinuation date (subjects who prematurely discontinued IP)

See Section 9.5.17 for detail on defining immunomodulatory medication use at baseline and treatment completion.

All immunomodulatory agents will be indicated in the listing of concomitant medications.

12.2.2. Hospitalizations

This information will be derived from the SAEs using the review process outlined in Section 9.3.

The number and percent of subjects hospitalized will be presented along with the number of hospitalizations per subject.

Subjects with hospitalizations and SAEs contributing to hospitalization will be indicated in the listing of SAEs and the number of hospitalization per subject (identified by clinical review, see Section 9.3) will also be listed.

12.2.3. SLICC/ACR Damage Index

SLICC/ACR is attached in Appendix 5: SLICC/ACR Damage Index.

A listing of all available SLICC/ACR data will be provided, including the analysis result for each item, the total score and the change from baseline at Week 52.

12.2.3.1. SLICC/ACR Damage Index Change from Baseline at Week 52

The change from baseline in SLICC/ACR Damage Index score at Week 52 will be summarized for belimumab and placebo.

The table will display the summary statistics for the SLICC/ACR Damage Index score at baseline and at Week 52. The table will also display the mean change from baseline, standard deviation, median, 25th and 75th percentiles, minimum and maximum. Only subjects who complete the full course of study agent through 48 weeks and complete the study to Week 52 will be included in the summary at Week 52.

A separate summary will be produced for subjects who complete the study through 52 weeks, i.e. subjects with off-treatment data will be included. The table will display the summary statistics for the SLICC/ACR Damage Index score at baseline and at Week 52. The table will also display the mean change from baseline, standard deviation, median, 25th and 75th percentiles, minimum and maximum.

12.2.3.2. SLICC/ACR Damage Index Worsening at Week 52

The number and percentage of subjects with worsening in their SLICC/ACR Damage Index score compared with baseline at Week 52 will be presented. Worsening is defined as a change in score (Week 52 visit minus Baseline) >0. The percentage of subjects with

worsening in their SLICC/ACR Damage Index score at Week 52 will be compared between belimumab and placebo using a logistic regression model. The independent variables in the model will include treatment group and randomization strata per the eCRF: steroid dose (≤7.5 mg/day vs >7.5 mg/day prednisone or equivalent used to treat SLE), region, screening SELENA SLEDAI score (≤9 vs. ≥10), and baseline SLICC/ACR Damage Index score.

The table will display the number and percentage of subjects with worsening in their SLICC/ACR Damage Index score by treatment group, the treatment difference versus placebo, the odds ratio and 95% CI versus placebo, and a p-value for the odds ratio.

Only subjects who complete the full course of study agent through 48 weeks and complete the study to Week 52 with a baseline and post-baseline assessment will be included in the analysis. See Section 9.5.19 for further detail.

A separate summary will present the number and percentage of subjects with worsening at Week 52 compared to baseline by organ domain in treatment completers who have a Week 52 SLICC assessment. Only subjects who have potential to worsen in a given domain will be summarized for that domain, i.e. subjects who do not have the maximum damage score for the domain at baseline.

A summary will also be produced for subjects who complete the study through 52 weeks, i.e. subjects with off-treatment data will be included. The table will display the number and percentage of subjects with worsening in their SLICC/ACR Damage Index score by treatment group and the treatment difference versus placebo.

Subgroups

The SLICC/ACR worsening at Week 52 will be summarized for treatment completers with a Week 52 assessment for subgroups listed in Section 8.3 using the eCRF data to derive randomization stratification factors.

13. PHARMACOGENETIC DATA ANALYSES

Any pharmacogenetic analyses will be described in a separate pharmacogenetic analysis plan and will be reported separately from the main clinical study report.

14. REFERENCES

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15. APPENDICES

15.1. Appendix 1: Countries by Region

Country	Region for Randomization Stratification
Canada USA	US/Canada
Argentina Brazil Chile Colombia Mexico Peru Puerto Rico	Central America/South America/Mexico
Australia Bulgaria Croatia Czech Republic Estonia Hungary Israel Italy Lithuania New Zealand Norway Poland Portugal Romania Russia Serbia Slovakia Spain Switzerland Turkey Ukraine	Europe/Australia/Israel
China Hong Kong India Indonesia Korea Malaysia Philippines Taiwan Thailand	Asia

15.2. Appendix 2: SELENA SLEDAI Organ System Domains

SELENA SLEDAI Organ System Domains

SELENA SLEDAI assessments consist of 24 individual weighted items in which signs and symptoms, laboratory tests, and physician's assessment for each of 8 organ systems are given a weighted score and summed if present (marked 'Yes') at the time of the visit or in the preceding 10 days. The maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No'), but in practice few subjects have scores >45 [Buyon, 2005; Petri, 2005].

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

In the eCRF, laboratory items on the SLEDAI may also be ticked 'unknown' to indicate the lab test was not available. The laboratory items are: urinary casts, hematuria, proteinuria, pyuria, low complement, increased DNA binding, thrombocytopenia, and leukopenia.

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

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

15.3. Appendix 3: SLE Allowable Medication Categories

Medication Category	Rule
Anti-malarials	Set to "ANTIMALARIALS" if the preferred term begins with "QUINACRINE", "QUININE", "HYDROXYCHLOROQUINE", "MEPACRINE", or "CHLOROQUINE" AND the route of administration is not 'TOPICAL', 'VAGINAL', 'CONJUNCTIVAL', 'INTRANASAL', 'INHALATION', 'INTRA-OCULAR', 'INTRATRACHEAL', 'EPIDURAL', 'INTRA-ARTICULAR', or 'OTHER'.
Steroids	Set to 'STEROIDS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02' AND Route of administration is "INTRADERMAL", "INTRAMUSCULAR", "INTRAVENOUS", "ORAL", "SUBCUTANEOUS", or "INTRA-ARTICULAR".
Immunosuppressants	Set to 'IMMUNOSUPPRESSANTS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04A' or the preferred term begins with "CYCLOPHOSPHAMIDE" (oral and parenteral routes) or "MERCAPTOPURINE" (oral route).
NSAIDs	Set to NSAIDs if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'M01A'.
Aspirin	Set to "ASPIRIN" if CMDECOD contains "ACETYLSALICYLIC ACID" or "ACETYLSALICYLATE LYSINE".
Prohibited	Set to "PROHIBITED" if any of the following conditions are met, if CMDECOD equals "INVESTIGATIONAL DRUG", "IMMUNOGLOBULIN", "ADALIMUMAB", "ETANERCEPT", "INFLIXIMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "GOLIMUMAB", "CERTOLIZUMAB" or "BELIMUMAB".

15.4. Appendix 4: Prednisone Equivalent Conversion

- A concomitant medication is identified as a steroid if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02.'
- The following routes are considered to provide systemic exposure: oral, subcutaneous, intramuscular, intradermal, and intravenous. Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).
- At data base release, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor exists for all terms with a systemic route of administration.
- Similarly, all routes of administration for preferred terms with an ATC code beginning with 'H02'will be reviewed to ensure all systemic routes have been identified in the list above.
- In order to be converted the frequency and dose of the steroid must be present with the unit dose in milligrams (mg).
- Reported dose for systemic steroid is converted to prednisone equivalent dose using conversion factor for each particular medication (refer to online calculator http://www.globalrph.com/corticocalc.htm).

A two-step process will be used to calculate the prednisone equivalent daily dose:

1. DOSE2 (prednisone equivalent dose in mg) = DOSE (collected dose in mg) x Conversion Factor
2. DD (daily dose in mg/day) = DOSE2 (prednisone equivalent dose in mg) x Frequency Factor

Where multiple steroids are taken on one day, the sum of these will be the prednisone equivalent daily dose. An intermediate dataset will contain the total daily prednisone equivalent daily dose for each study day. This will be used to derive prednisone endpoints.

Preferred term	Conversion factor for converting to a prednisone-equivalent dose
BETAMETHASONE	8.333
BETAMETHASONE DIPROPIONATE	8.333
BETAMETHASONE SODIUM PHOSPHATE	8.333
BETAMETHASONE VAL	8.333
BETROSPAM	8.333
CELESTONA BIFAS	8.333
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.333
DEFLAZACORT	0.8333
DEPO-MEDROL MED LIDOKAIN	1.25
DEXAMETHASONE	6.667

Preferred term	Conversion factor for converting to a prednisone-equivalent dose
DEXAMETHASONE ACETATE	6.667
DEXAMETHASONE PHOSPHATE	6.667
DEXAMETHASONE SODIUM PHOSPHATE	6.667
FLUOCORTOLONE	3
HYDROCORTISONE	0.25
HYDROCORTISONE ACETATE	0.25
HYDROCORTISONE HYDROGEN SUCCINATE	0.25
HYDROCORTISONE SODIUM SUCCINATE	0.25
MEPREDNISONE	1.25
METHYLPREDNISOLONE	1.25
METHYLPREDNISOLONE ACEP	1.25
METHYLPREDNISOLONE ACETATE	1.25
METHYLPREDNISOLONE HEMISUCCINATE	1.25
METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
PARAMETHASONE	2.5
PREDNISOLONE	1
PREDNISOLONE SODIUM PHOSPHATE	1
PREDNISOLONE SODIUM SUCCINATE	1
PREDNISONE	1
PREDNISONE ACETATE	1
TRIAMCINOLONE	1.25
TRIAMCINOLONE ACETATE	1.25
TRIAMCINOLONE ACETONIDE	1.25

Frequency Factors	
Frequency	**Factor**
BID	2
BIW	2/7
OAM	1/30
OD	1
Once	1
PRN	Null
Q2H	12
Q2W	1/14
Q3H	8
Q3D	1/3
Q3MO	1/84
Q3W	1/21
Q4H	6
Q4D	1/4
Q4W	1/28
Q6H	4
Q8H	3

Frequency Factors	
Frequency	**Factor**
Q12H	2
QAM	1
QD	1
QH	24
QHS	1
QID	4
QOD	½
QPM	1
QW	1/7
QWK	1/7
QM	1/30
TID	3
TIW	3/7
UNK	Null
2 TIMES PER WEEK	2/7
3 TIMES PER WEEK	3/7
4 TIMES PER WEEK	4/7
EVERY 2 WEEKS	1/14
EVERY 3 WEEKS	1/21
EVERY 4 WEEKS	1/28
EVERY WEEK	1/7

Unit Conversion Factors	
Unit	**Factor**
MCG	0.001
G	1000
MG/DAY	1
OZ	28349.5
UG	0.001
MG	1

Any additions to the conversion factors or frequency factors noted above, that are identified during final data reconciliation but after RAP approval, will be documented prior to unblinding the study.

15.5. Appendix 5: 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.

15.6. Appendix 6: 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.

<u>Algorithmic Search Criteria</u>

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

15.7. Appendix 7: Mortality Missing Data Exploratory Sensitivity Analyses

Whilst extensive efforts have been made to achieve complete ascertainment of vital status (alive, dead) at Week 52 for the As Treated Population, it is acknowledged that it will be unattainable for a low percentage of subjects.

This appendix outlines the methodology for potential exploratory sensitivity analyses of mortality (primary analyses defined in RAP Section 11.1.1). The need to conduct the supplemental estimand sensitivity analysis described in Section 15.7.1.3 will be assessed following study team review of the Statistical Analysis Complete (SAC) package.

The draft ICH E9 addendum has been used as guidance/a framework in determining the strategy for the exploratory sensitivity analyses, including the handling of intercurrent events occurring prior to Week 52. Intercurrent events are defined as "events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation" e.g. premature discontinuation of study agent or study withdrawal.

15.7.1. Estimand Framework

15.7.1.1. Main Estimand: While On Treatment

The main estimand aligns to the primary endpoint as defined in the main body of the RAP (Section 11.1.1). It is chosen as the main estimand because the endpoint is being evaluated to address safety objectives.

Therefore, whilst outlined here using an Estimand framework, it does not represent a different analysis to that specified in Section 11.1.1.

Endpoint/Variables

Mortality status while on treatment (to treatment stop date + 28 days).

Summary Measure

95% Confidence Interval around the difference in percentage of deaths while on treatment.

Population of Interest

The primary efficacy analyses are based on the As-Treated population, unless otherwise specified.

Strategy for Intercurrent (Post-Randomization) Events

Premature discontinuation of study agent and/or study withdrawal are not relevant here as we are only using data whilst subjects were on-treatment.

Statistical Analyses / Methods

Statistical Methodology Specification

Endpoint / Variables
Mortality status while on treatment
Model Specification
Simple asymptotic Chi-Square (Pearson) method for a 95% CI
Model Results Presentation
Number of deaths and percentage in each treatment group and the difference in percentage with 2-sided 95% CI.

15.7.1.2. Supplemental Estimand: While On Study

This estimand is defined to estimate the treatment difference while subjects were on-study. This will include observed on- and off- treatment data to Week 52 and aligns to the on-study estimate defined in the main body of the RAP (Section 11.1.1).

Therefore, whilst outlined using an Estimand framework, it does not represent a different analysis to that specified in Section 11.1.1.

Endpoint/Variables

Mortality status at Week 52 (observed data while on study).

Summary Measure

95% Confidence Interval around the difference in percentage of deaths while subjects were on-study.

Population of Interest

The primary efficacy analyses are based on the As-Treated population, unless otherwise specified.

Strategy for Intercurrent (Post-Randomization) Events

Premature discontinuation of study agent and/or study withdrawal are dealt with in the variable given that all data whilst subjects were in the study (i.e. on- and off- treatment data) is included. Data beyond the observed on-study period is not imputed.

Statistical Analyses / Methods

Statistical Methodology Specification

Endpoint / Variables
Mortality status at Week 52 (observed data while on study)
Model Specification
Simple asymptotic Chi-Square (Pearson) method for a 95% CI
Model Results Presentation
Number of deaths and percentage in each treatment group and the difference in percentage with 2-sided 95% CI will be presented.

15.7.1.3. Supplemental Estimand Sensitivity: Treatment Policy

A sensitivity to the Supplemental Estimand targeting the same estimand is defined with a Treatment Policy approach. Subjects with missing vital status at Week 52 have their vital status imputed using observed off-treatment data.

If the imputation of missing vital status is unsuccessful due to insufficient off-treatment data being available, the interaction term will be removed from the Cox Proportional Hazards model. If the imputation is still not possible, this estimand will not be estimated.

Endpoint/Variables

Mortality status at Week 52 (observed data while on study and imputed data to Week 52).

Summary Measure

95% Confidence Interval around the difference in percentage of deaths at Week 52.

Population of Interest

The primary efficacy analyses are based on the As-Treated population, unless otherwise specified.

Strategy for Intercurrent (Post-Randomization) Events

A Treatment Policy strategy will be used for all intercurrent events. If data are available after the intercurrent event, e.g. where subjects continue in the study post premature study agent discontinuation, these data will be included in the summary. For subjects with missing vital status at Week 52, time to death will be imputed using observed off-treatment data and from this vital status at Week 52 will be derived to allow us to calculate incidence at Week 52.

Statistical Analyses / Methods

Statistical Methodology Specification

Endpoint / Variables
Mortality status at Week 52 (observed data while on study and imputed data to Week 52)
Model Specification
Simple asymptotic Chi-Square (Pearson) method for a 95% CI
Model Results Presentation
Number of deaths and percentage in each treatment group and the difference in percentage with 2-sided 95% CI will be presented.
Methodology
The multiple imputation of vital status at Week 52 will be performed using time to event modelling to predict the time to death for subjects with missing vital status, with the treatment difference being estimated for each imputed dataset and then combined as described below: **Step 1:** The data will be structured so each subject has up to two records; one record for the on-treatment data and one record for the off-treatment data (where off-treatment data is present). Bootstrap from these data and fit a Cox Proportional hazard model $h(t) = h_0(t)\exp\{\beta x + \delta z + \gamma xz\}$, where x represents treatment groups (x=0 for placebo subjects and x=1 for belimumab subjects) and z is an indicator variable for either the "on" or "off" treatment component of the subjects' data (z=0 for on-treatment and z=1 for off-treatment), to estimate the hazard with censoring at random assumption. **Step 2:** Obtain the data from the subjects to be imputed. Use the above estimated baseline hazard to estimate hazard for subjects with missing vital status at Week 52. **Step 3:** Obtain the value of βx + δz + γxz for those subjects and modify the baseline hazard accordingly. **Step 4:** Impute the time to death for subjects who were censored prior to Week 52 based on their assigned hazard. **Step 5:** Aggregate the subjects' on and off-treatment records to obtain the subjects' time to death. For subjects whose time to death is ≤ Study Day 372 assign as death and for subjects whose time to death is > Study Day 372, censor at Study Day 372. **Step 6:** Repeat the above step for 'm' number of times to obtain 'm' imputed values in 'm' datasets. **Step 7:** For each imputed dataset, compute the proportions of deaths in each treatment arm and the associated standard errors. Then calculate the difference in proportions between the treatment arms and associated standard error. **Step 8:** Lastly use Rubin's rule [Rubin, 1987] to combine the results to estimate the treatment difference and 95% CI combined across 'm' datasets.

16. ATTACHMENTS

16.1. Table of Contents for Data Display Specifications

See separate TFL document.

16.2. Data Display Specifications

See separate TFL document.

16.3. Headline Results

The following TFLs will be included as headline results:

Display Type	Display Number	Display Title
Table	1.02	Summary of Study Populations
Table	1.06	Summary of Subject Status and Reason for Study Withdrawal
Table	1.07	Summary of Subject Status and Reason for Discontinuation of Study Agent
Table	1.12	Summary of Demographic and Baseline Characteristics
Table	1.20	Summary of Baseline Disease Activity
Table	2.01	Summary of Mortality (On-Treatment Period)
Table	2.03	Summary of Mortality (On-Study Period)
Table	2.05	Summary of Protocol-Defined Adverse Events of Special Interest (On-Treatment Period)
Table	2.06	Summary of Protocol Defined Adverse Events of Special Interest (On-Study Period)
Table	3.001	Adverse Events of Special Interest and Serious Adverse Events Summary (On-Treatment Period)
Table	3.003	Adverse Events of Special Interest and Serious Adverse Events by SOC (On-Treatment Period)
Table	3.004	Adverse Events of Special Interest and Serious Adverse Events by SOC and PT (On-Treatment Period)
Table	3.009	Serious Adverse Events by SOC (On-Treatment Period)

Display Type	Display Number	Display Title
Table	3.010	Serious Adverse Events by SOC and PT (On-Treatment Period)
Table	3.015	Study Agent Related Adverse Events of Special Interest and Serious Adverse Events by SOC (On-Treatment Period)
Table	3.019	Adverse Events of Special Interest and Serious Adverse Events leading to Study Agent Discontinuation by SOC and PT (On-Treatment Period)
Table	3.037	Adverse Events of Special Interest (PSAP-Defined) by Category (On-Treatment Period)
Table	3.048	Deaths by Category and PT (On-Treatment Period)
Figure	2.03	Time to Mortality (On-Treatment Period)
Figure	2.04	Time to Mortality (On-Study Period)

Additional TFLs may be added depending on the results of the study if agreed upon by the Study team.

16.4. Disclosure Outputs

The following outputs are required for disclosure:

Display Type	Display Number	Display Title	Required by
Table	1.01	Randomization by Site	EudraCT
Table	1.06	Summary of Subject Status and Reason for Study Withdrawal	FDAAA, EudraCT
Table	1.12	Summary of Demographic and Baseline Characteristics	FDAAA, EudraCT
Table	1.13	Summary of Age Ranges	EudraCT
Table	1.14	Summary of Race and Racial Combination Details	FDAAA, EudraCT
Table	3.010	Summary of Serious Adverse Events by	FDAAA, EudraCT

Display Type	Display Number	Display Title	Required by
		SOC and PT (On-Treatment Period)	
Table	3.024	Common (>=1%) Non-Serious Adverse Events of Special Interest by PT (On-Treatment Period)	FDAAA, EudraCT