Division: World Wide Development

Retention Category: GRS019
Information Type: Reporting and Analysis Plan Addendum

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

Compound Number: GSK1550188

Effective Date: 16-MAR-2018

Description: This is a multi-center study to evaluate the safety, pharmacokinetics (PK), and efficacy of belimumab intravenous (IV) in pediatric patients 5 to 17 years of age with active systemic lupus erythematosus (SELENA SLEDAI score ≥6 at Screening). The study will consist of three phases: a 52-week randomized, placebo-controlled, double-blind phase; a long term open label continuation phase; and a long-term safety follow up phase. Enrolment will be staggered by age cohorts to allow safety and PK analysis. Subjects will be randomized to belimumab or placebo while continuing to receive background standard therapy throughout the study. The randomization of Cohort 3 will be stratified by age and SELENA SLEDAI score. Efficacy will be measured by the SLE Responder Index (SRI) at Week 52, SELENA SLEDAI score, PRINTO/ACR Juvenile SLE Response Evaluation, Physician's Global Assessment (PGA) and BILAG A and B organ domain scores. In addition, corticosteroid use, flares, and biomarkers (immunoglobulins, complement, autoantibodies, B-cells) will be assessed. Safety will be assessed by adverse events, clinical laboratory evaluations, vital signs, immunogenicity and pharmacokinetics.

Subject: Systemic Lupus Erythematosus (SLE), belimumab, BENLYSTA (belimumab), efficacy, safety, placebo, SELENA SLEDAI, PRINTO/ACR Juvenile SLE Response Evaluation, BILAG, PedsQL

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-dsDNA	Anti-double-stranded DNA
BILAG	British Isles Lupus Assessment Group of SLE Clinics
CRF	Case Report Form
CRP	C Reactive Protein
DBR	Database Release
DO	Dropout
DO=NR	Dropout = Non-Responder
DO/TF=NR	Dropout/Treatment Failure = Non-Responder
IV	Intravenous
NR	Non-Responder
PK	Pharmacokinetic
PGA	Physician's Global Assessment
PRINTO	Pediatric Rheumatology International Trials Organization
PSAP	Program Safety Analysis Plan
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System Organ Class
SRI	SLE Responder Index
TF	Treatment Failure

1.   INTRODUCTION

After database release and the finalization of the reporting and analysis plan (RAP), but before database freeze and unblinding of the database to the blinded study team (unblinded labs have been sent to the SDTM conversion service), a meeting was held with the FDA during which ordering of the efficacy endpoints in order of relevance was discussed and agreement was reached to add a few additional analyses and data displays for BEL114055. This addendum to the RAP documents the ordering of the efficacy endpoints in order of relevance and the other additions to the RAP for the BEL14055 study. These additional analyses may not be included as part of the main Statistical Analysis Complete (SAC) package, but will be available soon after.

The RAP and this addendum were based upon the following study documents:
- Study Protocol Amendment Version 6 (December 6, 2016)
- Final Case Report Form (CRF) (April 25, 2016)
- Program Safety Analysis Plan (PSAP) Version 5 (December 13, 2017). Note: for reporting purposes, the most current version of the PSAP and associated MedDRA version at the time of database release (DBR) will be used.

2.   ADDITIONS TO THE RAP

2.1.   Endpoint Order of Relevance

The order of relevance for the efficacy endpoints is:
- Proportion of subjects achieving an SRI Response at Week 52 (including the components of the SRI: SELENA SLEDAI, PGA, and BILAG)
- Proportion of subjects with a Sustained SRI Response
- Proportion of subjects achieving an SRI6 Response at Week 52
- Time to First Severe SFI Flare in Part A
- Proportion of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation Criteria Definition 1 at Week 52
- Proportion of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation Criteria Definition 2 at Week 52

2.2.   SRI Response Rate and Components of SRI Response (DO/TF=NR)

SRI response at Week 52 of Part A along with the components of SRI Response (SELENA SLEDAI, PGA, and BILAG) will be summarized using logistic regression modeling comparing treatment groups for subjects with baseline age 5-11 years, subjects with baseline age 12-17 years, and subjects in Cohort 3 without adjustment for covariates. These analyses will use the Drop Out/Treatment Failure = Non-Responder (DO/TF = NR) method for missing data.

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% CI

for belimumab versus placebo for the SRI response and for the components of SRI Response (SELENA SLEDAI, PGA, and BILAG).

2.3.   SRI Response Rate for Subjects with Baseline Age 12-17 Years (DO/TF=NR)

The number and percentage of subjects achieving an SRI response at Week 52 for subjects with baseline age 12-17 years will be presented for belimumab and placebo. A logistic regression model will be used to estimate the odds of an Observed SRI response for belimumab vs. placebo. The independent variables in the model will include treatment group, cohort (cohort 1 vs. cohort 3), and baseline SELENA SLEDAI score ($\leq$ 12 vs. $\geq$ 13).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% CI for belimumab versus placebo. Odds ratio estimates and 95% CIs will also be displayed for each independent variable in the model. These confidence intervals will use the normal approximation.

2.4.   Observed SRI Response Rate (DO=NR)

For the Observed SRI endpoint, any subject who is classified as a drop out will be considered a non-responder. This imputation method is referred to as "Dropout = Non-Responder" (DO=NR). Treatment failures, who complete Part A, will not be imputed.

The number and percentage of subjects achieving an Observed SRI response at Week 52 will be presented for belimumab and placebo. A logistic regression model will be used to estimate the odds of an Observed SRI response for belimumab vs. placebo. The independent variables in the model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$ 12 vs. $\geq$ 13).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% CI for belimumab versus placebo.

2.5.   Adverse Events

The following adverse event (AE) summaries will be presented side by side for subjects with baseline age 5-11 years vs. subjects with baseline age 12-17 years vs subjects in Cohort 3:
- Adverse Events Summary by Baseline Age and Cohort 3 (Part A)
- Adverse Events by SOC and PT by Baseline Age and Cohort 3 (Part A)
- Serious Adverse Events by SOC and PT by Baseline Age and Cohort 3 (Part A)
- Adverse Events of Special Interest (AESI) by Category by Baseline Age and Cohort 3 (Part A)

2.6. Change from Baseline in Immunoglobulins, Anti-dsDNA and CRP (Observed)

The change from baseline for immunoglobulins and change from baseline in anti-dsDNA and CRP for subjects who were positive at baseline (anti-dsDNA $\geq$ 30 IU/mL and CRP $\geq$ 4 mg/L) will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. Similar analyses as described in Section 11.3.2 of the RAP will be carried out.

2.7. Change from Baseline in B Cell Subsets (Observed)

The change from baseline in B cell subsets will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. Similar analyses as described in Section 11.3.2 of the RAP will be carried out.

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Division: Worldwide Development

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

Compound Number: GSK1550188

Effective Date: 16-FEB-2018

Description: This is a multi-center study to evaluate the safety, pharmacokinetics (PK), and efficacy of belimumab intravenous (IV) in pediatric patients 5 to 17 years of age with active systemic lupus erythematosus (SELENA SLEDAI score ≥ 6 at Screening). The study will consist of three phases: a 52-week randomized, placebo-controlled, double-blind phase; a long term open label continuation phase; and a long-term safety follow up phase. Enrolment will be staggered by age cohorts to allow safety and PK analysis. Subjects will be randomized to belimumab or placebo while continuing to receive background standard therapy throughout the study. The randomization of Cohort 3 will be stratified by age and SELENA SLEDAI score. Efficacy will be measured by the SLE Responder Index (SRI) at Week 52, SELENA SLEDAI score, PRINTO/ACR Juvenile SLE Response Evaluation, Physician's Global Assessment (PGA) and BILAG A and B organ domain scores. In addition, corticosteroid use, flares, and biomarkers (immunoglobulins, complement, autoantibodies, B-cells) will be assessed. Safety will be assessed by adverse events, clinical laboratory evaluations, vital signs, immunogenicity and pharmacokinetics.

Subject: Systemic Lupus Erythematosus (SLE), belimumab, BENLYSTA (belimumab), efficacy, safety, placebo, SELENA SLEDAI, PRINTO/ACR Juvenile SLE Response Evaluation, BILAG, PedsQL

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ABBREVIATIONS

aCL	Anti-cardiolipin
ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
Anti-dsDNA	Anti-double-stranded DNA
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BILAG	British Isles Lupus Assessment Group
CI	Confidence Interval
CRF	Case Report Form
CRP	C Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DO/TF=NR	Dropout/Treatment Failure = Non-Responder
DRE	Disease Related Event
GEE	Generalized Estimating Equations
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscularly
IQR	Interquartile range
ITT	Intention-to-Treat
IV	Intravenous
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantitation
LS	Least Squares
MCID	Minimally Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non-melanoma skin cancer
NR	Non-Responder
ParentGA	Parent's Global Assessment
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PedsQL- GC	Pediatric Quality of Life Inventory – Generic Core Scale
PedsQL-Fatigue	Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PRINTO	Pediatric Rheumatology International Trials Organization
PSAP	Program Safety Analysis Plan
PSRQ	Possible Suicidality Related Questionnaire

PT	Preferred Term
QOD	Every Other Day
RAP	Reporting and Analysis Plan
RBC	Red blood cells
SAE	Serious Adverse Event
SC	Subcutaneously
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborative Clinics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRI	SLE Responder Index
SRT	Safety Review Team
SUPP	Supplemental
TF	Treatment Failure
TLFs	Tables, Listings and Figures
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
BENLYSTA (belimumab)	PASS 2005
	SAS

1. INTRODUCTION

BEL114055 is a multi-center study to evaluate the safety, pharmacokinetics (PK), and efficacy of belimumab intravenous (IV) in pediatric patients 5 to 17 years of age with active systemic lupus erythematosus (SLE) (Safety of Estrogen in Lupus National Assessment SLE Disease Activity Index [SELENA SLEDAI] Screening score ≥6).

This study is divided into three phases: a blinded treatment phase (Part A), followed by an open-label safety follow up phase for subjects who complete Part A (Part B), and/or a long-term safety follow-up phase for subjects who withdraw from Part A or Part B at any time (Part C).

Part A is a randomized, parallel group, double-blind study to evaluate the efficacy, safety and pharmacokinetics of 10 mg/kg belimumab IV administered at Weeks 0, 2, and 4, and then every 4 weeks, compared with placebo over a 52-week treatment period in pediatric subjects (aged 5 to 17 years) with active SLE (defined as SELENA SLEDAI score ≥6).

Part B is an optional open-label belimumab continuation phase for subjects who complete Part A of the study, regardless of treatment assignment. All subjects will receive belimumab at monthly infusion visits. Subjects participating in Part B will continue to be monitored for safety and efficacy.

Part C is an optional long term safety follow up phase for any subject who discontinues Part A or Part B at any time. Subjects participating in Part C will continue to be monitored for safety and limited efficacy.

This reporting and analysis plan (RAP) documents the planned analyses for Part A of the BEL114055 study.

This RAP is based upon the following study documents:

- Study Protocol Amendment Version 6 (December 6, 2016)
- Final Case Report Form (CRF) (April 25, 2016)
- Program Safety Analysis Plan (PSAP) Version 5 (December 13, 2017). Note: for reporting purposes, the most current version of the PSAP and associated MedDRA version at the time of database release (DBR) will be used.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

- Evaluate the safety and tolerability of belimumab in the pediatric SLE population

- Evaluate the pharmacokinetics of belimumab in the pediatric SLE population.

- Evaluate the efficacy of belimumab in the pediatric SLE population.

- Evaluate the effects of belimumab on the quality of life in the pediatric SLE population.

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the SLE Responder Index (SRI) response rate at Week 52 of Part A. A response is defined as:

- ≥ 4-point reduction from baseline in SELENA SLEDAI score,

AND

- No worsening (increase of <0.30 points from baseline) in Physician's Global Assessment (PGA),

AND

- No new British Isles Lupus Assessment Group (BILAG) A organ domain score or two new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52 of Part A).

2.2.2. Major Secondary Efficacy Endpoints

- Proportion of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation criteria for improvement in juvenile SLE at Week 52 using two different PRINTO/ACR Juvenile SLE Response Evaluation definitions of improvement
  a. At least 50% improvement in any 2 of 5 endpoints below and no more than 1 of the remaining worsening by more than 30%
  b. At least 30% improvement in 3 of 5 endpoints below and no more than 1 of the remaining worsening more than 30%.
     I. Percent change from baseline in Parent's Global Assessment (ParentGA) at Week 52.
     II. Percent change from baseline in PGA at Week 52.
     III. Percent change from baseline in SELENA SLEDAI score at Week 52.
     IV. Percent change from baseline in Pediatric Quality of Life Inventory (PedsQL) Physical Functioning Domain at Week 52
     V. Percent change from baseline in proteinuria at Week 52 (g/24hour equivalent by spot urine protein to creatinine ratio (mg/mg)).
- Percent change from baseline in ParentGA at Week 52
- Percent change from baseline in PGA at Week 52
- Percent change from baseline in SELENA SLEDAI at Week 52
- Percent change from baseline in PedsQL Physical Functioning Domain Score at Week 52
- Percent change from baseline in proteinuria at Week 52
- Proportion of subjects with a sustained SRI response

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- Proportion of subjects with a sustained ParentGA response

2.2.3. Other Study Endpoints

- Safety of belimumab

- Observed serum concentrations of belimumab

- PK comparison with adult PK

- Quality of life evaluated using Pediatric Quality of Life Inventory – Generic Core (PedsQL - GC) and PedsQL Multidimensional Fatigue Scale (PedsQL – Fatigue)

- Evaluation of biological markers

2.3. Statistical Hypotheses

The study is designed to descriptively evaluate the efficacy and safety of belimumab, and as such no formal statistical hypothesis testing is planned.

3. STUDY DESIGN

This is a multi-center study to evaluate the safety, efficacy and pharmacokinetics of belimumab plus background standard therapy in at least 70 pediatric subjects 5 years to 17 years of age with active SLE. The study will consist of three separate phases:

- Randomized, placebo-controlled, double-blind 52-week treatment phase (Part A)

- Long term belimumab open label safety follow up for any subject who completes Part A (Part B)

- Long term safety follow-up phase for subjects who withdraw from Part A or Part B at any time (Part C)

Part A is a randomized, placebo-controlled, double-blind study to evaluate the efficacy, safety, and pharmacokinetics of 10 mg/kg belimumab IV in pediatric subjects with active SLE (SELENA SLEDAI score $\geq$ 6). In this study, at least 70 subjects will be randomized in three cohorts with Cohort 3 stratified by age (5-11 years vs. 12-17 years) and screening SELENA SLEDAI scores (6-12 vs. $\geq$ 13). Cohorts 1 and 2 will be randomized in a 5:1 ratio, and Cohort 3 subjects will be randomized in a 1:1 ratio to receive belimumab or placebo for 48 weeks on a background of standard of care. Cohort 1 will consist of the first 12 subjects, age 12 to 17 years. No further enrolment of the study will proceed until after the PK of this cohort is evaluated. Once the PK and safety profile of Cohort 1 is evaluated and any potential dose adjustments are determined as a result of this analysis, additional subjects 12-17 years of age will then be enrolled in Cohort 3. In addition, at this point, Cohort 2 will enroll at least 10 subjects 5-11 years of age at the dose determined from the PK analysis of Cohort 1. Once the PK and safety profile of Cohort 2 is evaluated and any potential dose adjustments are determined as a result of this analysis, additional subjects 5-11 years of age will then be enrolled in Cohort 3.

Belimumab will be infused over a minimum of 1 hour on Days 1, 15, 29, and then every 28 days through the Week 48 (Day 337) visit. See Section 9.4.4 and Appendix 17 for Study Day convention. All subjects will continue to receive their standard SLE therapy with progressive restrictions on the changes that are permitted throughout the 52-week randomized period. Enrolment will be staggered to allow PK analysis of the first 2 age cohorts (Cohorts 1 and 2).

Safety monitoring and PK analysis from the initial 12 subjects from Cohort 1 will be used to confirm or adjust the belimumab dose for the remaining subjects enrolling in Cohort 2 and 3.

- **Cohort 1:** The first 12 subjects aged 12 to 17 years of age will be randomized in a 5:1 ratio to belimumab 10 mg/kg (n=10) or placebo (n=2) on a background of standard of care for 48 weeks. After all 12 subjects in Cohort 1 have received at least 8 weeks of treatment, safety and PK analysis will be conducted. Cohort 1 subjects will continue in the treatment period while the Study Team progresses the PK analysis, but no other subjects will enroll until the PK analysis is completed. If the belimumab dose is adjusted because of the PK analysis, the Cohort 1 subjects will continue the study with the adjusted dose. Enrolment will be initiated for Cohort 2 (at least the first 10 subjects age 5 to 11 years) and Cohort 3 (subjects age 12-17 years) after the Cohort 1 PK analysis is completed.

- **Cohort 2**: At least the first 10 subjects aged 5 to 11 years will be randomized in a 5: 1 ratio to belimumab (10 mg/kg confirmed or adjusted dose) or placebo for 48 weeks on a background of standard of care. After all subjects in Cohort 2 have received at least 8 weeks of treatment, safety and PK analysis will be conducted. Administration of study agent in Cohort 2 will continue while safety monitoring and PK analysis progresses but no additional subjects ages 5-11 will be enrolled into the study until after the safety and PK analysis have been completed. If the belimumab dose is adjusted, the Cohort 2 subjects aged 5 to 11 years will continue with the dose-adjusted blinded treatment.

- **Cohort 3**: This cohort will consist of at least 48 subjects aged 5 to 17 years old. These subjects will be randomized in a 1:1 ratio to belimumab (10 mg/kg confirmed or adjusted dose) or placebo on a background of standard of care for 52 weeks. Randomization will be stratified by age group and screening SELENA SLEDAI scores (6-12 vs. ≥ 13). Subjects aged 12 to 17 years will begin enrolment after Cohort 1 enrolment PK analysis is completed. Subjects aged 5 years to 11 years will begin enrolment after Cohort 2 safety and PK analysis is completed.

Two separate blinded dose assessment meetings will be held in which members of the GSK Safety Review Team (SRT) will review the safety, tolerability and preliminary PK data obtained from Cohorts 1 and Cohorts 2, respectively. The objective of these meetings will be to either confirm the initial dose or to adjust the dose if a substantial difference in exposure is observed compared to adult Phase 3 PK data based on 10 mg/kg dosing. An assessment of any safety signal may also factor into the decision to confirm or adjust the initial dose. The SRT will review the available blinded safety, key biomarker and PK data and a recommendation by consensus will be made regarding dose confirmation or adjustment and the initiation of the subsequent cohorts. The PK analysis

and recommendation regarding dose confirmation or adjustment will be reviewed by the IDMC. Final decisions will be made by the sponsor considering the recommendation from the IDMC and independent pharmacokineticist. The Study Team will remain blinded to treatment during these dose assessments. Decisions regarding dose confirmation or adjustment will be summarized and distributed to study team members, investigators, the IDMC and IRBs and/or regulatory authorities according to local regulations.

A target enrolment of at least 70 subjects will be randomized. In Cohorts 1 and 2, subjects will be randomized in a 5:1 ratio (belimumab:placebo), and the remaining subjects (at least 48) in Cohort 3 will be randomized in a 1:1 allocation ratio. Therefore, at least 42 subjects will be randomized to belimumab and 28 to placebo. The study will also enroll at least 14 subjects who are younger than 13 years of age. Enrollment will ensure that at least 50% of the randomized subjects will have presented with SELENA SLEDAI $\geq$ 8 at screening.

Subjects may withdraw or discontinue from the study at any time for any reason. All subjects withdrawing from Part A of the study will return for an exit visit 4 weeks after their last dose of study agent, and then continue in the safety follow-up period (Part C) where safety evaluations and limited disease activity assessments will be performed for up to 10 years from the first administration of study agent or open label belimumab. Subjects choosing not to continue in Part A or participate in Part B and who do not wish to be monitored in the safety follow-up period (Part C), will return for a safety follow-up visit approximately 8 weeks following their last dose of study agent. Additional withdrawal criteria are presented in Section 4.4 of the protocol.

Subjects completing the randomized, double-blind, placebo-controlled phase of the study may continue to Part B of the study, the open label safety follow up and receive monthly belimumab treatment.

The study sponsor will remain blinded to subjects' treatment until all data from the Part A of the study are locked and the data are unblinded. Clinical sites will remain blinded until after the results of Part A are publicly disclosed.

Part B: Open Label Belimumab Continuation

Subjects who complete 48 weeks of belimumab or placebo on a background of standard of care and the Week 52 assessments, regardless of treatment assignment, may progress to Part B of the study, the open-label belimumab continuation phase. In this phase, all subjects will receive belimumab (10 mg/kg or adjusted dose) at monthly infusion visits. The Week 52 administration will be considered the 1st administration of the open-label continuation phase. Safety will be assessed at each monthly visit, and disease activity assessments will be performed every 6 months. Subjects will continue in Part B of the study for up to 10 years from the first administration of belimumab. However, the study may conclude earlier if all subjects continuing belimumab treatment have received at least 5 years of treatment with belimumab (Part B or a combination of Part A and Part B) and if there are 15 or fewer subjects continuing to receive belimumab in the study (See Section 5.7.1 of the protocol, Study Conclusion). Any subject who withdraws during the continuation phase will return for an exit visit at 4 weeks after their last dose and proceed

to Part C, safety follow-up phase. Subjects choosing to discontinue from the study and not be monitored in the safety follow-up period (Part C) will return for a follow-up visit approximately 8 weeks following their last dose of open label belimumab.

Part C Safety Follow-up Phase

Part C will include any subject who discontinues study agent from Part A or open label belimumab from Part B. These subjects will return for safety follow up visits in Part C monthly for 3 months and then annually after their last dose of study agent or open label belimumab. In Part C safety evaluations and limited disease activity assessments will be performed for up to 10 years from the first administration of study agent or open label belimumab. However, the study may conclude earlier if all subjects continuing belimumab treatment have received at least 5 years of treatment with belimumab (Part B or a combination of Part A and Part B) and if there are 15 or fewer subjects continuing to receive belimumab in the study (See Section 5.7.1 of the protocol, Study Conclusion). For subjects that withdraw from the study 8 weeks or less from the last administration of IV belimumab, an 8 Week Follow-up Visit (and a 16 Week Follow-up Visit post administration for female subjects of child-bearing potential) must be performed and recorded in the IVR system and the eCRF. An Exit Visit may be conducted by phone for any subject who withdraws completely from the study while in Part C.

A schematic of the study is provided in Figure 1

Figure 1   BEL114055 Study Schematic
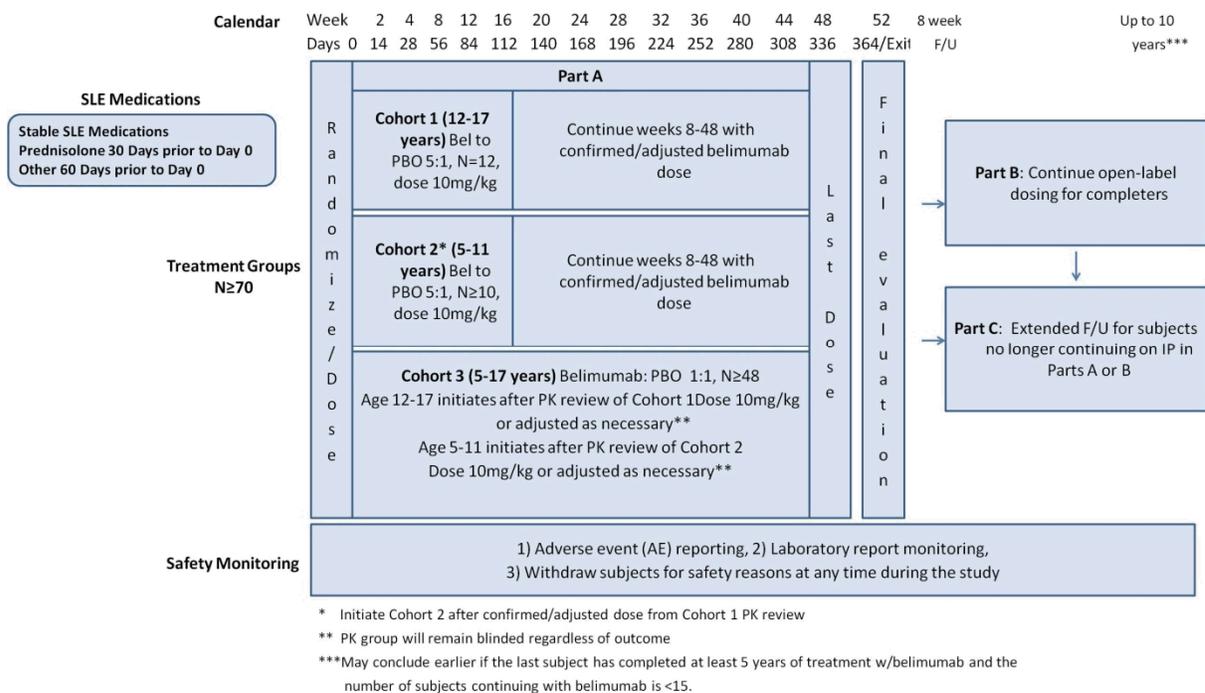
4. PLANNED ANALYSES

4.1. Interim Analyses

Two separate blinded dose assessments will be made by the SRT based on safety, tolerability and preliminary PK data obtained from Cohorts 1 and Cohorts 2, respectively. The study dose may be revised based upon this review.

An independent data monitoring committee (IDMC) will conduct safety and PK data reviews throughout the study. The PK analysis and decision regarding dose confirmation or adjustment will be reviewed by the IDMC.

All interim analyses are described in the BEL114055 IDMC RAP.

The GSK SRT performs blinded in stream adjudication of subject level safety data for Adverse Events of Special Interest (AESIs; serious and non-serious) in accordance with GSK Standardized Operating Procedures (SOPs) and the Belimumab Program Safety Analysis Plan (PSAP) and as outlined in Section 12.3 and Appendix 15. AESIs include malignancy; serious hypersensitivity and post-infusion/injection systemic reactions; potential opportunistic infections; other infections of interest but not generally considered opportunistic, i.e., Mycobacterium tuberculosis and Herpes Zoster; suicide/self-injury; and fatalities.

AESIs are flagged in the clinical trial database, according to SRT adjudication. The SRT performs a blinded periodic review of instream study data (at least every 3 months), reviewing the cumulative incidence of AEs, SAEs, and adjudicated AESIs. These periodic reviews of cumulative adverse event incidence are compared with previous SRT reviews and where appropriate, the pivotal SLE pooled data to assess for any new safety signals.

4.2. Final Analysis

There will be three database locks for this study, corresponding to the primary analysis of Part A, the follow-up analysis of Part B and the follow-up analysis of Part C. Following completion of the double-blind treatment phase (Part A) of the study, this portion of the study database will be locked and the primary analysis will be performed. Only outputs from Part A will be prepared and included in this Clinical Study Report. Part B and Part C of the study will be summarized separately at a later date, and the final analysis performed after completion of each of the phases. Periodic analyses of these two phases may be performed before their completion, but following primary analysis of the double-blind treatment phase (Part A).

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

As juvenile SLE is a rare disease, recruitment of subjects will be challenging. The original decision to enroll 100 subjects was based on feasibility estimations. The following is a description of what statistical information these 100 subjects would have provided. Combining the subject cohorts, a total of 100 subjects would have been

randomized. In the first two cohorts, at least 24 subjects would have been randomized in a 5:1 ratio (belimumab:placebo), and the remaining 76 subjects would have been randomized in a 1:1 allocation ratio. Therefore, 58 subjects would have been randomized to belimumab and 42 to placebo. Using the methods of PASS 2005 [Hintze, 2006] for the precision of a confidence interval around a single proportion; a sample size of 42 would have produced a 95% confidence interval around the sample proportion ± 0.15191 when the estimated proportion of subjects attaining the primary efficacy response at Week 52 is 0.39 (for placebo), and a sample size of 58 would have produced a 95% confidence interval around the sample proportion ± 0.12793 when the estimated proportion is 0.51 (for belimumab).

5.2. Sample Size Sensitivity

The estimated proportions cited above are the Week 52 results for placebo and belimumab 10mg/kg from the combined Phase 3 studies in adults with SLE. The estimated proportions of subjects attaining the primary efficacy response at Week 52 from the 76 week Phase 3 studies in adults with SLE were 34% and 43% for placebo and belimumab 10 mg/kg, respectively, and for the Week 52 study in adults with SLE were 43% and 57%.

Sample size sensitivity calculations were performed considering these results. In this study, for estimated proportions ranging from 0.31 to 0.69, the precision for the 95% confidence interval ranges from approximately 0.12 to 0.13 when the sample size is 58, and from approximately 0.14 to 0.15 when the sample size is 42.

5.3. Sample Size Re-estimation

As a consequence of continuing enrolment challenges, despite an increase in the number of participating clinical sites worldwide and concentrated outreach efforts, a sample size reduction based on the extrapolation of recruitment performance to January 2017 was agreed to with EMA/PDCO and FDA.

A reduction in subjects from 100 to 'at least 70', although affecting the sample size calculations, will not alter the fact that this study was designed to descriptively evaluate the efficacy and safety of belimumab in pediatric SLE.

In the first two cohorts, at least 22 subjects will be randomized in a 5:1 ratio (belimumab:placebo), and the remaining subjects (at least 48) will be randomized in a 1:1 allocation ratio. Therefore, approximately 42 subjects will be randomized to belimumab and 28 to placebo. Using the methods of PASS 2005 [Hintze, 2006] for the precision of a confidence interval around a single proportion; a sample size of 28 will produce a 95% confidence interval around the sample proportion ±0.18143 when the estimated proportion of subjects attaining the primary efficacy response at Week 52 is 0.39 (for placebo), and a sample size of 42 will produce a 95% confidence interval around the sample proportion±0.15286 when the estimated proportion is 0.51 (for belimumab).

Sample size sensitivity calculations were performed considering the primary efficacy response at Week 52 in the Phase 3 studies in adults with SLE. In this study, for estimated proportions ranging from 0.31 to 0.69, the precision for the 95% confidence

interval ranges from approximately 0.14 to 0.15 when the sample size is 42 (Belimumab), and from approximately 0.17 to 0.20 when the sample size is 28 (Placebo).

6.   ANALYSIS POPULATIONS

Screened

The screened population is defined as all subjects who were screened for the trial, irrespective of whether they were randomized or not. The screened population will be presented overall, not split into treatment groups.

Randomized

The randomized population is defined as all subjects who are randomized in Part A. 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.

Intent-to-Treat (ITT)

The analysis of the double-blind treatment phase (Part A) will be performed on the intent-to-treat (ITT) population. The ITT population is defined as all subjects who are randomized and treated with at least one dose of study agent in Part A. Summaries using the ITT population will group subjects according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

Completers

The completers population is defined as all subjects who complete all 52 weeks of Part A. A sensitivity analysis will be performed on the completers population.

As-Treated

The as-treated population is defined as all subjects who receive at least one dose of study treatment in Part A. Summaries using the as-treated population will group subjects according to the actual treatment administered to the subject. If a subject receives an incorrect treatment, the as-treated analysis will be performed according to the treatment that the subject receives most of the time (>50% of the time).

The as-treated population will only be used for a sensitivity analyses of the primary efficacy endpoint if more than 15% of subjects received the incorrect treatment.

Per-Protocol (PP)

Prior to breaking the blind, data for all subjects in the ITT Population will be reviewed to identify protocol violations which could affect the primary endpoint. Subjects with violations with the potential to impact the efficacy analyses will be excluded from the Per-Protocol (PP) Population.

The PP population will be used only for a sensitivity analysis of the primary efficacy endpoint if more than 15% of subjects had a violation that could affect the primary efficacy endpoint.

Pharmacokinetic (PK)

The pharmacokinetic (PK) population will comprise all subjects included in the As-Treated population for whom at least one post belimumab treatment PK sample was obtained and analyzed. Summaries using this population will be based on the actual treatment received if this differs from that to which the subject was randomized.

6.1. Analysis Datasets

Drop-out/Treatment Failure = Non-responder (DO/TF=NR)

The DO/TF=NR dataset will be used for all efficacy (DO/TF) endpoints, including the primary efficacy endpoint and each of the three components of the primary efficacy endpoint. The basic premise of the DO/TF=NR analysis is that a subject who withdraws and does not have a visit within ±28 days of the Day 365 (Week 52) visit, i.e., a dropout (see Section 9.2 for further detail), and/or uses a prohibited medication or a non-allowed dose of a restricted medication resulting in treatment failure designation will be considered a non-responder in the analysis for Part A.

LOCF

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

If a subject withdraws or takes a protocol-prohibited medication or a dose of allowable (but protocol restricted) medication that results in treatment failure designation (see Section 9.1) prior to the study visit being evaluated, the LOCF value will be handled by using the result from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

Observed

Observed data are the data collected or observed for the subject with no imputation for missing data.

7. TREATMENT COMPARISONS

The primary comparison of interest is the comparison between belimumab and placebo for the SRI response rate at Week 52 in the ITT population using the DO/TF=NR imputation. However, since the study was not sized based on statistical power considerations, no p-values will be presented.

7.1. Data Display Treatment and Other Sub-Group Descriptors

Table 1 gives the treatment descriptors, colors and symbols that will appear on all tables, listings, and figures for Part A.

Table 1   Treatment Descriptors, Colors, and Symbols for Reporting in Part A

Treatment Descriptor	Color	SAS Color	Line Style	Symbol
Belimumab 10mg/kg	Blue	CX0000FF	Dashed	Triangle (filled)
Placebo	Black	CX000000	Solid	Circle (open)

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 Section 18.2, which will follow the Benlysta program standards and, as far as possible, follow the agreements proposed by the GSK Integrated Data Standards Library (IDSL).

Unless otherwise stated, the following will apply:

- Continuous variables will be summarized with mean, median, standard deviation (SD), minimum, 25th percentile, 75th percentile, 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.

- Where means or medians are displayed graphically, standard error bars or interquartile ranges (IQRs) will be presented, respectively.

- Percentages will be calculated using the number of non-missing observations as the denominator.

- 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. A count of zero will have no corresponding percentage.

- When the data are summarized by visit, only scheduled visits will be presented.

- Listings will be sorted by treatment group, investigator number, subject number and visit (where appropriate).

Distributions will be reviewed and if there is significant evidence of skewness, medians will be used as the summary measure instead of means; in this case the corresponding figures will display medians.

8.1.　　Multi-center Studies

This is a multi-center trial and subjects will be centrally randomized. Analyses will not be adjusted for center.

8.2.　　Other Strata and Covariates

Cohort 1 will include subjects aged 12-17 years only. Cohort 2 will include subjects aged 5-11 years only. Randomization of subjects in Cohort 3 will be stratified by subjects' age at screening (5-11 years vs. 12-17 years) and screening SELENA SLEDAI score (6-12 vs. $\geq$13). Analyses will be adjusted for baseline age (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13).

8.3.　　Examination of Subgroups

The comparison of the primary efficacy endpoint in Part A between belimumab and the placebo group will be performed by the following subgroups:

- Baseline Age (5-11 years vs. 12-17 years). Note: subjects screened at the age of 17 may be 18 at baseline; these subjects will be included in the 12-17 years category and a footnote will be added to the Stratification Factors table.

- Baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13)

- Baseline SELENA SLEDAI score ($\leq$9 vs. $\geq$10)

- Baseline SELENA SLEDAI score ($\leq$7 vs. $\geq$8)

- Baseline C3/C4 levels and anti-double-stranded DNA (anti-dsDNA) (at least one C3/C4 low and anti-dsDNA positive vs. other)

8.4. Multiple Comparisons and Multiplicity

Since the study was not sized based on statistical power considerations, no formal statistical hypothesis testing is planned, and no p-values will be presented. Hence no adjustment for multiple comparisons is required.

9. DATA HANDLING CONVENTIONS

This section describes data handling conventions for the efficacy data in Part A; this includes the handling of treatment failures, dropouts, and missing data for the SRI endpoint and each of the three components that make up the SRI endpoint, along with the key secondary efficacy endpoints in Part A. Data handling conventions for the time to severe flare are covered in Section 11.4.2.1. For other endpoints, handling of withdrawals and missing data will be described in Section 11.

9.1. Treatment Failures

A treatment failure is defined as any subject who receives a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that results in treatment failure designation (see Section 5.6.1 of the study protocol) **prior** to Day 365 (Week 52) Visit (Part A only).

The treatment failure rules are detailed in the protocol (Section 5.6) with the programming rules further clarified in Appendix 14 – Treatment Failure Rules.

9.2. Dropouts

For the purposes of the analysis imputation, a dropout is defined as any subject who withdraws from the study prior to the Day 365 (Week 52) Visit and has no visit within ± 28 days of Day 365 (excluding follow-up visits).

This rule is applied consistently across all efficacy (DO/TF) endpoints. The assessment of whether or not a subject had a visit within the ± 28 day of Week 52 is performed at the domain level (e.g., a subject who had visit within 28 days for SLEDAI but not SLICC would be assessed on their observed data for SLEDAI but would be considered a dropout [non-responder] in SLICC).

Any subject not otherwise classified as a non-responder who misses the Day 365 (Week 52) visit will be handled as follows:

- If the subject does not have a visit within ± 28 days of Day 365 (Week 52) Visit, the subject will be considered a dropout for the Week 52 analysis.

- If a subject has at least 1 visit within ± 28 days of Day 365 (Week 52) Visit, the data from the visit closest to Day 365 (Week 52) Visit will be used for the Week 52 analysis.

- If a subject has 2 visits with equal distance within ± 28 days of Day 365 (Week 52) Visit, the data from the visit prior to Day 365 (Week 52) Visit will be used for the Week 52 analysis.

- If a subject has a visit within the required window, but partial data of the endpoint are missing (including individual items of any component of the primary endpoint), LOCF will be used for the missing item or component. This will be modified for items in the BILAG for which scoring is dependent on both the actual score and the change from the previous visit (see Section 9.3.6 for details).

9.3. Missing Data Rules

9.3.1. Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listings.
Concomitant Medications	• Where CMSTDT is completely missing but CMENDT is on or after Day 1, the CMSTDT will be imputed as TRTSDT. • Where CMSTDT is completely missing and CMENDT is missing and CMONGO = "Y", the CMSTDT will be imputed as TRTSDT and the medication will be considered as ongoing. Medication End Date (CMENDT) • Missing end dates for concomitant medications will not be imputed, and the medication will be considered ongoing.
Adverse Events	• The eCRF does not allow for the possibility of partial AE dates. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. AEs with missing start dates will be considered as treatment emergent.

9.3.2. Partial Dates

Element	Reporting Detail
Concomitant Medications	Medication Start Date (CMSTDT) CMSTDT is imputed as 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 CMSTDT is imputed with JAN

25

Element	Reporting Detail
	for missing month and 01 for missing day, whatever is applicable.
	Medication End Date (CMENDT)
	• If month and year are present, then set to the earlier of (last contact date and last day of that month).
	• If only year present, then set to the earlier of (31DEC of the year and last contact date).
SLE Disease Duration	• For records where month and day are missing for start 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.

9.3.3. Proteinuria

The LOCF method will be employed for subjects with missing data on proteinuria at the Part A visit being evaluated for the percent change from baseline endpoint that is included in the PRINTO endpoint. All other proteinuria endpoints will use Observed data.

Specifically, if a subject misses the visit being evaluated, the missing data will be handled by using the last observation available. However, if a subject withdraws or is a treatment failure prior to the visit being evaluated, the proteinuria data will be handled by using the result from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.4. SRI and PRINTO/ACR

For the SRI endpoint and its components, any subject who is classified as a treatment failure will be considered a non-responder for the primary efficacy analysis and the supportive analyses of the primary efficacy endpoint in Part A. For the PRINTO/ACR endpoint and its components, any subject who is classified as a treatment failure will be considered a non-responder for the analysis and supportive analyses of the PRINTO/ACR juvenile SLE criteria. This imputation method is referred to as "dropout/treatment failure = non-responder" (DO/TF=NR).

9.3.5. SELENA SLEDAI

The LOCF method will be employed for subjects with missing data on the SELENA SLEDAI at the Part A visit being evaluated.

Specifically, if a subject misses a regularly scheduled visit or if partial data are missing from a subject's visit, the missing data will be handled by using the last observation (or item) carried forward method. For example, if the data on one or more items of the 24 SELENA SLEDAI questions are missing, the last available answer(s) to the

corresponding question(s) from the most recent visit where the corresponding item(s) are non-missing will be assigned to the missing item(s) in order to obtain a total score.

If a subject misses an entire visit, the missing data on SELENA SLEDAI will be handled by using the last score from the previous visit. However, if a subject withdraws or is a treatment failure prior to the study visit being evaluated, the SELENA SLEDAI data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.6.   BILAG

The LOCF method will be employed for subjects with missing data on the BILAG at the Part A visit being evaluated.

Specifically, if a subject misses a regularly scheduled visit or if partial data are missing from a subject's visit, the missing data will be handled by using the last observation (or item) carried forward method. For example, if the data on one or more items of the 86 BILAG questions are missing, the last available answer(s) to the corresponding question(s) from the previous visit will be assigned to the missing item(s) in order to obtain a score for each organ system domain.

For the following items, both the actual value from the last visit and the change observed at that last visit will be carried forward: BILAG dipstick (BIL0171), BILAG 24-hour urinary protein (BIL0172A), BILAG creatinine (BIL0175), and BILAG creatinine clearance (BIL0176).

If a subject misses an entire visit, the missing data on BILAG will be handled by using the last score from the previous visit. However, if a subject withdraws or is a treatment failure prior to the study visit being evaluated, the BILAG data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.7.   PGA

The LOCF method will be employed for subjects with missing data on PGA score at the Part A visit being evaluated.

Specifically, if a subject misses the visit being evaluated; the missing data will be handled by using the last observation available. However, if a subject withdraws or is a treatment failure prior to the visit being evaluated, the PGA data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.8. ParentGA

The LOCF method will be employed for subjects with missing data on ParentGA score at the Part A visit being evaluated.

Specifically, if a subject misses the visit being evaluated; the missing data will be handled by using the last observation available. However, if a subject withdraws or is a treatment failure prior to the visit being evaluated, the ParentGA data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.9. Pediatric SLICC/ACR Damage Index

The LOCF method will be employed for subjects with missing data on the Pediatric SLICC/ACR Damage index at the Part A visit being evaluated.

Specifically, if a subject misses the Week 52/Exit visit or if items are missing; the missing data will be handled by using the last observation (or item) carried forward method. However, if a subject withdraws or is a treatment failure prior to the visit being evaluated, the SLICC data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first.

9.3.10. PedsQL GC Domains and Total Score

The LOCF method will be employed for subjects with missing data on PedsQL GC scores at the Part A visit being evaluated.

Specifically, if a subject misses a regularly scheduled visit or if partial data are missing from a subject's visit, the missing data will be handled by using the last observation carried forward method. For example, if the scores for one or more of the PedsQL GC domains or total score are missing, the missing data will be handled by using the last scores from the previous visit in order to obtain a score for each domain and the total score. If a subject misses an entire visit, the missing data will be handled by using the last scores from the previous visit. However, if a subject withdraws or is a treatment failure prior to the study visit being evaluated, the PedsQL GC data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first. LOCF will only be applied to the domain and total scores (when it is not possible to calculate them); it will not be applied to individual items within a domain.

9.3.11. PedsQL Multidimensional Fatigue Domains and Total Score

The LOCF method will be employed for subjects with missing data on PedsQL multidimensional fatigue scores at the Part A visit being evaluated.

Specifically, if a subject misses a regularly scheduled visit or if partial data are missing from a subject's visit, the missing data will be handled by using the last observation carried forward method. For example, if the scores for one or more of the PedsQL multidimensional fatigue domains or total score are missing, the missing data will be handled by using the last scores from the previous visit in order to obtain a score for each

domain and the total score. If a subject misses an entire visit, the missing data will be handled by using the last scores from the previous visit. However, if a subject withdraws or is a treatment failure prior to the study visit being evaluated, the PedsQL multidimensional fatigue data will be handled by using the score from the last visit on or prior to the date of withdrawal or date of treatment failure, whichever is first. LOCF will only be applied to the domain and total scores (when it is not possible to calculate them); it will not be applied to individual items within a domain.

9.4. Derived and Transformed Data

Data cut-off rules for Part A, as derived in the SDTM datasets, are given in Appendix 1 - Data Cut-off Rules for Part A for reference.

9.4.1. Baseline

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

The baseline value of a variable will be defined as the value of the variable measured at Day 1 of Part A prior to dosing, unless otherwise specified.

If timing of assessment is not collected on Day 1, then the assessment will be assumed to be prior to dosing. Noted exceptions to this rule are concomitant medications and adverse events; these will be considered as being on-treatment and treatment-emergent, respectively, if the start date occurs on the first day of dosing.
If there are multiple results on Day1 prior to dosing, the latest result will be used (e.g., if multiple lab tests are performed).

If a Day 1 value is not available, the last available value prior to Day 1 will be used in the calculation of baseline.

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

9.4.2. Change from Baseline

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

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

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

9.4.3. Percent Change from Baseline

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

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

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

9.4.4. Study Day

For Part A, Study Day is the number of days from the treatment start date to a study date of interest (e.g., adverse 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.

See Appendix 17 Study Day for Reporting for comparison to protocol definitions of Study Day and CDISC standards.

9.4.5. Analysis Visit and Analysis Visit Number

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

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

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

Analysis Visit	Analysis Visit Number	Target Study Day[1]	Interval Start Day	Interval End Day
Screening	10	-34	na	na
Double-Blind visits:				
Baseline	20	1	na	na
Week 2	30	15	2	21
Week 4	40	29	22	42
Week 8	50	57	43	70
Week 12	60	85	71	98
Week 16	70	113	99	126
Week 20	80	141	127	154
Week 24	90	169	155	182
Week 28	100	197	183	210
Week 32	110	225	211	238
Week 36	120	253	239	266
Week 40	130	281	267	294

Analysis Visit	Analysis Visit Number	Target Study Day[1]	Interval Start Day	Interval End Day
Week 44	140	309	295	322
Week 48	150	337	323	350
Week 52	160	365	351	378
8 Week Follow-up[2]	180	393	na	na
16 Week Follow-up[3]	185	421	na	na

[1]Study Day with Baseline/Treatment Start Date as Day 1.

[2]The 8-week follow-up occurs 4-weeks after early withdrawal or 8 weeks after last dose for subjects who withdraw from Part A or B and do not enter Part C.

[3]Female subjects of child-bearing potential will be provided with a pregnancy test and contacted by phone approximately 16 weeks after last dose.

9.4.6. Analysis Age

Screening Age

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

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

Screening age (years) will be calculated as:

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

Screening age in months will be calculated as follows:

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

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

Age in months – (Age in years * 12)

Baseline Age

Baseline age (years) will be calculated as:

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

9.4.7.   Body Mass Index (BMI)

Baseline body mass index (BMI) will be calculated from baseline weight and height measurements as:

$$BMI\ (kg/m^2) = weight\ (kg)/[height\ (m)]^2$$

Since height is collected in centimetres (cm), it needs to be converted to meters (m) by dividing by 100 before using it in the formula above. If weight or height is missing, then BMI will be missing.

9.4.8.   Race Hierarchy

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
- African American/African Heritage
- White/Caucasian

For example, if African American/African Heritage and Asian are both checked, then the subject will be assigned as Asian since it appears highest in the list. Race assigned based on this hierarchical rule will be applied to all analyses related to race. 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.

9.4.9.   SLE Disease Duration

SLE disease duration is defined as

(Treatment Start date – SLE diagnosis date + 1)/365.25

If either date is missing, then SLE disease duration will be missing.

9.4.10.   ACR Criteria at Baseline

- Subjects were required to meet at least 4 of the 11 ACR criteria to be eligible for the study. Details of specific ACR criteria can be found in Appendix 3 ACR Criteria for SLE.

- The total number of ACR criteria met will be summed for a total score with a maximum possible score of 11.

- Sub-criteria exist for serositis, renal disorder, neurologic disorder, hematologic disorder, and immunologic disorder. If at least one sub-criterion is met, then the subject is considered to have met the overall criterion. If a subject meets multiple sub-criteria, the score for the overall criterion will be one.

9.4.11.   Low Complement and Positive anti-dsDNA

Low C3 is defined as <90 mg/dL; Low C4 is defined as <10 mg/dL; Positive anti-dsDNA is defined as ≥30 IU/mL.

9.4.12.   Proteinuria

For analysis, urine protein in g/24-hour will be approximated by the urine protein/creatine (PC) ratio in mg/mg. The unit of mg/mmol is used for scoring the BILAG only.

9.4.13.   SRI Response

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from SRI analyses.

SRI response is defined as

- ≥4-point reduction from baseline in SELENA SLEDAI score,

AND

- No worsening (increase of <0.30 points from baseline) in PGA,

AND

- No new BILAG A organ domain score or two new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52 of Part A).

9.4.14.   SRI-S2K Response

Subjects with baseline SELENA SLEDAI-2K score less than 4 or missing SRI components at baseline are excluded from SRI-S2K analyses.

SRI-S2K is the SLE responder index (SRI) response rate with the modified SLEDAI-2K (S2K) scoring for proteinuria at Week 52. This S2K rule scores proteinuria as 4 points anytime the value is >0.5 g/24hr. This endpoint will be referred to as the SRI-S2K for reporting and is defined as:

- ≥4-point reduction from baseline in SELENA SLEDAI score using the SLEDAI-2K proteinuria scoring [SS-S2K 4pt],

AND

- No worsening (increase of <0.30 points from baseline) in Physician's Global Assessment (PGA) [PGA No Worsening],

AND

- No new British Isles Lupus Assessment Group of SLE Clinics (BILAG) A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52 visit) [BILAG No new 1A/2B].

9.4.15.   SELENA SLEDAI and SLEDAI-2K Scoring

The SELENA SLEDAI assessment consists of 24 individual weighted items in which signs and symptoms, laboratory tests, and physician's assessment for each of 8 organ systems are given a weighted score and summed if present (marked 'Yes') at the time of the visit or in the preceding 10 days. The maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No').

For reporting, SLEDAI-2K will be approximated by adjusting only the proteinuria item of SELENA SLEDAI. If the laboratory P/C ratio value exceeds 0.5 mg/mg, the proteinuria item of the SLEDAI is given a positive score (4-point weight) creating an approximation to the SLEDAI-2K assessment. If the P/C ratio value is missing, then the value from the previous visit will be used.

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. See Section 9.3.5 for details on carrying forward these items using LOCF. If any item is missing and does not have a previous value to carry forward, the SLEDAI score will be missing.

9.4.15.1.   SLEDAI 4-point reduction

Subjects with baseline SLEDAI total score less than 4 or missing at baseline are excluded from the analyses.

If the change from baseline for SLEDAI total score for the visit of interest is ≥4, then a subject is considered a responder for the SLEDAI 4 point-reduction endpoint. If the change from baseline for the visit of interest is <4, then a subject is considered a non-responder for the SLEDAI 4 point-reduction endpoint. See Section 9.3.5 for details on carrying forward missing scores using LOCF.

The SLEDAI-2K 4-point reduction endpoint is calculated similarly using the SLEDAI-2K total score.

9.4.15.2.   SLEDAI Improvement

For any given domain, an improvement is defined as a decrease (compared to baseline) in the SLEDAI score within the same organ system at a post-baseline visit.

Subjects with organ system involvement (i.e., SLEDAI score >0) at baseline are included. If a subject withdraws early or is deemed a treatment failure, the subject will be considered as having no improvement.

9.4.15.3. SLEDAI Worsening

For any given domain, worsening is defined as an increase (compared to baseline) in the SLEDAI score within the same organ system at a post-baseline visit.

Subjects with no organ system involvement (i.e., SLEDAI score =0) at baseline are included. Missing data due to treatment failure or study withdrawal will be imputed using LOCF.

9.4.16. BILAG Scoring

BILAG
BILAG Score
• The British Isles Lupus Assessment Group (BILAG) score is an assessment of current lupus disease activity, as well as an indicator of historical disease activity in subjects with SLE. The Classic BILAG index was used in this study (See Appendix 5 – BILAG Index Assessment). • Eight systems are given scores ranging from A to E where: 　• A = Active disease sufficient to require disease-modifying treatment (prednisolone >20mg or immunosuppressants) 　• B = Mild reversible problems requiring only symptomatic therapy (anti-malarials, NSAIDs, or prednisolone <20mg/day) 　• C = Stable, mild disease 　• D = Previous disease but currently inactive 　• E = Never active; no history • If a subject meets the requirements for more than one letter score (A-E, with A being the highest), then the highest score met will be assigned for the organ system. • Scoring of the BILAG is based on three publications including Hay (1993), Isenberg (2000), and a doctoral thesis written by Yee (2008).
BILAG Flare Definition
• BILAG flare is defined as one new BILAG A organ domain score or 2 new BILAG B organ domain scores at the time of assessment compared with baseline.

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.
General	Modified HGS BILAG Scoring using Hay	**First Assessment:** = 'A' if Pyrexia (BILAG01)>0 AND 2 of the other scores (BILAG02-BILAG05)>0 = 'B' if Pyrexia (BILAG01)>0 OR 2 of the other scores (BILAG02-BILAG05)>0 = 'C' if any of BILAG02-BILAG05 are >0 = 'E' if no involvement **Subsequent Assessments:** = 'A' if Pyrexia (BILAG01)>1 AND 2 of the other scores (BILAG02-BILAG05)>1 = 'B' if Pyrexia (BILAG01)>1 OR 2 of the other scores (BILAG02-BILAG05)>1 = 'C' if any of BILAG01-BILAG05 are >0 = 'D' if any previous value was in (A,B,C,D) = 'E' if at least one non-missing item score and no previous assessments were above E.

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.
Mucocutaneous	Modified HGS BILAG Scoring using Hay for first assessments and Yee for subsequent assessments	**First Assessment:** = 'A' if any of BILAG06, BILAG08, BILAG13, or BILAG14 are >0 = 'B' if any one of BILAG16, BILAG07, BILAG12, BILAG09, BILAG10, BILAG17, or BILAG18 are >0 = 'C' if any one of BILAG19, BILAG20, BILAG21, BILAG22, BILAG23, BILAG11, or BILAG15 are >0 for 0-4 items or Yes for Yes/No items = 'E' if no involvement **Subsequent Assessments:** = 'A' if any of BILAG06, BILAG08, BILAG13, or BILAG14 are >1 = 'B' if any one of BILAG16, BILAG07, BILAG12, BILAG09, BILAG10, BILAG17, or BILAG18 are >1 = 'C' if (any one of BILAG19, BILAG20, BILAG21, BILAG22, BILAG23, BILAG11, or BILAG15 are >0 for 0-4 items or Yes for Yes/No items) or (any of BILAG06, BILAG08, BILAG13, BILAG14, BILAG16, BILAG07, BILAG12, BILAG09, BILAG10, BILAG17, or BILAG18 are =1) = 'D' if any previous value was in (A,B,C,D) = 'E' if at least one non-missing item score & no previous assessments were above E.
Neurological	Modified HGS BILAG Scoring using Yee	**All Assessments:** = 'A' if any of BILAG24, BILAG25, BILAG26, BILAG27, BILAG28, BILAG29, BILAG30, BILAG31, BILAG33, BILAG34 are in (3,4) = 'B' if (any of BILAG35, BILAG36, BILAG37, or BILAG32 are in (3, 4)) OR ((if any of BILAG24, BILAG25, BILAG26 are in (1,2)) = 'C' if BILAG38>0 OR (if any of BILAG27, BILAG28, BILAG29, BILAG30, BILAG31, BILAG33, BILAG34, BILAG35, BILAG36, BILAG37, or BILAG32 are in (1, 2)) = 'D' if any previous value was in (A,B,C,D) = 'E' if at least one non-missing item score & no previous assessments were above E.

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.
Musculoskeletal	**Modified HGS BILAG Scoring using Hay for first assessments and Yee for subsequent assessments**	**First Assessments:** **= 'A' if at least one of BILAG39 or BILAG40 is >0** **= 'B' if at least one of BILAG41 or BILAG42 is >0** **= 'C' if at least one of BILAG44, BILAG45, BILAG46, BILAG47, or BILAG43 is >0 for 0-4 items or Yes for Yes/No items** **= 'E' if no involvement** **Subsequent Assessments:** **= 'A' if at least one of BILAG39 or BILAG40 is >1** **= 'B' if at least one of BILAG41 or BILAG42 is >1** **= 'C' if (at least one of BILAG44, BILAG45, BILAG46, BILAG47, or BILAG43 is >0 for 0-4 items or Yes for Yes/No items) OR (one of BILAG39, BILAG40, BILAG41, BILAG42 is =1)** **= 'D' if any previous value was in (A, B, C, D)** **= 'E' if at least one non-missing item score and no previous assessments were above E.**

Cardiovascular and Respiratory	**Modified HGS BILAG Scoring using Hay for first assessments and Yee for subsequent assessments**	**First Assessments:**
		= 'A' if four of the following are >0 for 0-4 items or Yes for Yes/No items:
		    BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, BILAG59
		    OR
		    BILAG50>0 AND 2 of BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, BILAG59 are >0 for 0-4 items or Yes for Yes/No items
		    OR
		    BILAG52>0 AND 2 of BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, BILAG59 are >0 for 0-4 items or Yes for Yes/No items
		
		= 'B' if two of BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, BILAG59 , BILAG50, BILAG52
		    Are >0 for 0-4 items or Yes for Yes/No items
		
		= 'C' if any of BILAG53, BILAG50, BILAG52, BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, or BILAG59 are >0 for 0-4 items or Yes for Yes/No items
		
		= 'E' if no involvement
		
		Subsequent Assessments:
		='A' if four of the following are >1 for 0-4 items or Yes for Yes/No items:
		    BILAG48, BILAG49, BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, BILAG59

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.

		OR
		    BILAG50>1 AND 2 of BILAG48, BILAG49, BILAG51, BILAG54,
		       BILAG55, BILAG56, BILAG57, BILAG58, BILAG59 are >1 for 0-4 items
		or Yes for Yes/No items
		    OR
		    BILAG52>1 AND 2 of BILAG48, BILAG49, BILAG51, BILAG54,
		       BILAG55, BILAG56, BILAG57, BILAG58, BILAG59 are >1 for 0-4 items
		or Yes for Yes/No items
		
		= 'B' if two of BILAG48, BILAG49, BILAG51, BILAG54, BILAG55,
		     BILAG56, BILAG57, BILAG58, BILAG59, BILAG50, BILAG52
		     Are >1 for 0-4 items or Yes for Yes/No items
		
		= 'C' if any of BILAG53, BILAG50, BILAG52, BILAG48, BILAG49,
		     BILAG51, BILAG54, BILAG55, BILAG56, BILAG57, BILAG58, or
		     BILAG59 are >0 for 0-4 items or Yes for Yes/No items
		
		= 'D' if any previous value was in (A,B,C,D)
		
		= 'E' if at least one non-missing item score and no previous assessments were above E.

Vasculitis	Modified HGS BILAG Scoring using Hay for first assessments and Yee for subsequent assessments	**First Assessments:** ='A' if at least one of BILAG60, BILAG61, or BILAG62 is >0 ='B' if at least one of BILAG66, BILAG65, or BILAG67 is >0 for 0-4 items or Yes for Yes/No item ='C' if at least one of BILAG63 or BILAG64 is >0 ='E' if no involvement **Subsequent Assessments:** ='A' if at least one of BILAG60, BILAG61, or BILAG62 is >1 ='B' if at least one of BILAG66, BILAG65, or BILAG67 is >1 for 0-4 items or Yes for Yes/No item ='C' if (at least one of BILAG63 or BILAG64 is >0) or (at least one of BILAG60, BILAG61, BILAG62, BILAG65, or BILAG66 = 1 for 0-4 items) ='D' if any previous value was in (A,B,C,D) ='E' if at least one non-missing item score and no previous assessments were above E.

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.
Renal	Modified HGS BILAG Scoring using Isenberg and memo to file regarding items 72 and 73. Item 74 added to category D but no reference. Note: Typo in Isenberg (2000) paper where A3c creatinine clearance >50 ml/min and last time was >50/ml/min , in Yee this is <50 ml/min and last time >50 ml/min	**All Assessments (per memo to file, only use items 72b and 73b, and disregard 72a and 73a):** **Define Proteinuria as:** **(BILAG71 has a change from previous BILAG71 record >=2) OR (previous BILAG72B<0.2*100 mg/mmol and current BILAG72B>1*100 mg/mmol) OR (BILAG72B>1*100 mg/mmol and percentage change from previous BILAG72B value >=100%) or BILAG73B=1/yes and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record** **Define Deteriorating Renal Function as follows:** **(BILAG75*88.4>130 mg/dl and percentage change from previous BILAG75>30%) OR (BILAG76<67% of previous BILAG76 value) OR (BILAG76<50 ml/min and previous BILAG76 value was >50 ml/min) and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record** **='A' if (two or more of the following occur: Proteinuria, BILAG70=1/yes,** ** Deteriorating renal function, BILAG77=1/yes, BILAG78=1/yes) and at least one of the two or more is Proteinuria, BILAG77, or BILAG78, and corresponding SLE relationship boxes=YES (Not NO or MISSING) for the current record** **='B' if (one or more of the following occur: Proteinuria, BILAG70=1/yes,** ** Deteriorating renal function, BILAG77=1/yes, BILAG78=1/yes)** ** OR** ** (BILAG71>=2 and has risen from previous assessment by 1 or more)** ** OR** ** (BILAG72B has risen by >1*100 mg/mmol from previous BILAG72B record and increased by >50% but <100%) or (BILAG75*88.4>130 mg/dl and percentage change from previous record was >15%) and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record** **='C' if SLE related and (BILAG72B>.25*100 mg/mmol) or (BILAG71>=1) or**

Age at visit*	Condition
3 – 5 yr.	BILAG68 ≥ 116 and BILAG69 ≥ 76
6 – 9 yr.	BILAG68 ≥ 122 and BILAG69 ≥ 78
10 – 12 yr.	BILAG68 ≥ 126 and BILAG69 ≥ 82
13 – 15 yr.	BILAG68 ≥ 136 and BILAG69 ≥ 86
16 – 18 yr.	BILAG68 ≥ 142 and BILAG69 ≥ 92

* Age at visit will be calculated as: *INTCK ('YEAR', Date of birth, Assessment date, 'C').*

='D' if any previous value was in ('A', 'B', 'C', 'D') or BILAG74=1/yes and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record

BILAG System	Computational References Used	Source / Derivation / Comments * Variables named by question number.
		='E' if no involvement
Hematology	Modified HGS BILAG Scoring (all the same scoring algorithm), plus additional criterion for D from "See email from MChevrier dated 01Sep05 re neutrophils."	**All Assessments:** ='A' if BILAG80<1.0x10^9/L or BILAG83<25 x10^9/L or BILAG79<8 g/dl and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record ='B' if BILAG80<2.5x10^9/L or BILAG83<100 x10^9/L or BILAG79<11 g/dl or (BILAG84=YES and BILAG85=YES) and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record (no checkbox for BILAG85) ='C' BILAG80<4.0x10^9/L or BILAG83<150 x10^9/L or BILAG82<1.5x10^9/L or (BILAG85=YES and BILAG84^=YES) or BILAG86=YES and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record (no checkbox for BILAG85 or BILAG86) ='D' if any previous value was in (A,B,C,D) or (.z< BILAG81 <0.5 x10^9/L and corresponding SLE relationship box=YES (Not NO or MISSING) for the current record ='E' if at least one non-missing item score and no previous assessments were above E.

9.4.16.1. BILAG Improvement

For any given domain, subjects who have an A at baseline and change to a B, C, or D will be considered to have improvement for that domain. Similarly, subjects with a B at baseline who change to a C or D will be considered to have improvement.

Subjects with a domain category C, D, or E at baseline are excluded. If a subject withdraws early or is deemed a treatment failure, the subject will be considered as having no improvement.

9.4.16.2. BILAG Worsening

Subjects who have a domain category B at baseline and change to an A will be considered to have worsening for that domain. Similarly, subjects who have a domain category C, D, or E at baseline and change to an A or B will be considered to have worsening for that domain. Subjects with a domain category A at baseline are excluded since they cannot worsen. Missing data due to treatment failure or study withdrawal will be imputed using LOCF.

9.4.17. PGA Scoring

- The PGA is collected on a 10cm visual analogue scale (VAS).

- The standard scoring range for the PGA is 0 to 3, therefore the score will be rescaled for standard reporting by multiplying the collected score on the centimeter scale by 3/10.

9.4.17.1.   PGA No Worsening

PGA No Worsening is defined as (Post-baseline PGA – Baseline PGA) <0.3 using the re-scaled score (0-3 scale).

9.4.18.   Sustained SRI Response

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from SRI analyses.

A sustained SRI response is defined as having a response on the SRI endpoint at Weeks 44, 48 and 52. Otherwise a subject is considered to be a non-responder.

9.4.19.   SRI6 Response

Subjects with baseline SELENA SLEDAI score less than 6 or missing SRI components at baseline are excluded from SRI6 analyses.

A SRI6 response is defined as ≥6-point reduction from baseline in SELENA SLEDAI score, no worsening (increase of <0.3 points from baseline) in PGA, no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52).

9.4.20.   PRINTO/ACR Scoring

The five endpoints considered in the PRINTO/ACR Juvenile SLE Response Evaluation definition are percent change in ParentGA, percent change in PGA, percent change in SELENA SLEDAI score, percent change in proteinuria, and percent change in PedsQL GC physical functioning domain score.

The two definitions of PRINTO/ACR Juvenile SLE Response Evaluation responders are:

1. At least 50% improvement compared to baseline in 2 of 5 endpoints, with no more than 1 of the remaining worsening by more than 30%;

2. At least 30% improvement compared to baseline in 3 of 5 endpoints above, with no more than 1 of the remaining worsening by more than 30%.

9.4.21.   Sustained ParentGA Response

A sustained ParentGA response is defined as having >0.7 improvement in ParentGA score compared to baseline at Weeks 44, 48 and 52. Otherwise a subject is considered to be a non-responder. An improvement of 0.7 corresponds to the minimally clinically important difference (MCID) for the instrument using the physician external rating [Filocamo, 2010].

An improvement is defined as a negative change, with zero being the best score and ten being the worst score. An improvement of >0.7 corresponds to a change of <-0.7.

Subjects with a baseline score ≤0.7 cannot experience an improvement of greater than 0.7 and these subjects will be excluded from this analysis.

9.4.22. Pediatric SLICC/ACR Damage Index Scoring

- The SLICC/ACR Damage Index (Appendix 7) score is calculated as the sum of all the item scores, which will be the value summarized and displayed for reporting.

- Worsening is defined as an increase from baseline in SLICC/ACR Damage Index score [(post-baseline visit score – baseline score)] >0.

9.4.23. Modified Severe SLE Flare Index (SFI) Scoring

The following scoring rules are based on the modified SELENA SLEDAI SLE flare index:

- SFI reports the first mild /moderate or severe flare occurrence since the last visit assessment.

- The SLEDAI criteria will be assessed programmatically to determine if the SELENA SLEDAI criteria for a flare has been met and used for the assessment of flare, irrespective of what was recorded on the SFI form.

- Although there are boxes on the form for the investigator to classify the most recent flare to mild/moderate or severe, the classification will be re-derived from the subcategory scores. Flares originally marked severe will be downgraded to "Not Severe" if the only reason marked is a change in SELENA SLEDAI score to >12.

  - In this case, if any of the mild/moderate reasons are checked or if the modified SELENA SLEDAI score has a change from previous visit of at least 3, then the flare will be considered mild/moderate.

- Flares that are marked mild/moderate where the only reason checked is SELENA SLEDAI increase of at least 3 points but not more than 12 points will be re-derived using the modified SELENA SLEDAI score.

  - If it is found that the change is not actually ≥3, and no other reasons are checked, then the flare will not be counted.

9.4.24. Renal Flare

An SLE renal flare is defined as the occurrence of one or more of the following at two or more consecutive visits during the study:

1. A reproducible increase in 24-hour urine protein equivalent levels to

   a. >1 g if the baseline value was <0.2 g,
   b. >2 g if the baseline value was 0.2 to 1 g, or
   c. More than twice the value at baseline if the baseline value is >1 g.

2. A reproducible decrease in GFR of >20%, accompanied by at least one of the following: proteinuria (>1 g/24 hour equivalent) and/or cellular (RBC or WBC) casts [Alarcón-Segovia, 2003].

Time to first renal flare is calculated as:

Time to first renal flare (days) = Date of first renal flare in Part A – treatment start date + 1.

This definition expresses proteinuria in g/24-hour. Proteinuria is assessed using the urine protein:creatinine ratio (uPCR) in mg/mg as a 1:1 equivalent for urine protein in g/24-hours.

"Reproducible" requires the criterion to be met at two consecutive visits, including any unscheduled visits or the 8 Week Follow-up Visit.

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

Criterion	Parameter	SDTM Dataset LBTESTCD
Proteinuria	Urine Protein:Creatinine Ratio (mg/mg)	PROTCRT
GFR*	Creatinine Clearance estimated by the Schwartz formula (mL/sec/1.73m^2) or Cockcroft-Gault formula (mL/min)	GFRSTZ or CRTCE
RBC cellular casts	RBC cellular casts	CSRBC
WBC cellular casts	WBC cellular casts	CSWBC

* If both GFR by Schwartz formula and Cockroft-Gault formula are present, GFR by Schwartz formula will be used.

9.4.25. Steroids for SLE

Concomitant medications will be coded according to drug name as defined in the GSK Drug Dictionary, and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

The use of steroids to treat SLE flare shall be considered a usage of steroids for SLE disease activity. The classification of treatment failure due to steroid use shall follow the protocol, which is further clarified as follows.

The Day 309 (Week 44) visit steroid dose is the sum of steroid dose over 7 consecutive days leading up to, and including the Day 309 (Week 44) visit, divided by 7. The Day 309 (Week 44) visit steroid dose is used to determine if there is a new increase in steroids above the Day 1 (Baseline) visit or Day 309 (Week 44) visit within 8 weeks of the Day 365 (Week 52) visit.

To determine whether a subject shall be classified as a treatment failure due to steroid use within 8 weeks prior to the Week 52 visit, the 8-week window is defined from the day after Day 309 (Week 44) visit to the Day 365 (Week 52) visit.

In all instances in which the protocol states that a subject's steroid dose must return to a specified level (e.g., within 5 mg or 25% whichever is higher) by a specific visit day (e.g., Day 169 visit), the calculation of the 7-day average steroid dose to determine whether a subject is a treatment failure will begin on the day after the visit.

If a critical visit (Day 113, 169, 309) is missing then the date is imputed e.g., date of day 169 visit is imputed as day 169. This imputed date is used to assess TF, not the date the medication changes.

Details for prednisone equivalent conversion factors are included in Appendix 13.

Full details of TF rules are given in Appendix 14 – Treatment Failure Rules.

9.4.26.   Average Daily Prednisone Equivalent

Average daily prednisone equivalent dose will be expressed in milligrams per day (mg/day). To determine average daily prednisone equivalent, all steroid dosages are converted to a prednisone equivalent in milligrams at each visit. See Appendix 12 for conversion factors and detail of how values should be converted.

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

9.4.26.1.   Baseline Prednisone Dose

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

9.4.26.2.   Average Daily Prednisone Dose Between Visits

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

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

9.4.26.3.   Average Daily Prednisone Dose at the Visit

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

The average daily prednisone equivalent dose will be calculated for each scheduled visit. For subjects who withdraw from the study or are treatment failures prior to a scheduled visit, the average dose will be calculated at the date of withdrawal or date of treatment failure, whichever is earlier.

Note: for the treatment failure adjudication, an intermediate dataset containing the rolling 7-day average daily prednisone for each study day will be used to capture treatment failures occurring between visits.

9.4.26.4. Cumulative Prednisone Dose

Cumulative prednisone dose (area under the curve [AUC]) is defined as the sum of daily prednisone equivalent dose from Day 1 to Day 365 (Week 52) Visit.

The daily prednisone equivalent dose after the last Part A visit day or the day of treatment failure in Part A, if prior to Day 365 (Week 52) Visit, will be imputed using the average of the last 28 daily prednisone equivalent doses prior to the day of last visit/treatment failure (i.e., not including day of visit/treatment failure).

For subjects who drop out or have treatment failure before Day 28, the daily prednisone equivalent dose after early dropout or treatment failure will be imputed using the average post-baseline daily doses available prior to dropout/treatment failure.

9.4.27. Pediatric Quality of Life Generic Core Scale Scoring

Details of the questions of the PedsQL Generic Core Scale can be found in Appendix 10 – PedsQL Generic Core Scale. There are four domains: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items) [Varni, 2002].

Subjects ≥8 years of age will complete the PedsQL directly (Child Report version for subjects 8-12 years of age and Teen Report version for subjects 13-18 years of age). For subjects aged 5-7 years, a parent/guardian will complete the Parent Report version of the PedsQL on their child's behalf. The PedsQL will only be administered to those subjects for which a validated translation exists in their language. All subjects will be reported together, irrespective of the version of the scale used.

So that higher scores indicate better health, items are reversed scored and linearly transformed to a 0-100 scale, as follows:

Response choices	Never	Almost never	Sometimes	Often	Almost always
Raw score	0	1	2	3	4
1-100 scale score	100	75	50	25	0

Total Score

The total score is calculated as the sum of all the items divided by the number of items answered on all domains.

If 50% or less of the items are missing (i.e., if 12 or more items are complete), the total score is the mean of the non-missing item scale scores. If more than 50% of the items (i.e., 12 or more items) are missing, the total score should not be computed.

Domain Score

The PedsQL GC domain scores are the mean of the 1-100 scale scores for the 8 items in the Physical Functioning (PF) domain or 5 items in the other domains.

If 50% or less of the items in the domain are missing (i.e., if 4 or more items are complete for PF domain or three or more items for the other domains), the domain score is the mean of the non-missing item scale scores. If more than 50% of the items in the domain (i.e. 5 or more items for PF domain or 3 or more items for the other domains) are missing, the domain score should not be computed.

9.4.28. Pediatric Quality of Life Multidimensional Fatigue Scale Scoring

The recently developed 18-item PedsQL Multidimensional Fatigue Scale was designed to measure fatigue in pediatric patients and is comprised of three domains: General Fatigue Scale (6 items), Sleep/Rest Fatigue Scale (6 items), and Cognitive Fatigue Scale (6 items) [Varni, 2004]. (See Appendix 11 – PedsQL Multidimensional Fatigue Sc).

Subjects ≥8 years of age will complete the PedsQL-Fatigue directly (Child Report version for subjects 8-12 years of age and Teen Report version for subjects 13-18 years of age). For subjects aged 5-7 years, a parent/guardian will complete the Parent Report version of the PedsQL-Fatigue on their child's behalf. The PedsQL-Fatigue will only be administered to those subjects for which a validated translation exists in their language. All subjects will be reported together, irrespective of the version of the scale used.

So that higher scores indicate better health, items are reversed scored and linearly transformed to a 0-100 scale, as follows:

Response choices	Never	Almost never	Sometimes	Often	Almost always
Raw score	0	1	2	3	4
1-100 scale score	100	75	50	25	0

Total Score

The total score is calculated as the sum of all the items divided by the number of items answered on all domains.

If 50% or less of the items are missing (i.e., if 9 or more items are complete), the total score is the mean of the non-missing item scale scores. If more than 50% of the items (i.e., 10 or more items) are missing, the total score should not be computed.

Domain Score

The PedsQL multidimensional fatigue scale domain scores are the mean of the 1-100 scale scores for the 6 items in each of the domains.

If 50% or less of the items in the domain are missing (i.e., if 3 or more items are complete), the multidimensional fatigue domain score is the mean of the non-missing item scale scores. If more than 50% of the items in the domain (i.e., 4 or more items) are missing, the multidimensional fatigue domain score should not be computed.

9.4.29. Extent of Exposure

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

Duration of exposure in days for each subject will be calculated in Part A as:

Last infusion date in Part A – first infusion date in Part A + 28.

Overall exposure in Part A for each treatment group will be calculated in total subject-years as:

$$\frac{Sum\ of\ duration\ of\ Part\ A\ exposure\ (all\ subjects\ in\ treatment\ group)}{365.25}$$

Percent compliance is calculated as:

$$100 * \frac{Number\ of\ infusions\ prescribed - Number\ of\ infusions\ missed}{Number\ of\ infusions\ prescribed}$$

9.4.30. Laboratory Assessments

If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 Decimal Places = '< x ' becomes x – 0.01

- Example 2: 1 Decimal Place = '> x' becomes x + 0.1

- Example 3: 0 Decimal Places = '< x' becomes x – 1

9.4.31. Belimumab Concentrations

If a concentration value has a non-detectable level reported in the database (NQ), the value will be set to 0.

Belimumab concentration values will be converted from (ug/L) to (ug/mL):

Concentration value (ug/mL) = Concentration value (ug/L) / 1000

9.4.32. B cell unit conversions and Normalization of Rare B cell Subsets

- The Benlysta program standard is to report common B cells (CD19, CD20, naïve, and memory) in counts per uL (/uL).

- To convert values reported as count per GI/L (= 10^9/L) to count per uL multiply the value by 10^3 or 1000.

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

- Rare B cell subsets reported in GI/L (=10^9/L) will be normalized and converted to count/mL using the following formula:

*Normalized count/mL = [(rare cell event count) / (CD19+ event count)] * (CD19+ count per mm3 or uL) * 1000.*

For additional detail, please see Section 8.6.3 of the PSAP located in IMMS at the following path:

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

The list of B cell item mappings and display labels are listed in Appendix 16.

Rare B cell endpoints to be normalized and values to be substituted into the formula are given in Table 2.

Table 2   Rare B cell subsets requiring normalization

Rare B cell subset	Rare cell event count	CD19+ Event Count [1]	CD19+ Counts [2]
Activated	CD20+CD69+ (EVENTS)	CD19+ (EVENTS) [a]	CD19+ (/uL)
Plasmacytoid	CD20+ CD138+ (EVENTS)	CD19+ (EVENTS)[a]	CD19+ (/uL)
Plasma	CD20- CD138+ (EVENTS)	CD19+ (EVENTS) [a]	CD19+ (/uL)
Short-lived plasma	CD27+b CD20- (EVENTS)	CD19+ (EVENTS) [a]	CD19+ (/uL)
SLE subset	CD27+CD38+CD19+ (EVENTS)	CD19+ (EVENTS) [a]	CD19+ (/uL)

[1] From corresponding panel – [a] Plasma panel
[2] Source data require conversion from GI/L to /uL.

The required parameters in the source data can be identified in Table 3.

Table 3   Source data from Q2 Solutions required for Normalization of Rare B Cell Subsets

Rare B cell subset	Lab Test Code (LBTESTCD)	Lab Test (LBTEST)	B cell Panel (LBMETHCD) [1]	Units of Measurement (LBORRESU)
CD19 [2]	CD19	CD19_Concentration	FLWTBNK	10^9/L [2]
CD19 Event (Plasma B cell panel)	CD19E	CD19_Number of events	FLWPLSM	EVENTS
Activated	CDX155E	CD19+CD20+CD69+ Number of Events	FLWPLSM	EVENTS
Plasmacytoid	CDX145E	CD20+CD138+ Number of Events	FLWPLSM	EVENTS
Plasma	CDX143E	CD20-CD138+ Number of Events	FLWPLSM	EVENTS
Short-lived plasma	CDX154E	CD27+bCD20- Number of Events	FLWPLSM	EVENTS
SLE subset	CDX156E	CD27+CD38+CD19+ Number of Events	FLWPLSM	EVENTS

[1] FLWPLSM=Flow Plasma and LWTBNK=Flow TBNK.
[2] Source data require conversion from GI/L (=10^9/L) to /uL.

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 summarized overall and by treatment group.

Using the screened population, the number of subjects in each population (Screened, Randomized, ITT, Completers, As-treated, Pharmacokinetic [PK], and Per-protocol) will be summarized overall and by treatment group (not including the screened population). A summary of the reasons for the screen failures will be provided along with a listing of the subjects who were screen failures.

If there are any subjects who are randomized but do not receive any study drug, they will be included on the populations listing in the Randomized population, but not the ITT population.

For the ITT population, the subject's completion status will be assessed to evaluate percentages of dropouts by treatment group as well as the reasons for dropout. The number and percentage of subjects who completed through Week 52 and who withdrew from Part A, including reasons for withdrawal, will be displayed by treatment group and overall. Additionally, the cumulative number and percentage of subjects who withdrew from Part A by study visit will be displayed by treatment group and overall. A Kaplan-Meier (KM) plot of time to withdrawal from Part A will be generated to evaluate the pattern of dropouts over time. Subjects who complete through Week 52 will be censored at the Week 52 visit date.

A listing of subject disposition will be provided showing completion status and whether or not they are included in each population. A listing of subjects who withdrew from the study, including reason and time to withdrawal will also be provided.

To aid stage 3 review of the KM curve, the SAS LIFETEST output will be provided. This will not be a reported output.

10.2.   Protocol Deviations

Please refer to the Protocol Deviation Management Plan (PDMP): Dated: 11Jan2018 (Version 0.3) for full details describing important deviations and important deviations which result in exclusion from the PP population.

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized by treatment group. Important protocol deviations and deviations which result in exclusion from the PP population will be listed. (See Appendix 2 – Important Protocol Deviations for details of important protocol deviations and deviations leading to exclusion from PP population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the PDMP. Data will be reviewed prior to database release to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the eCRF and protocol deviations dataset. This dataset will be the basis for the summaries and listings of protocol deviations.

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

10.3.   Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the continuous demographic and baseline characteristics of age at screening (years), height (cm), weight (kg), BMI (kg/m^2) and vital signs (temperature, heart rate and blood pressure). Age at screening will be presented in years and months (e.g., 12 y 2 mo) in the listing.

Counts and percentages of the following categorical demographic and baseline characteristics will be presented: country, sex, Hispanic or Latino origin, age group at screening (<13 years and ≥13 years), cardiovascular history (family history [yes/no]), tobacco use (never smoked, current smoker, former smoker), family history of autoimmune disorder and SLE (mother, father, brother, sister). A summary of the number and percentage of subjects reporting each general medical history term will also be provided.

The summary of demographic and baseline characteristics will be repeated for the age subgroups, as defined in Section 8.3.

A summary of race will be presented, including the 9 categories collected on the CRF. If multiple races of different types are selected, each individual race and the multiracial category will be used. A subject may be represented in more than one category. See Section 9.4.8.

A summary of stratification factors will also be presented. This will include age at screening (5-11 years, 12-17 years), SELENA SLEDAI score at screening (6-12 vs. ≥13), age at baseline (5-11 years, 12-17 years), and SELENA SLEDAI at baseline (≤12, ≥13).

Demographic and baseline characteristics, as well as stratification factors, will be listed for all subjects.

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

- BILAG organ domain involvement (at least 1A or 2B, at least 1A, at least 1B, no A or B [subjects may be included in more than one category])

- SELENA SLEDAI stratification category (≤12, ≥13)

- SELENA SLEDAI category (≤7, ≥8)

- PGA category (0-1, >1 – 2.5, >2.5)

- ParentGA category (0-2.5, >2.5 – 5, >5 – 7.5, >7.5)

- Pediatric Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) category (0, 1, >1)

- Proteinuria category (≤0.5, >0.5-<1, 1-<2, ≥2)

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

- SELENA SLEDAI

- PGA

- ParentGA

- Pediatric SLICC/ACR Damage Index

- Proteinuria levels

The summary of baseline disease activity will be repeated for the age subgroups, as detailed in Section 8.3.

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

- SLE disease duration (years) and ACR classification criteria (count and percentage with each symptom present)

- SELENA SLEDAI category by organ domain and item (count and percentage with each item present, see Section 17.1 for details)

- BILAG category (count and percentage of each A – E score) by organ domain

- Autoantibody levels (anti-dsDNA [IU/mL] – positive/negative and summary statistics, ANA [Titer] – positive/negative and summary statistics, anti-cardiolipin (aCL) [positive/negative] (if any of the three IgG, IgA or IgM parameters are above the lower limit of quantification then the subject is aCL positive. If at least one is non-missing, then the subject is aCL negative. Otherwise a subject's aCL is considered to be missing), anti-dsDNA and/or ANA positive [yes/no], and C Reactive Protein (CRP) [mg/L] – positive/negative and summary statistics

- Immunoglobulin levels (IgG [g/L], IgA [g/L] and IgM [g/L] – summary statistics and count and percentage below the lower limit of normal [LLN] and above upper limit of normal [ULN])

- B cells (CD19+, CD20+, CD20+/27+ memory, CD20+/27– naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset, CD20-/138+ plasma cells, and CD27+BRIGHT/CD20– short-lived plasma cells) – summary statistics

- Levels of complement and other biomarkers (C3 [mg/dL], C4 [mg/dL] – summary statistics and count and percentage of high, normal and low results, and BLyS [ng/mL] – summary statistics and count and percentage of results below/above limit of quantification [LOQ])

- Columbia Suicide Severity Rating Scale (C-SSRS) scores by behavior and ideation components for lifetime and over the last 2 months – counts and percentages

- Allowable SLE medication usage– counts and percentages by class (Steroids, Anti-malarials, and Other Immunosuppressive/Immunomodulatory Agents) and drug as well as summary statistics for average daily prednisone dose (mg/day) at baseline.

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

The following indicators of quality of life will also be summarized at baseline using descriptive statistics (N, Min, Median, Max, Mean, SD, 25th and 75th percentiles):

- Pediatric Quality of Life Inventory (PedsQL) scale scores (physical functioning, emotional functioning, social functioning, school functioning, total)

- PedsQL Multidimensional Fatigue scale scores (general fatigue, sleep/rest fatigue, cognitive fatigue, total)

10.4. Concomitant Medications

Concomitant medications will be coded according to drug name as defined in the GSK Drug Dictionary, and classified according to the GSK-Drug ATC classification level 1 and ATC level 4.

Concomitant medications for Part A are defined as medications that start on or before the first dose date of Part A treatment, and end on or after the first dose date of Part A treatment, or medications that start after the first dose date of Part A treatment but before the first dose date of belimumab in Part B or the first visit date in Part C (as applicable).

Medications may be defined and summarized as concomitant for more than one study period.

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 the appropriate treatment/visit and if the month and year are the same or later, then the medication will be considered concomitant for the study period.

A summary of the number and percentage of subjects with concomitant medications by ATC level 1 term and ATC level 4 term will be displayed. A further summary of concomitant medications by ATC level 4 term and preferred term will be provided. A listing of all concomitant medication data will be displayed by treatment and subject.

The number and percentage of subjects who receive a protocol-prohibited medication or a dose of allowable medication that results in treatment failure designation before week 52 will be summarized (see Section 5.6 of the protocol).

A medication that is started pre-treatment or on-treatment and has no stop date will be assumed to be on-going for the remainder of the study. A medication that is stopped on-treatment or post-treatment and has no start date recorded will be assumed to have been on-going from the pre-treatment phase.

The rules for determining concomitancy have been summarized in Table 4.

Table 4   Concomitant Medication Classification

Pre-treatment	Part A	Part B	Part C	Concomitant in Treatment Periods
x------y				
x------	-----y			A,
x-----------	----------	--------y		A, B
x-----------	--------------	------------	---------y	A,B,C
	x-------y			A
	x-----------	---------y		A,B
	x--------	-------------	---------y	A,B,C
		x-------y		B
		x-----------	------y	B,C
			x----------y	C
			x-------------	C
x--------------	--------------	-----------------	---------------	A,B,C
	x-----------	-------------------	-------------?	A,B,C
		x----------------	------------------?	B,C
			x----------------?	C
x=medication start date; y=medication stop date.				

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10.5. Extent of Exposure

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

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

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

Exposure data will be listed for all subjects.

11. EFFICACY ANALYSES

Treatment failures and handling of missing data will be managed as described in Section 9 for all efficacy analyses and supporting summaries, unless otherwise specified.

The efficacy analyses for Part A will be performed on the ITT population as defined in Section 6 unless otherwise stated, and will use baseline as defined in Section 9.4.1. The data will be presented by treatment group.

11.1. Primary Efficacy Analysis for Part A

The primary efficacy endpoint is the SRI response rate at Week 52 of Part A.

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

The number and percentage of subjects achieving an SRI response at Week 52 will be presented for belimumab and placebo. A logistic regression model will be used to estimate the odds of an SRI response for belimumab vs. placebo. The independent variables in the model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% CI for belimumab versus placebo. Odds ratio estimates and 95% CIs will also be displayed for each independent variable in the model. These confidence intervals will use the normal approximation.

In the event that the model does not converge due to baseline age group (5-11 years vs. 12-17 years), baseline age as a continuous variable will be included in the model to analyze the response at Week 52. In the event that the model does not converge due to baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13), a model with adjustment for baseline SELENA SLEDAI score ($\leq$7 vs. $\geq$8) will be used. If the model does not converge using

baseline SELENA SLEDAI score (≤7 vs. ≥8), a model with adjustment for baseline SELENA SLEDAI score (≤9 vs. ≥10) will then be used. If any factor still causes a failure in model convergence, the factor will be removed from the model. The model that is used for the SRI will be used for all endpoints.

11.2.   Supportive Summaries of the Primary Efficacy Endpoint

The model that is selected for the primary efficacy analysis for SRI at Week 52 (Section 11.1) will be the model that is used for all endpoints. If any factor still causes a failure in model convergence, the factor will be removed from the model.

Components of SRI Response

Subjects will be excluded from summaries and analyses for which they are missing a baseline value of the SRI component. They will be excluded for the SELENA SLEDAI component if their baseline score is less than 4.

In support of the primary endpoint, the number and percentage of subjects meeting each of the three components of the primary endpoint at Week 52 will be presented. Similar analyses and displays as described in Section 11.1 will be provided.

For the PGA component, the model will include treatment group, baseline PGA, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

For the BILAG component, the model will include treatment group, baseline BILAG organ domain involvement (at least 1A/2B vs. at most 1B), baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

Reason for No Response

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

For the primary SRI endpoint, the disposition of factors contributing to response or non-response will be presented as the number and percentage of subjects in each of the following categories at Week 52 of Part A by treatment group:

- Response
- No response:
    - o   Dropout (not a treatment failure)
    - o   Treatment failure
    - o   <4-point reduction in SELENA SLEDAI
    - o   ≥4-point reduction in SELENA SLEDAI with the following:
        - ▪   Worsening in PGA only
        - ▪   New 1A/2B BILAG only

- Both worsening in PGA and new 1A/2B BILAG.

Unadjusted

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

The primary efficacy analysis at Week 52 of Part A will be repeated unadjusted for covariates. Similar analyses and displays as described in Section 11.1 will be conducted.

LOCF

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

The primary efficacy analysis at Week 52 of Part A will be repeated using LOCF imputation. For this analysis, any subject who receives a protocol-prohibited medication or a dose of allowable medication that results in treatment failure designation (see Section 5.6.1 of the protocol) prior to the Day 365 (Week 52) visit will be considered a treatment failure for the Week 52 efficacy analysis. For any subject not otherwise classified as a failure that withdraws prior to Week 52 or is missing the Week 52 visit, missing data will be handled by using the LOCF method, as opposed to being considered a treatment failure (DO/TF=NR). Similar analyses and displays as described in Section 11.1 will be conducted.

Completers Population

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

The primary efficacy analysis at Week 52 of Part A will be repeated on the Completers population. Similar analyses and displays as described in Section 11.1 will be conducted.

SRI-S2K

Subjects with baseline SELENA SLEDAI-2K score less than 4 or missing SRI components at baseline are excluded from the analysis.

The SRI-S2K will use the SLEDAI 2K proteinuria scoring rule. This rule scores proteinuria as 4 points anytime the value is >0.5 g/24hr.

A logistic regression model will be used to estimate the odds of an SRI-S2K response for belimumab vs. placebo. The independent variables in the model will include treatment group, baseline SELENA SLEDAI S2K score ($\leq$12 vs. $\geq$13), and baseline age (5-11 vs. 12-17). Similar analyses and displays as described in Section 11.1 will be conducted.

Note, the proteinuria scoring for the baseline SELENA SLEDAI independent variable uses the SELENA SLEDAI proteinuria scoring rule.

A table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, the odds ratio and 95% CI versus placebo.

Response over Time

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

To evaluate the response over time, the number and percentage of subjects achieving a response on the primary endpoint and each of the three components will be summarized by treatment group and visit.

For the SRI, the logistic regression model for each visit will only include treatment group without any adjustment for covariates. Similar analyses and displays as described in Section 11.1 will be conducted for the SLEDAI component, PGA component, and BILAG component.

For the SLEDAI component, the model for Week 52 will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

For the PGA component, the model for Week 52 will include treatment group, baseline PGA, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

For the BILAG component, the model for Week 52 will include treatment group, baseline BILAG organ domain involvement (at least 1A/2B vs. at most 1B), baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

The percentage of subjects with a response on the SRI and each of the 3 components at each visit in Part A will be presented graphically using line graphs by treatment group.

SRI6

Subjects with baseline SELENA SLEDAI score less than 6 or missing SRI components at baseline are excluded from the SRI6 analysis.

To evaluate the sensitivity of the endpoint using different thresholds for disease improvement, the number and percentage of subjects achieving a response using a 6-point reduction (SRI6) from baseline in SELENA SLEDAI score will be summarized by treatment group and visit. A logistic regression model will be used to estimate the odds of an SRI6 response over time for belimumab vs. placebo without any adjustment for covariates.

The percentage of subjects with an SRI6 at each visit will be presented graphically using a line graph by treatment group.

Subgroups

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline are excluded from the analysis.

SRI response at Week 52 of Part A will be summarized using a logistic regression modeling comparing treatment groups for each of the subgroups listed in Section 8.3 without adjustment for covariates. These analyses will use the DO/TF = NR method for missing data.

11.3. Secondary Efficacy Analyses for Part A

The model that is selected for the primary efficacy analysis for SRI at Week 52 (Section 11.1) will be the model that is used for all endpoints. If any factor still causes a failure in model convergence, the factor will be removed from the model.

11.3.1. Percent of Subjects Meeting PRINTO/ACR Juvenile SLE Response Evaluation Criteria for Improvement in SLE using two Definitions (DO/TF=NR)

The 5 endpoints considered in the PRINTO/ACR Juvenile SLE Response Evaluation definition are percent change in ParentGA, percent change in PGA, percent change in SELENA SLEDAI score, percent change in proteinuria, and percent change in PedsQL GC physical functioning domain score.

The two definitions of PRINTO/ACR Juvenile SLE Response Evaluation responders are:

1. At least 50% improvement compared to baseline in 2 of 5 endpoints, with no more than 1 of the remaining worsening by more than 30%;

2. At least 30% improvement compared to baseline in 3 of 5 endpoints above, with no more than 1 of the remaining worsening by more than 30%.

The number and percentage of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation criteria will be presented in tables for each definition at Week 52, as in Section 11.1. A similar model as in Section 11.1 will be used for the analysis at Week 52. The model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.3.2. Percent Change from Baseline in ParentGA (LOCF)

The percent change from baseline in ParentGA will be summarized by treatment group and visit. The mean percent change from baseline in ParentGA score at each visit will be presented graphically using a line graph by treatment group and visit.

Belimumab and placebo will be compared at Week 52 using an analysis of covariance (ANCOVA) model with treatment group, baseline ParentGA score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates. The least squares (LS) mean and its standard error for each treatment group, the estimated difference in means and 95% CI will also be displayed.

11.3.3. Percent Change from Baseline in PGA (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for percent change in PGA. The model will include treatment group, baseline PGA score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.3.4. Percent Change from Baseline in SELENA SLEDAI Score (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for percent change in SELENA SLEDAI score. The model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.3.5. Percent Change from Baseline in Proteinuria (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for percent change in proteinuria, without any adjustment for covariates other than treatment group.

11.3.6. Percent Change from Baseline in PedsQL GC Physical Functioning Domain Score (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for percent change in PedsQL GC Physical Functioning Domain Score. The model will include treatment group, baseline PedsQL Physical Functioning domain score, baseline age group (5 11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.3.7. Percent of Subjects with a Sustained SRI Response (DO/TF=NR)

The proportion of subjects with a sustained SRI response (defined as having a response on the primary efficacy endpoint at Weeks 44, 48 and 52) will be summarized including 95% CIs as described in Section 11.1. The model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.3.8. Percent of Subjects with a Sustained ParentGA Response (DO/TF=NR)

The proportion of subjects with a sustained ParentGA response (defined as having >0.7 improvement at Weeks 44, 48, and 52 compared to baseline) will be summarized including 95% CIs as described in Section 11.1. The model will include treatment group, baseline Parent GA score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.4. Other Efficacy Analyses for Part A

The model that is selected for the primary efficacy analysis for SRI at Week 52 (Section 11.1) will be the model that is used for all endpoints. If any factor still causes a failure in model convergence, the factor will be removed from the model.

11.4.1. Disease Activity

11.4.1.1. Duration of Longest SRI Response among Subjects with at Least 1 SRI Response

The duration of longest SRI response among subjects with at least 1 SRI response is defined as entire duration of a response that first occurs at or before Week 52 to the last visit in which a subject responds consecutively. It will be calculated by: last consecutive responder date - first consecutive responder date + 1.

11.4.1.2. Absolute Change from Baseline in SELENA SLEDAI (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted. The model will include treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.4.1.3. SELENA SLEDAI Organ System Improvement by Organ System and Visit among Subjects with Organ System Involvement at Baseline (DO/TF=NR)

Details of the grouping of the SELENA SLEDAI organ systems can be found in Appendix 4. Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided. The number and percentage of subjects with organ system improvement and treatment difference by organ system, treatment group, and visit will be presented for subjects with organ system involvement at baseline.

11.4.1.4. SELENA SLEDAI Organ System Worsening by Organ System and Visit among Subjects with no Organ System Involvement at Baseline (LOCF)

Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided. The number and percentage of subjects with organ system worsening and treatment difference by organ system, treatment group, and visit will be presented for subjects with no organ system involvement at baseline.

11.4.1.5. BILAG Improvement by Organ Domain and Visit in Subjects with an A or B Domain Score at Baseline (DO/TF=NR)

Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided. The number and percentage of subjects with BILAG improvement and treatment difference by organ domain, treatment group, and visit will be presented for subjects with an A or B domain score at baseline.

11.4.1.6. BILAG Worsening by Organ Domain and Visit among Subjects with no A Domain Score at Baseline (LOCF)

Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided. The number and percentage of subjects with BILAG worsening and treatment difference by organ domain, treatment group, and visit will be presented for subjects with no A or B domain score at baseline.

11.4.1.7. Absolute Change from Baseline in PGA (LOCF)

Similar analyses as described in Section 11.3.2 will be conducted. The model will include treatment group, baseline PGA score, baseline age group (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates

11.4.1.8. Percent of Subjects with ≥ 0.3 Point Improvement in PGA (DO/TF=NR)

To evaluate the response over time, the number and percentage of subjects with a $\geq$0.3 point improvement in PGA will be summarized by treatment group and visit. The logistic regression model for Week 52 will include treatment group, baseline PGA score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13).

11.4.1.9. Absolute Change from Baseline in ParentGA (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted. The model will include treatment group, baseline ParentGA score, baseline age group (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.4.1.10. Absolute Change from Baseline in Pediatric SLICC/ACR Damage Index at Week 52/Exit Visit

Details of the items and scoring of the Pediatric SLICC/ACR Damage Index can be found in Appendix 7. Similar analyses and displays as described in Section 11.3.2 will be conducted. The model will include treatment group, baseline Pediatric SLICC/ACR damage index score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score ($\leq$12 vs. $\geq$13) as covariates.

11.4.1.11. Worsening (Change >0) in Pediatric SLICC/ACR Damage Index at Week 52/Exit Visit (LOCF)

Similar analyses and displays as described in Section 11.1 will be provided. The model will include treatment group, baseline pediatric SLICC/ACR damage index score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.2. Flares

11.4.2.1. Time to First Severe SFI Flare in Part A

The time to the first modified severe SFI flare over the 52 weeks of Part A will be compared between belimumab and placebo using a Cox proportional hazards model, adjusting for baseline age group (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score (≤12 vs. ≥13). To aid stage 3 review, the SAS LIFETEST output will be provided but this will not be a reported output.

Flares observed at or prior to the baseline visit will not be included in this analysis.

Time to first modified severe SLE flare is defined as the number of days from first exposure until the subject meets an event in Part A (event date – first exposure date + 1). The disposition of subjects is defined as follows in Table 5.

Table 5   Subject Disposition Rules for SFI Flares

Subject Disposition	Event Met	Event Date
Subject has a severe SFI flare or receives protocol restricted medication		
Subject has a severe SFI flare during Part A [1]	Yes	Date of first severe SFI flare in Part A
Subject receives protocol restricted medication resulting in treatment failure during Part A [1]	Yes	Treatment failure date
Subject does not have a severe SFI flare and does not receive protocol restricted medication		
Subject withdraws from Part A	No	Censored at last flare assessment date in Part A
Subject dies during Part A	No	Censored at date of death
Subject completes Part A	No	Censored at last study visit in Part A

[1] If a subject has a severe SFI flare and receives protocol restricted medication then the event date is the earliest of the first severe SFI flare date and the date of treatment failure.

The table will display the number and percentage of subjects with a severe SFI flare in Part A, the median of days to first severe flare and the hazard ratio (and 95% CI) versus placebo from the Cox proportional hazards model. For subjects who experience a severe

flare in Part A, the study day of the flare will be summarized and the table will display the median, minimum, and maximum. A Kaplan-Meier plot for time to first severe SFI flare in Part A will also be produced.

11.4.2.2. Time to First SFI Flare in Part A

Analyses of SFI flare (defined as mild, moderate, or severe) will be performed on the modified SELENA SLEDAI SFI as defined in Section 11.4.2.1. The model will include treatment group, baseline age group (5-11 years vs. 12-18 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.3. Organ-specific Measures

11.4.3.1. Time to First Renal Flare over 52 Weeks

The time to the first renal flare over the 52 weeks of Part A will be compared between belimumab and placebo using a Cox proportional hazards model, adjusting for baseline age group (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score (≤12 vs. ≥13). To aid stage 3 review, the SAS LIFETEST output will be provided but this will not be a reported output.

Data observed at or prior to the baseline visit will not be included in this analysis.

Time to first renal flare is defined as the number of days from first exposure until the subject meets an event in Part A (event date – first exposure date + 1). The disposition of subjects is defined as follows in Table 6.

Table 6   Subject Disposition Rules for Renal Flares

Subject Disposition	Event Met	Event Date
Subject has a renal flare		
Subject has a renal flare during Part A	Yes	Date of first renal flare in Part A
Subject does not have a renal flare		
Subject withdraws during Part A	No	Censored at last flare assessment date in Part A
Subject dies during Part A	No	Censored at date of death
Subject is a treatment failure during Part A	No	Censored at treatment failure date
Subject completes Part A	No	Censored at the Week 52 study visit

The table will display the number and percentage of subjects with a renal flare in Part A, the median of days to first renal flare and the hazard ratio (and 95% CI) versus placebo from the Cox proportional hazards model. For subjects who experience a renal flare in Part A, the study day of the flare will be summarized and the table will display the

median, minimum, and maximum. A Kaplan-Meier plot for time to first renal flare in Part A will also be produced.

11.4.3.2. Time to First Renal Flare over 52 Weeks among Subjects with Baseline Proteinuria >0.5g/24 h

Time to first renal flare over the 52 weeks will be calculated in the same way as described in Section 11.4.3.1 among subjects with baseline proteinuria >0.5g/24 h.

The table will display the number and percentage of subjects with a renal flare in Part A.

11.4.3.3. Shifts in Proteinuria (Observed)

Baseline proteinuria data will be summarized as the number and percent of subjects who are normal (≤0.5 g/24 hour) or high (>0.5 g/24 hour). For each post-baseline visit the data will be summarized by baseline status defined as normal or high. Among subjects normal at baseline the shifts presented will be 'No change' or 'to High'. Among subjects high at baseline, the shifts presented will be 'No change' or 'to normal'.

Additionally, the proteinuria values will be summarized based on shifts occurring any time while on treatment. Among subjects with normal proteinuria at baseline, the percentage of subjects with at least one high post-baseline value will be presented as 'High'; subjects who never experience a high proteinuria value post-baseline will be presented as 'No change'. Among subjects with high baseline proteinuria, subjects with at least one normal post-baseline value will be presented as 'Normal'; subjects who never experience a normal post-baseline value will be presented as 'No change'. No statistical tests will be performed.

11.4.3.4. Percent Change in Proteinuria among Subjects with Baseline Proteinuria >0.5 g/24 h (Observed)

The percent change from baseline in proteinuria among subjects with baseline proteinuria >0.5 g/24 h will be summarized by treatment group and visit. The mean percent change from baseline in proteinuria among subjects with baseline proteinuria >0.5 g/24 h will be presented graphically using a line graph by treatment group and visit.

11.4.3.5. Change from Baseline in Proteinuria (Observed)

Similar analyses as described in Section 11.3.2 will be conducted for change from baseline in proteinuria, without any adjustment for covariates other than treatment group.

11.4.4. Prednisone

For analyses, all corticosteroids are converted to a prednisone equivalent average daily dose (mg/day), therefore analyses refer to average daily prednisone equivalent dose instead of average daily steroid dose. The definition and derivation of this can be found in Section 9.4.26.

11.4.4.1.   Absolute Change from Baseline in Prednisone (Observed)

The absolute change from baseline in average daily prednisone equivalent dose (mg/day) at each post-baseline visit in Part A up to and including Week 52 will be summarized by treatment group. This summary will be based on the observed data only. No imputation will be done for missing data.

The absolute change from baseline in daily prednisone dose at each visit will be presented graphically using a line graph by treatment group. Analyses similar to Section 11.3.2 will be provided. The model will include treatment group, baseline prednisone dose, baseline age group (5-11 years vs. 12-18 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.4.2.   Any Decrease from Baseline in Prednisone (DO/TF=NR)

Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided for the percent of subjects with any decrease in daily prednisone equivalent dose. The model for Week 52 will include treatment group, baseline prednisone dose, baseline age group (5-11 years vs. 12-18 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

A responder is defined as having any reduction in prednisone compared to baseline. If a subject withdraws from Part A and/or receives a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that results in treatment failure designation prior to a scheduled visit, the subject will be considered a non-responder (i.e., no decrease in prednisone) for that and subsequent visits in Part A.

11.4.4.3.   Any Increase from Baseline in Prednisone (LOCF)

Similar analyses and displays as described in Section 11.1 and Section 11.2 (Response over Time) will be provided for the percent of subjects with any increase in daily prednisone equivalent dose. The model for Week 52 will include treatment group, baseline prednisone dose, baseline age group (5-11 years vs. 12-18 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

Missing data due to treatment failure or study withdrawal will be imputed using LOCF.

11.4.4.4.   Percent of Subjects whose Average Prednisone Dose has been Reduced by ≥25% from Baseline during Week 44 to Week 52 (DO/TF=NR)

For this analysis, the average prednisone dose will be the total prednisone dose during Week 44 through Week 52 divided by the number of days during Week 44 through Week 52.

Similar analyses and displays as described in Section 11.1 will be provided. The model will include treatment group, baseline prednisone dose, baseline age group (5-11 years vs. 12-18 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

A responder is defined as having a prednisone reduction by ≥25% from baseline during Week 44 to Week 52. The analysis will be performed on subjects who used prednisone at baseline.

Any subject who withdraws from Part A prior to the Week 52 visit and/or receives a dose of protocol prohibited/restricted medication that results in treatment failure designation prior to the Week 52 visit will be considered a non-responder for this analysis.

11.4.4.5. Cumulative prednisone dose

Cumulative prednisone dose (area under the curve [AUC]) is defined as the sum of daily prednisone dose from Day 1 to Day 365. The daily prednisone dose after the last Part A visit or the day of treatment failure in Part A, if prior to Day 365, will be imputed using the average of the last 28 daily prednisone doses prior to the day of last visit/treatment failure. For subjects who drop out or have treatment failure before Day 28, the daily prednisone dose after early dropout or treatment failure will be imputed using the average post-baseline daily doses available prior to dropout/treatment failure.

The AUC will be summarized by treatment group. The table will display the unadjusted mean, median, SD, minimum and maximum of AUC.

11.4.5. Patient Reported Outcomes

11.4.5.1. Percent Change from Baseline in PedsQL Score (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for each domain and total PedsQL score. The model will include treatment group, baseline PedsQL score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.5.2. Absolute Change from Baseline in PedsQL Score (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for each domain and total PedsQL score. The model will include treatment group, baseline PedsQL score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.5.3. Proportion of subjects who exceeded the Minimal Clinical Important Difference (MCID) in Absolute Change from Baseline in PedsQL Total Score (DO/TF=NR)

Similar analyses and displays as described in Section 11.1 and Section 11.2 will be provided. The model for Week 52 will include treatment group, baseline PedsQL total score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

For the self-reported PedsQL, the MCID is 4.4.

For the parent proxy reported PedsQL, the MCID is 4.5.

11.4.5.4. Percent Change from Baseline in PedsQL Multidimensional Fatigue Scale Scores (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be conducted for each domain and total score. The model will include treatment group, baseline PedsQL Fatigue score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

11.4.5.5. Absolute Change from Baseline in PedsQL Multidimensional Fatigue Scale Scores (LOCF)

Similar analyses and displays as described in Section 11.3.2 will be provided for each domain and total score. The model will include treatment group, baseline PedsQL Fatigue score, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates.

12.   SAFETY ANALYSES

Safety will be evaluated by adverse events, changes in laboratory parameters, vital signs and immunogenicity.

Safety analyses for Part A will be performed on the ITT population. However, if there are more than 15% of subjects who receive a study treatment that is different from the randomized treatment (i.e. >50% of assigned treatment) through the entire study, selected safety analysis will be performed on the as-treated population.

12.1.   Adverse Events

Unless otherwise specified, all adverse event (AE) displays will be presented separately for each study period.

All subjects will be followed for safety through at least 8 weeks post-treatment (unless continuing in Part C).

All AEs will be classified using the standard Medical Dictionary for Regulatory Activities (MedDRA version 20.1) dictionary version available at GSK at the time of reporting, and grouped by system organ class (SOC) and preferred term (PT), unless otherwise stated. The investigator will evaluate all AEs with respect to seriousness, severity, and causality. The severity of an AE is to be evaluated according to the Adverse Event and Laboratory Value Severity Grade Tables in Appendix 5 of the study protocol, if a grade is defined for the AE of interest.

Disease related events (DREs) are AEs which occur in the study population regardless of belimumab exposure, and are defined as any AE with one of the following PTs:

Butterfly rash	Lupus pancreatitis
Cutaneous lupus erythematosus	Lupus pleurisy
Glomerulonephritis	Lupus pneumonitis
Glomerulonephritis membranoproliferative	Lupus vasculitis
Glomerulonephritis membranous	Nephritic syndrome
Glomerulonephritis proliferative	Nephritis
Lupus encephalitis	Neuropsychiatric lupus
Lupus endocarditis	Pericarditis lupus
Lupus enteritis	Peritonitis lupus
Lupus hepatitis	SLE arthritis
Lupus myocarditis	Systemic lupus erythematosus rash
Lupus nephritis	Systemic lupus erythematosus

Events meeting the DRE criteria will be summarized in a table for Part A by SOC, PT, and treatment group but will also be included in all other AE displays.

A table summarizing AEs that occurred prior to treatment start date will be presented, for each SOC and PT by treatment group.

For the following summaries, only treatment-emergent AEs (for Parts A) will be summarized, unless otherwise stated.

A treatment-emergent AE for Part A is an AE that starts during Part A (i.e., on or after the first dose date of randomized Part A treatment but before the first dose date of belimumab in Part B or the first visit date in Part C [as applicable]).

AEs with missing start and/or stop dates will be assumed to be treatment/follow-up emergent. The duration of the AE will be calculated as follows:

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

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

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

- The overall summary of AEs will be repeated for the baseline age group subgroup (5-11 years, 12-17 years).

The number and percentage of subjects experiencing an AE and the incidence of AEs during Part A will be summarized for each of the following AE categories:

- All AEs (by SOC; by SOC and PT; by PT only)
- Serious AEs (by SOC; by SOC and PT; by PT only)
- Severe AEs (by SOC; by SOC and PT; by PT only)
- Study Agent Related AEs (by SOC; by SOC and PT; by PT only)
- AEs Resulting in Study Agent Discontinuation (by SOC; by SOC and PT; by PT only)
- Common Non-Serious Adverse Events (by SOC and PT)
- Serious Adverse Events (Number of Subjects and Occurrences) (by SOC and PT)
- Study Agent Related Serious Adverse Events (by SOC and PT)
- Fatal Serious Adverse Events (by SOC and PT)
- Study Agent Related Fatal Serious Adverse Events (by SOC and PT)
- Non-Fatal Serious Adverse Events (by SOC and PT)
- Study Agent Related Non-Fatal Serious Adverse Events (by SOC and PT)

The tabular summary for each category of AE listed above will include the number of events in the period, number of subjects who reported at least one event during the period, and percentage of subjects who reported at least one AE during the period (incidence) by treatment group for each SOC (where applicable), each PT, and overall. By default, AEs will be sorted by MedDRA System Organ Classes (SOCs), in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any AE within the class, to the SOC with the lowest total incidence. If the total incidence for any two or more AEs 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 internally of SOC.

The tables above for all AEs by SOC and PT and Serious AEs by SOC and PT will be repeated for the baseline age group subgroup (5-11 years, 12-17 years).

A summary of AEs by SOC and severity will also 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 during the specified study period for a given subject.

A summary of AEs by SOC, PT and severity will also be provided by treatment group. The number and percentage of subjects will be summarized as mild, moderate, or severe based on the maximum severity observed within each PT, and within each SOC, during the specified study period.

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

A listing that displays which subject(s) reported each AE will also be produced. AEs will be grouped and sorted by SOC and PT.

A listing of all AEs will be presented, including duration and study day.

Listings for all SAEs, non-fatal SAEs, and all deaths will be produced.

12.2. Adverse Events Leading to Discontinuation of Investigational Product

In addition to the tabular summaries described in Section 12.1, a listing of all AEs leading to permanent discontinuation of study treatment will be produced.

12.3. Adverse Events of Special Interest

The PSAP has been developed to include adverse event of special interest (AESI) summaries for consistent reporting across belimumab studies.

AESI will be adjudicated on a regular basis and finalized prior to database lock as per the process described in Appendix 15.

Categorizations for the AESIs will be defined in Section 15 and Section 16 of the PSAP and reporting of AESIs for these analyses is defined below.

An overall summary of AESI will be presented and each specific category of AESI will be presented separately by PT. Infection AESIs will also be presented by PT for all infections leading to discontinuation. 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)
    - Malignancies Including NMSC
    - Solid Tumour
    - Hematologic
    - Skin (All)
        - NMSC
        - Excluding NMSC
        - Skin (all Skin)
    - 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
        - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction Customized MedDRA Query (CMQ) narrow search
    - Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search
        - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search
    - Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ algorithmic search
        - Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ algorithmic search
    - 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
  - 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)
  - Suicide/self-injury
    - Serious Suicide/self-injury
  - Serious Suicide/Self-injury per GSK Adjudication
    - Suicidal behaviour per GSK Adjudication
    - Completed Suicide per GSK Adjudication
    - Suicidal Ideation per GSK Adjudication

> ▪ Self-injurious Behaviour Without Suicidal Intent per GSK Adjudication
- Deaths

In addition to the tabular summary of Adverse Events of Special Interest, a listing will also be produced along with separate listings of serious/severe infections and Malignancy Adverse Events of Special Interest.

The overall summary of AESIs (above) will be repeated for the baseline age group subgroup (5-11 years, 12-17 years).

For Part A, infusion, hypersensitivity, and anaphylactic reactions will be presented using the definitions from the PSAP. A summary of infusion, hypersensitivity, and anaphylactic reactions leading to study agent discontinuation and serious infusion, hypersensitivity, and anaphylactic reactions will also be presented by category and PT for Part A.

For Part A, an overall summary of AEs falling into the infections category will be presented by treatment group. Tables of infection AEs will also be presented by PT for all infections leading to discontinuation for Part A. The tabular summaries will include the number of events, number of subjects who reported at least one event, and percentage of subjects who reported at least one AE (incidence) by treatment group.

Depression, suicide and self-injury AESI will be presented by Category and PT.

Deaths will also be presented by Category and PT.

12.3.1.   Infusion/Anaphylaxis/Hypersensitivity Reactions by Infusion

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

- Post-Infusion Systemic Reactions per Anaphylactic Reactions CMQ Broad Search by PT, in First Six Infusions

- Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ Broad search by PT, in First Six Infusions

- Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK Adjudication by PT, in First Six Infusions

- Serious Delayed Acute Hypersensitivity Reactions per GSK Adjudication by PT, in First Six Infusions

- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Adjudication by PT, in First Six Infusions

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

Suicidality assessments are completed at every visit in Part A for subjects aged 12 years and older. 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 3, 4 or 5 on the C-SSRS, the investigator will be prompted to complete the Possible Suicidality Related Questionnaire (PSRQ).

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)

- Behavior details for subjects who have any suicidal behavior recorded at any point on the study (including screening)

- The most severe suicidal ideation details for subjects who have any suicidal ideation recorded at any point on the study (including screening)

12.4.1. C-SSRS Suicidal Ideation or Behavior

The number and percentage of subjects with each category of suicidal ideation or behavior during treatment (post Day 1 assessment onwards) will be presented, selecting the worst record a subject has for each category. The categories of suicidal ideation and behavior are presented in increasing order of severity from 1 to 10. For the rows pertaining to suicidal behavior, the number of subjects who have the specified behavior at least once during treatment are presented. For the rows pertaining to suicidal ideation, the number of subjects whose maximum ideation at any on-treatment assessment in Part A is the specified ideation is presented. Within each category, subjects may have more than one type of suicidal ideation and behavior.

12.4.2. C-SSRS Suicidal Ideation or Behavior Relative to Pre-treatment

The number and percentage of subjects with treatment-emergent (i.e. new or worsened values compared to the screening results) suicidal ideation or behavior during Part A (post Day 1 assessment onwards) will be presented. A subject must have at least one pre-treatment assessment and at least one on-treatment assessment in Part A in order to be included in this display. A subject may have more than one treatment-emergent suicidal ideation and/or behavior.

12.4.3. 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 in Part A (up to and including Week 52) category will be produced. The pre-treatment period is based on the lifetime evaluation at screening. A subject must have at least one pre-treatment assessment and at least one on-treatment assessment in Part A in order 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.

12.5. Clinical Laboratory Evaluations

For laboratory analyses, only analytes with a numeric normal range will be analyzed. Summaries and analyses will be performed based on the observed data. No imputation will be done for missing data. Baseline is defined as described in Section 9.4.1. See Appendix 5 of the Protocol for a list of laboratory parameters and a definition of the toxicity grades.

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

12.5.1. Laboratory Descriptive Statistics by Visit

Descriptive statistics for each analyte will be displayed by treatment group for each visit during that study period. No statistical tests will be performed.

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

12.5.2. Worst Laboratory Toxicity Grade Post-baseline

Laboratory toxicity will be graded using Adverse Event Severity Grading Tables when possible. The worst laboratory toxicity grade during the study period, including unscheduled visits, for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries, urinalysis, and immunoglobulins) will be presented.

12.5.3. Laboratory Toxicity ≥ 2 Grade Shift Post-baseline

Toxicity grade shifts from baseline of ≥ 2 grades during the study period, including unscheduled visits, will be summarized for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries, urinalysis, and immunoglobulins). The table will display the number and percentage of subjects with at least one ≥ 2 grade shift as well as the specific shift categories: Grade 0 to 2, Grade 0 to 3, Grade 0 to 4, Grade 1 to 3, Grade 1 to 4 and Grade 2 to 4.

12.5.4. Laboratory Reference Range Shifts from Baseline

For laboratory tests without toxicity grades within each laboratory category (hematology, liver function, electrolytes, other chemistries, and urinalysis), shifts relative to the normal range will be summarized for each analyte as shifts 'to low' and shifts 'to high'. For the 'to low category' the percentage of subjects with at least one low post-baseline value, including unscheduled visits, in the study period relative to baseline will be displayed using the categories: no shift to low and normal/high to low. For the 'to high category' the percentage of subjects with at least one high post-baseline value in the study period relative to baseline will be displayed using the categories: no shift to high and normal/low to high. No statistical tests will be performed.

A laboratory value that is above the testing laboratory's normal range will be considered a high abnormal laboratory value. A laboratory value that is below the testing laboratory's normal range will be considered a low abnormal value.

12.5.5. Immunoglobulin Levels Reference Range Shifts from Baseline

For immunoglobulins (IgG, IgA, and IgM), reference range shifts will be summarized across all visits in the study period based on the baseline normal range category. For subjects with immunoglobulin values below the LLN, the number and percentage of subjects who 'remained low' or went 'to normal/high' post-baseline will be summarized. Similarly, for subjects with immunoglobulin values within the normal range or above the ULN, the number and percentage of subjects who 'remained normal/high' or went 'to low' post-baseline will be summarized.

12.5.6. Immunoglobulin Levels Below LLN by Visit

The number and percentage of subjects with immunoglobulin values (IgG, IgA, and IgM) below the LLN at each visit in the study period will also be presented for all subjects and then repeated for subjects above LLN at baseline. No statistical tests will be performed.

12.5.7. Immunoglobulin Levels Above LLN by visit

The number and percentage of subjects with immunoglobulin values (IgG, IgA, and IgM) above the LLN at each visit in the study period will also be presented for all subjects and then repeated for subjects below LLN at baseline. No statistical tests will be performed.

12.5.8. Functional Antibodies

The percent change from baseline for functional antibodies (Anti-tetanus toxin IgG, anti-diptheria IgG, and anti-pneumococcal IgG) among subjects positive at baseline will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. No statistical tests will be performed.

A listing will be produced for all functional antibody data during Part A.

12.5.9. Vaccine Antibody Titers

A listing will be produced for all vaccine antibody titer data during Part A.

12.5.10. Liver Events

A listing will be produced for liver monitoring/stopping events reported during Part A.

12.6. Immunogenicity

For immunogenicity assessment, a tiered testing approach is used. A screening assessment is performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay is then carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titer value will be also obtained to quantify the degree of binding in a titration assay

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

For incidence of subjects with positive binding antibody during the study period, a table will be produced summarizing results for the binding antibody assay by treatment group and visit. The table will include the number and proportion of subjects in each results category for each visit in the study period (including early withdrawal visit). Binding confirmatory assay results will be categorized as negative, persistent positive (defined as a positive immunogenic response at least two consecutive assessments during the study period or a single result at the final assessment in the study period) or transient positive (defined as a single positive immunogenic response that does not occur at the final assessment in the study period). This table will also summarize the highest binding assay confirmatory result obtained for each subject for Any Time Post-Baseline (lowest to highest result is Negative, Transient Positive, Persistent Positive). A listing of immunogenicity results will also be presented.

12.7. Vital Signs

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

A listing of all subjects' vital signs will be presented.

12.8. Concomitant Procedures/Surgery

A listing of all concomitant procedures/surgery will be presented.

13. CLINICAL PHARMACOLOGY DATA ANALYSES

13.1. Pharmacokinetic Analyses

13.1.1. Drug Concentration Measures

Pharmacokinetic data in Part A will be listed, presented in a graphical and tabular form. It will be summarized by visit, nominal time and age group or cohort (All Cohorts, Cohorts 1 and 3 versus Cohort 2). Standard summary statistics will be calculated (i.e. mean, geometric mean and SD, 95% confidence intervals for mean/geometric means, CV%, median, minimum, and maximum). Median and geometric mean belimumab concentrations will be graphically presented.

To assess the effect of body size on belimumab exposure, the table described above (Cohorts 1 and 3 versus Cohort 2) will also be repeated for the following subgroups: baseline body weight quartiles and baseline BMI categories.

PK samples will be collected from all subjects during Part A. Additional PK samples will be obtained from the first 12 subjects in each of the two age groups (i.e. Cohorts 1 and 2) for interim PK assessment.

The reconciliation of the PK eCRF and SMS2000 data will be performed by, or under the direct auspices of Clinical Pharmacology Science & Study Operations Clinical Pharmacology Data Sciences (CPSSO), GlaxoSmithKline.

The merge of PK concentration data, randomization and eCRF data will be performed by, or under the direct auspices of, Clinical Statistics (Programmer), GlaxoSmithKline.

13.1.2.   Population Pharmacokinetic (PopPK) Analyses

Belimumab serum concentration-time data will be analyzed by population pharmacokinetic (PopPK) methods using a non-linear mixed-effects modelling approach.

The key objectives of this analysis are:

- Develop a population PK model that characterizes the PK disposition of belimumab following intravenous administration in pediatric subjects with SLE and evaluate the potential effect of selected covariates on PK parameters

- Compare belimumab exposure in pediatric SLE patients to exposure in adult SLE Phase 3 patients

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

The details for this PopPK analysis are provided in Appendix 18.

13.2.   Pharmacodynamic Analyses

Pharmacodynamic (PD) analyses are not prospectively planned for this study.

13.3.   Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/Pharmacodynamic (PK/PD) analyses are not prospectively planned for this study.

14.   BIOMARKER DATA ANALYSIS

Biomarker analyses for Part A will be performed on the ITT population.

The model that is selected for the primary efficacy analysis for SRI at Week 52 (Section 11.1) will be the model that is used for all endpoints. If any factor still causes a failure in model convergence, the factor will be removed from the model.

For the duration of Part A, biomarker data that have the potential to unblind the study team (serum immunoglobulin isotypes IgA and IgM and B cell results) will not be transferred to the blinded study team. Instead, blinded datasets will be required which contain dummy results. These blinded datasets will be exact models of the real datasets which will be received following unblinding at the database lock for Part A. This will

ensure that programs written using blinded data will still run on the real treatment codes and real unblinded data following the first database lock.

14.1. Immunoglobulins, Autoantibodies, and Complement

Serum immunoglobulin isotypes (IgG, IgA, and IgM), autoantibodies (anti-dsDNA), CRP, and complement (C3 and C4) will be assessed in Part A.

14.1.1. Percent Change from Baseline in Immunoglobulins, Anti-dsDNA, CRP, and Complement (Observed)

The percent change from baseline for immunoglobulins, percent change from baseline in anti-dsDNA and CRP for subjects who were positive at baseline (anti-dsDNA ≥ 30 IU/mL and CRP ≥4 mg/L), and percent change from baseline in complement for subjects with low values at baseline (C3 <90 mg/dL and C4 <10 mg/dL) will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. Similar analyses as described in Section 11.3.2 will be carried out.

A line graph for the median percent change from baseline in each of these biomarkers will be presented by treatment group.

14.1.2. Absolute Change from Baseline in Complement (Observed)

The absolute change from baseline for complement for subjects with low values at baseline (C3 <90 mg/dL and C4 <10 mg/dL) will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. Similar analyses as described in Section 11.3.2 will be carried out.

A line graph for the median absolute change from baseline in each of these biomarkers will be presented by treatment group.

14.1.3. Shifts in Immunoglobulins, Anti-dsDNA, CRP, and Complement (Observed)

Shift tables will be used to summarize the changes in immunoglobulins, autoantibodies, and complement by visit.

For IgG, IgA, and IgM baseline data will be summarized as the number and percent of subjects who are low or normal/high at baseline. For post-baseline visits the data will be summarized by baseline status defined as low (IgG, IgA, IgM < LLN) or normal/high (IgG, IgA, IgM ≥ LLN). Among subjects who are low at baseline, the shifts presented will be low to normal/high and low to low. Among subjects normal/high at baseline, the shifts presented will be normal/high to normal/high and normal/high to low.

For anti-dsDNA, baseline data will be summarized as the number and percent of subjects who are positive and negative at baseline. For post-baseline visits the data will be summarized by baseline status defined as positive (≥30 IU/mL) or negative (<30 IU/mL). Among subjects who are positive at baseline, the shifts presented will be positive to

negative and positive to positive. Among subjects negative at baseline, the shifts presented will be negative to negative and negative to positive.

For CRP, baseline data will be summarized as the number and percent of subjects who are positive and negative at baseline. For post-baseline visits the data will be summarized by baseline status defined as positive ($\geq$4 mg/L) or negative (<4 mg/L). Among subjects who are positive at baseline, the shifts presented will be positive to negative and positive to positive. Among subjects negative at baseline, the shifts presented will be negative to negative and negative to positive.

For C3 and C4, baseline data will be summarized as the number and percent of subjects who are low or normal/high at baseline. For post-baseline visits the data will be summarized by baseline status defined as low (C3 <90 mg/dL, C4 <10 mg/dL) or normal/high (C3 $\geq$90 mg/dL, C4 $\geq$10 mg/dL). Among subjects who are low at baseline, the shifts presented will be low to normal/high and low to low. Among subjects normal/high at baseline, the shifts presented will be normal/high to normal/high, and normal/high to low.

14.2. B Cell Analyses

The following B cell subsets will be summarized: CD19+, CD20+, CD20+/27+ memory, CD20+/27– naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset, CD20-/138+ plasma cells, and CD27+BRIGHT/CD20– short-lived plasma cells.

14.2.1. Percent Change from Baseline in B Cell Subsets (Observed)

The percent change from baseline in B cell subsets will be summarized by treatment group and visit. This summary will be based on the observed data. No imputation will be done for missing data. Similar analyses as described in Section 11.3.2 will be carried out.

A line graph for the median percent change from baseline in each of the B cell subsets will be presented by treatment group.

15. 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.

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17. APPENDICES

17.1. Appendix 1 - Data Cut-off Rules for Part A

Data cut-off rules will be applied to the SDTM datasets.

Therefore, for the Supplemental (SUPP) datasets which do not contain any date information, date information will be merged from the main/parent datasets prior to applying cut-off.

Note1:

For the purpose of the cut-off:

1) A subject who goes from PART A to PART B is defined as:

- a subject with a 'PART B WEEK 4' dose in Exposure OR
- a subject who does not have 'PART B WEEK 4' dose in Exposure BUT has status question data DS.DSREGCD = 3 (Yes, continuing on to Part B)

2) A subject who goes from PART A to PART C is defined as:

- a subject having a 'PART C WEEK 4' assessment date OR
- a subject who does not have a 'PART C WEEK 4' assessment date BUT has status question DS.DSREGCD = 4 (Yes, continuing on to Part C)

Cut-off rules:

1) If subject does not have any PART B assessment date AND

subject does not have any PART C assessment date AND

DS.DSCONT (Is subject continuing in the study) at VISIT= 'END OF PART A' is **missing**

THEN **do not apply any cut off** and include all data

2) If subject does not have any PART B assessment date AND

subject does not have any PART C assessment date AND

DS.DSCONT (Is subject continuing in the study) at VISIT='END OF PART A' is **'N'**

THEN **do not apply any cut off** and include all data

3) If a subject has gone from **PART A** to **PART B** (see Note1)

OR subject has gone from **PART A** to **PART B** to **PART C**

then:

- assessments with dates falling **on the same date/time or before** END OF PART A dose in Exposure (first PART B dose or WEEK 52 data) will be **included** in PART A

- assessments with dates falling **after the date/time** of END OF PART A dose in Exposure (first PART B dose or WEEK 52 data) will be **excluded** from PART A

- for any LOG data with dates (except CONMEDs), follow the same rule as assessments

- AEs/SAEs/AESIs with dates falling **before** the date/time of END OF PART A dose in Exposure (first PART B dose) will be **included** in PART A

- AEs/SAEs/AESIs with dates falling **after** the date/time of END OF PART A dose in Exposure (first PART B dose) will be **excluded** from PART A

- AEs/SAEs/AESIs occurring on the date of END OF PART A dose in Exposure (first PART B dose) will be **included** in PART A *unless* the onset time is available and is later than the infusion start time.

4) If a subject has gone from **PART A** to **PART C** (see Note1) then:

- Assessments and AEs/SAEs/AESIs falling on or before the latest Part A assessment date (including 8 week and 16 week follow ups), should be included in PART A.

- Anything falling after this date should be excluded from PART A.

5) The following Data Cut Off Algorithm will be used for CONMEDS Part A Data:

Include all medications with start date completely missing.

Include all medications for untreated "screening only" subjects.

For the remaining cases:

a. Refer to the rules in Section 9.3 to impute any missing/partial dates.

b. Categorize each subject as one of:
   - "Part A Only"
   - "Part A to Part B" (including subjects who eventually go on to Part C)
   - "Part A to Part C"

See above for details of how to do this.

c. Derive the cut-off date and time (CUTOFFDT/CUTOFFTM) in accordance with the above rules. In summary:
   - For "Part A Only" subjects: Leave CUTOFFDT/CUTOFFTM missing
   - For "Part A to Part B" subjects: Set CUTOFFDT/CUTOFFTM to the date/time of the first Part B (open label) dose

- For "Part A to Part C" subjects: Set CUTOFFDT to the date of the final Part A assessment and leave CUTOFFTM missing.

d. Now decide whether to include/exclude each medication depending on the subject category:

   For "Part A only" subjects: Include all medications.

   For "Part A to Part B" subjects: Only exclude medications which start on/after the first Part B dose. I.e. include **unless**:
   - (Imputed) CMSTDT > CUTOFFDT or
   - CMSTDT=CUTOFFDT and CMSTTM >= CUTOFFTM
   - (Include meds with CMSTDT=CUTOFFDT and CMSTTM missing.)

   For "Part A to Part C" subjects: Only exclude medications which start after the final Part A assessment. I.e. include **unless** (imputed) CMSTDT > CUTOFFDT.

17.2.　Appendix 2 – Important Protocol Deviations

A summary of important protocol deviations is given below. Further detail is given in the Protocol Deviation Management Plan (PDMP): Dated:　11Jan2018 (Version 0.3).

<u>**Important Violations**</u>

According to the Reporting and Analysis Plan (RAP) and the PDMP, if a subject fails to meet the following major study criteria as recorded on the protocol deviations eCRF page, then they will be considered as having an important protocol violation:

- Eligibility Criteria Not Met
  - Any inclusion/exclusion criteria deviation.
  - Study drug administered at Day 0 prior to confirmation that subject meets all eligibility criteria
- Subject developed withdrawal criteria specified in the protocol but were not withdrawn and continued dosing/study
  - Subject became pregnant.
  - In Part A or Part B, received prohibited therapy
  - In Part A are deemed a treatment failure
  - Liver chemistry stopping criteria
  - IgG stopping criteria
- Subject used prohibited medication(s) and/or therapies at any time during the study (not including medications resulting in treatment failure)
- Received wrong treatment or incorrect dose
  - Site administered wrong IP to subject
  - Dose of ≥20mg/kg/day given at more than 2 consecutive visits
  - Missed 3 or more consecutive infusions
  - Infusion given in under 50 mins
  - Total Volume of infusion is not in the range 0-250mL. (100ml may be allowed but this is mainly for small children and the belimumab concentration must not exceed 5mg/mL)
- Informed consent form (ICF) process
  - Subject never signed ICF or its amendment
  - ICF was signed after study procedure was done
- Failure to report SAE, pregnancy, or liver function abnormalities per protocol
- Study blind/unblind procedures:　Investigator/site staff/GSK blinded staff did not remain blinded to treatment assignment through Week 52/Exit visit efficacy evaluation

- Randomization procedures

  o Study drug assigned in IXRS prior to confirming subject eligibility on Day 0; then determined not to be eligible and subject NEVER dosed

  o Subject was not stratified correctly in IXRS

- Missed assessments or procedures

  o Failure to implement adequate safety monitoring for key potential risks as described in the protocol (for example, infections, malignancy, suicidality, post-infusion reactions, pregnancy - where applicable)

  o Missing BILAG, SELENA SLEDAI, Physician's Global Assessment (components of primary endpoint: SRI) at Day 0 (Baseline) or Week 52

  o Missing PK samples required for dose determination for subjects in Cohort 1 and Cohort 2

- Equipment Procedure: Physician's Global Assessment (PGA) scales: the 10cm ruler GSK provided for the VAS measurement was not used or a photocopy of the scale was used which was less than 10cm

- Other, a deviation that does not satisfy the above criteria, however, in the judgment of the clinical team, including the medical monitor, constitutes an important protocol violation

Per Protocol Population Exclusions

According to the RAP and the PDMP, if a subject meets the following major study criteria, then they will be excluded from the Per Protocol population:

- Received an incorrect treatment most of the time (>50% of the time).

- Did not have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria (Inclusion Criterion 2)

- Did not have active SLE disease defined as a SELENA SLEDAI score >= 6 at screening (Inclusion Criterion 3)

- Did not have unequivocally positive anti-nuclear antibody (ANA) and/or anti-dsDNA test results from 2 independent time points as defined in the inclusion criteria (Inclusion Criterion 4)

- Was not on a stable SLE treatment regimen at baseline as defined in the protocol (Inclusion Criterion 5)

- Received an excluded medication prior to Day 0 (Exclusion Criteria 1-7)

- Missed 3 or more consecutive study agent infusions

- Study blind/unblind procedures: Investigator/site staff/GSK Clinical team did not remain blinded to treatment assignment through Week 52/Exit visit efficacy evaluation

- Other, a deviation that does not satisfy the above criteria, however, in the judgment of the clinical team, including the medical monitor, constitutes an exclusion from the Per Protocol population

Specific Adjudications: All violations will be discussed and adjudicated as important or not important and for exclusion from the Per Protocol population.

17.3.   Appendix 3 – American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of Systemic Lupus Erythematosus*
[Tan, 1982; Hochberg, 1997]

Criterion	Definition
1. Malar "butterfly" rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration usually painless.
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints characterized by tenderness.
6. Serositis	a. Pleuritis (convincing history or pleuritic pain or rub heard by physician or evidence of pleural effusion), *OR* b. Pericarditis (documented by ECG, rub, or evidence or pericardial effusion).
7. Renal disorder	a. Persistent proteinuria (>0.5 grams/day or >3 + if quantitation not performed) *OR* b. Cellular casts (may be red cell, hemoglobin, granular, tubular, or mixed).
8. Neurologic disorder	a. Seizures (in the absence of offending drugs or known metabolic derangements; ie, uremia, ketoacidosis, or electrolyte imbalance) *OR* b. Psychosis (in the absence of offending drugs or known metabolic derangements; ie, uremia, ketoacidosis, or electrolyte imbalance.
9. Hematologic disorder	a. Hemolytic anemia (with reticulocytosis) *OR* b. Leukopenia (<4000/mL total on 2 or more occasions), *OR* c. Lymphopenia (<1500/mL on 2 or more occasions), *OR* d. Thrombocytopenia ($<100,000$/mL in the absence of offending drugs).
10. Immunologic disorder	a. Anti-DNA (antibody to native DNA in abnormal titer), *OR* b. Anti-Sm (presence of antibody to Sm nuclear antigen), *OR* c. Positive-finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization (TPI) or fluorescent treponemal antibody (FTA) absorption test.
11. Antinuclear antibody (ANA)	Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

*   The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval or observation.

17.4.   Appendix 4 – SELENA SLEDAI Assessment

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.
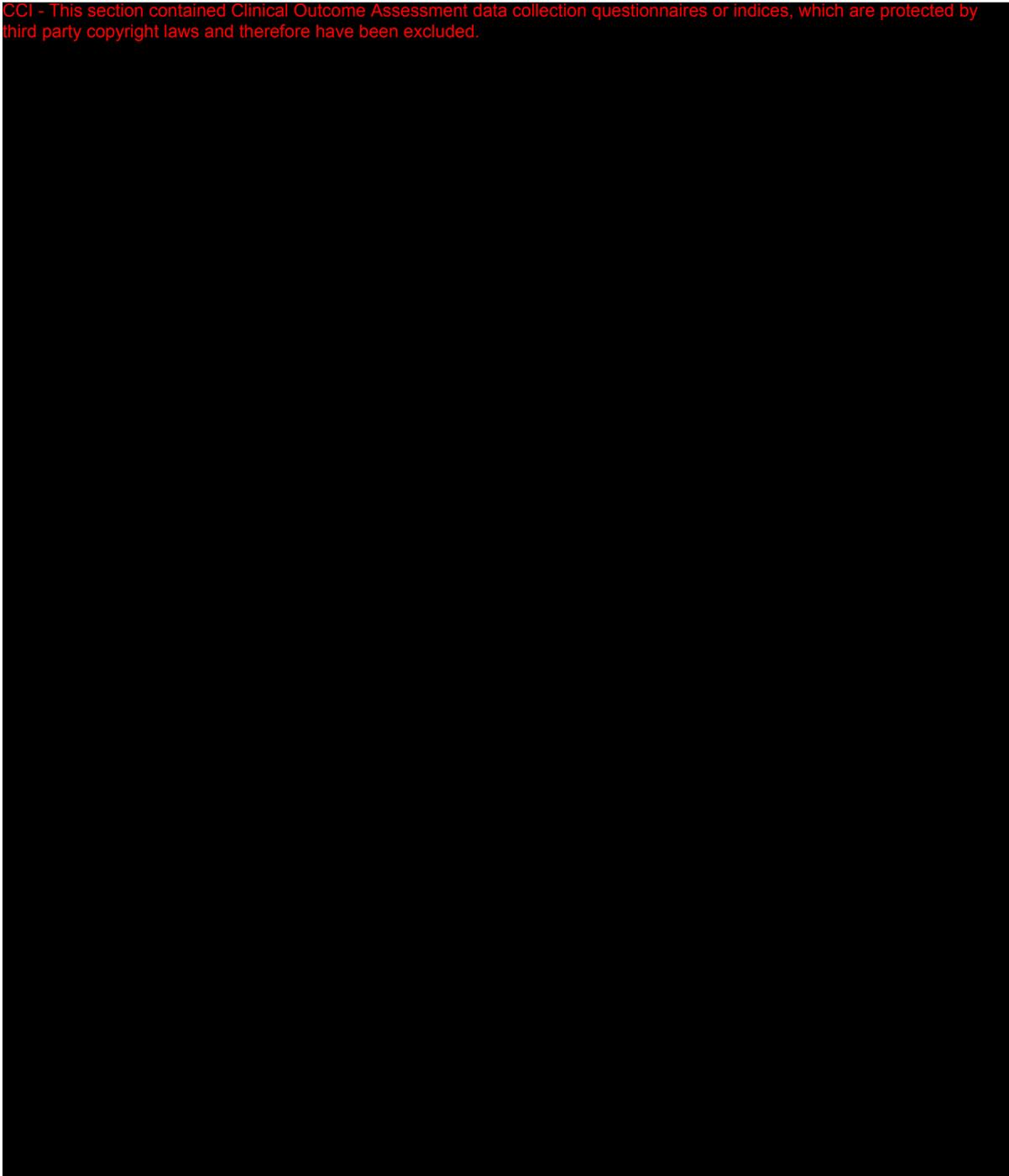
17.5. Appendix 5 – BILAG Index Assessment

17.6.   Appendix 6 – SLE Flare Index
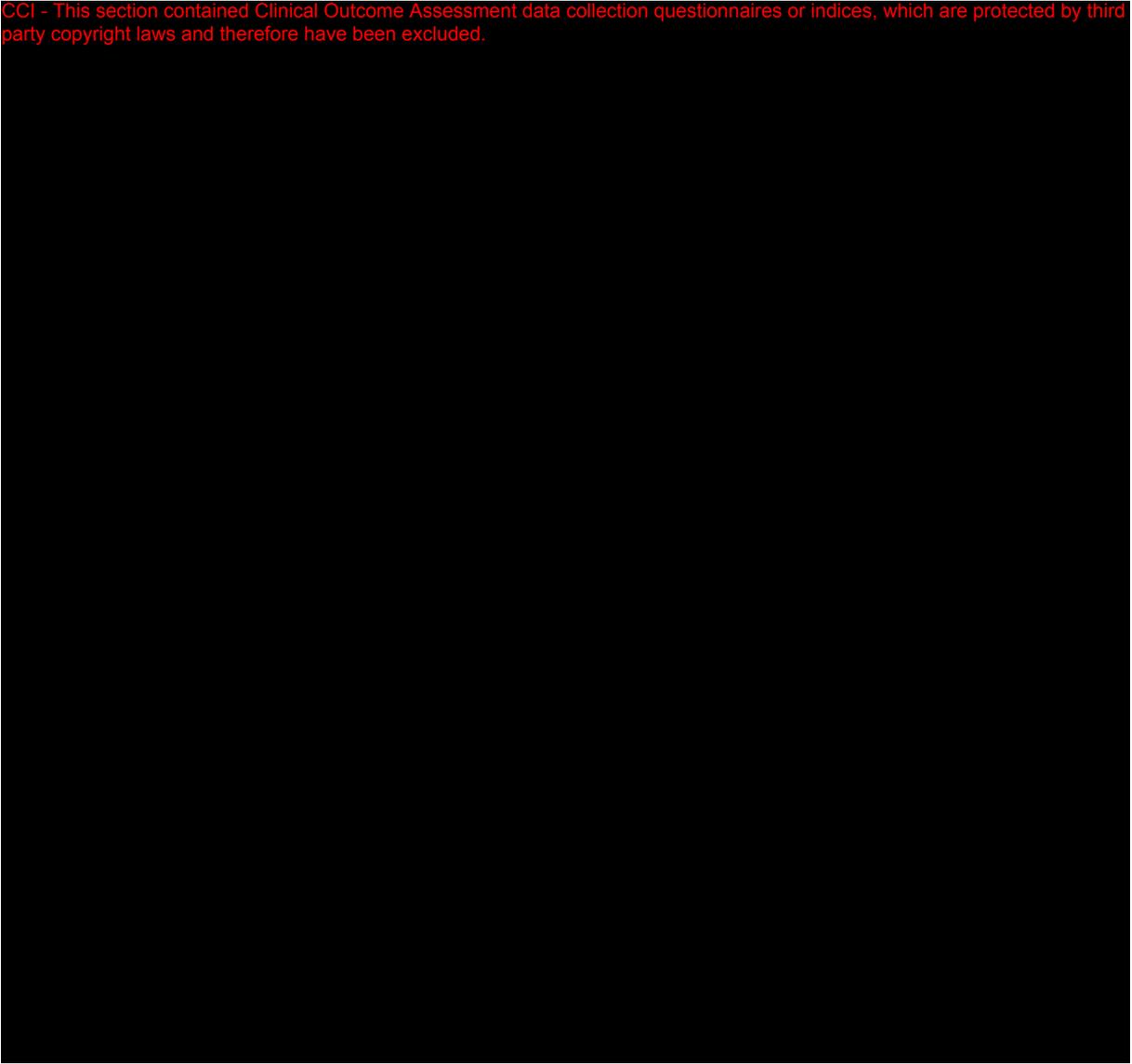
17.7.   Appendix 7 – Pediatric SLICC/ACR Damage Index
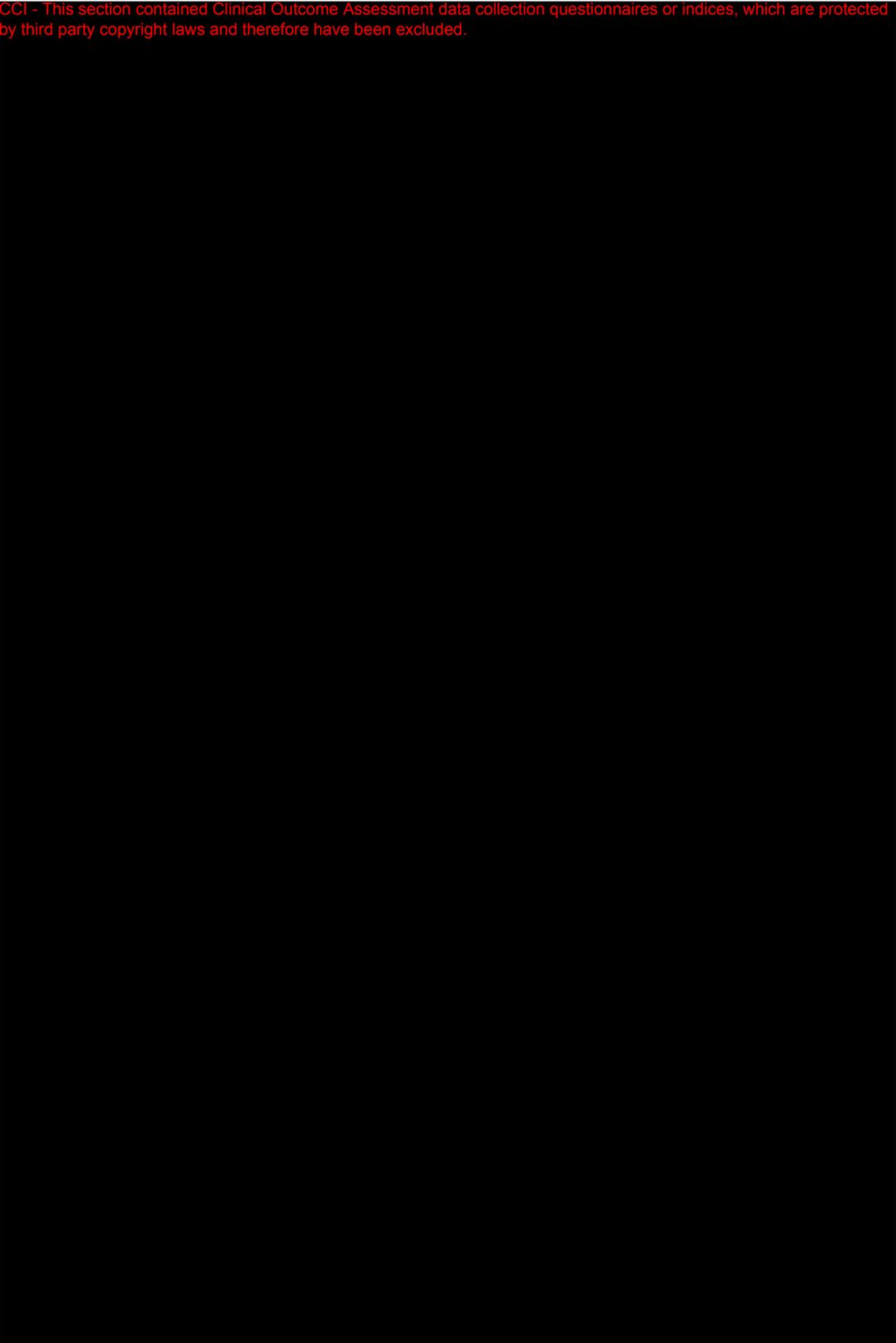
17.8.   Appendix 8 - Physician's Global Disease Assessment

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.

17.9.   Appendix 9 - Parent's Global Disease Assessment

Considering all the ways the illness affects your child, please evaluate how he/she feels <u>at the moment</u>

(choose the most accurate score)

VERY WELL																					VERY POORLY

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10
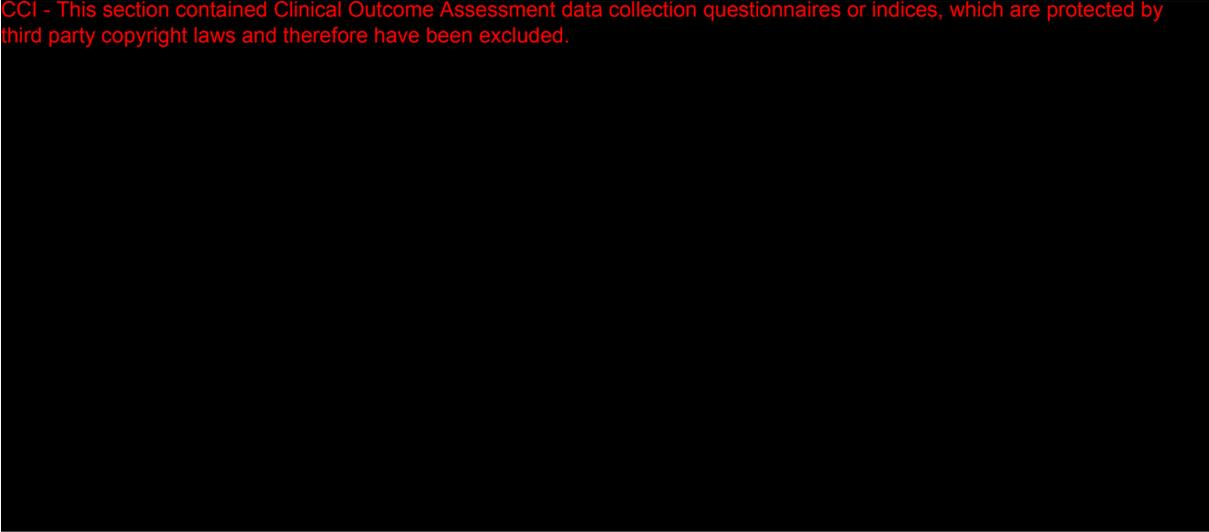
17.10. Appendix 10 – PedsQL Generic Core Scale

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
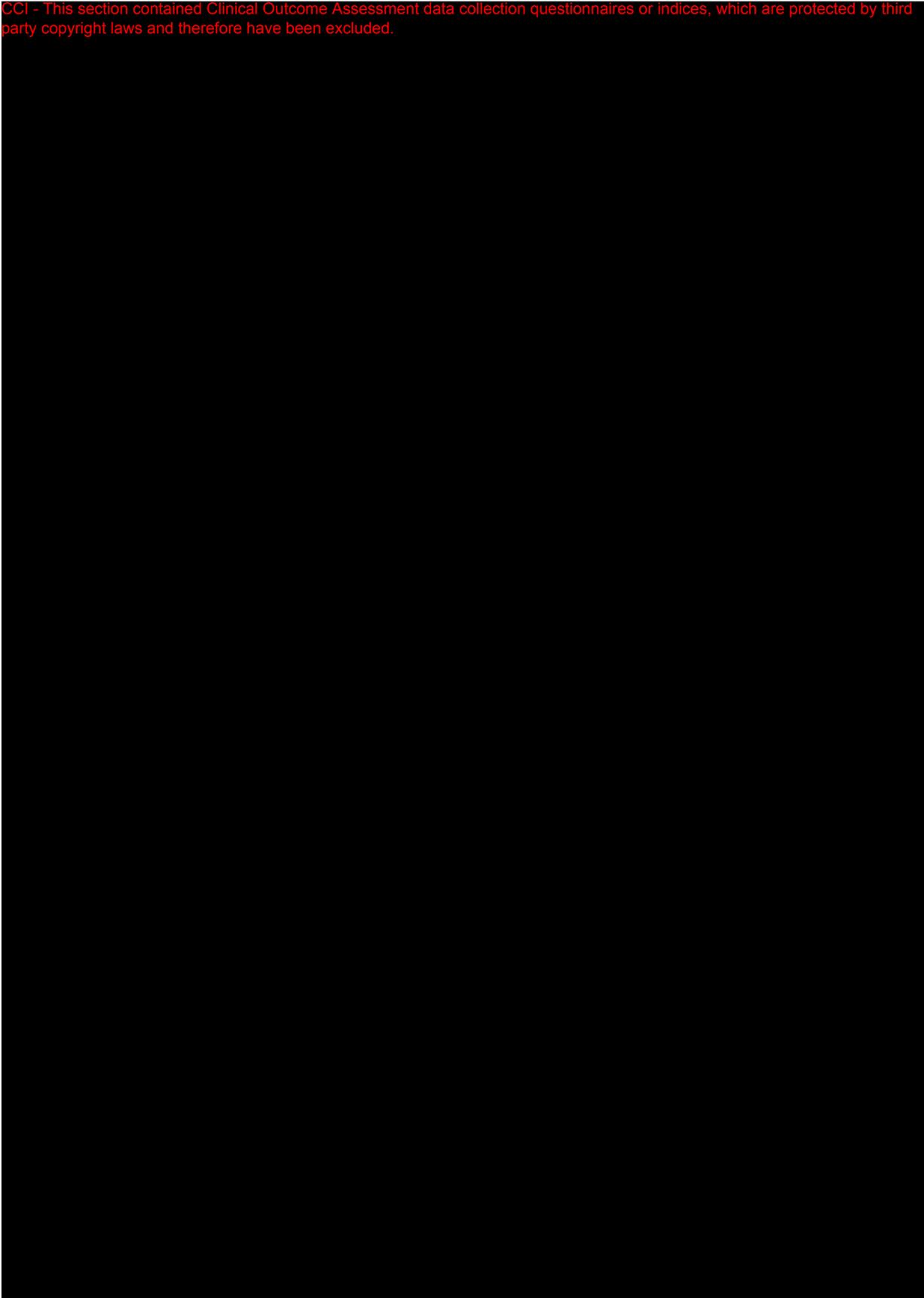
17.11. Appendix 11 – PedsQL Multidimensional Fatigue Scale
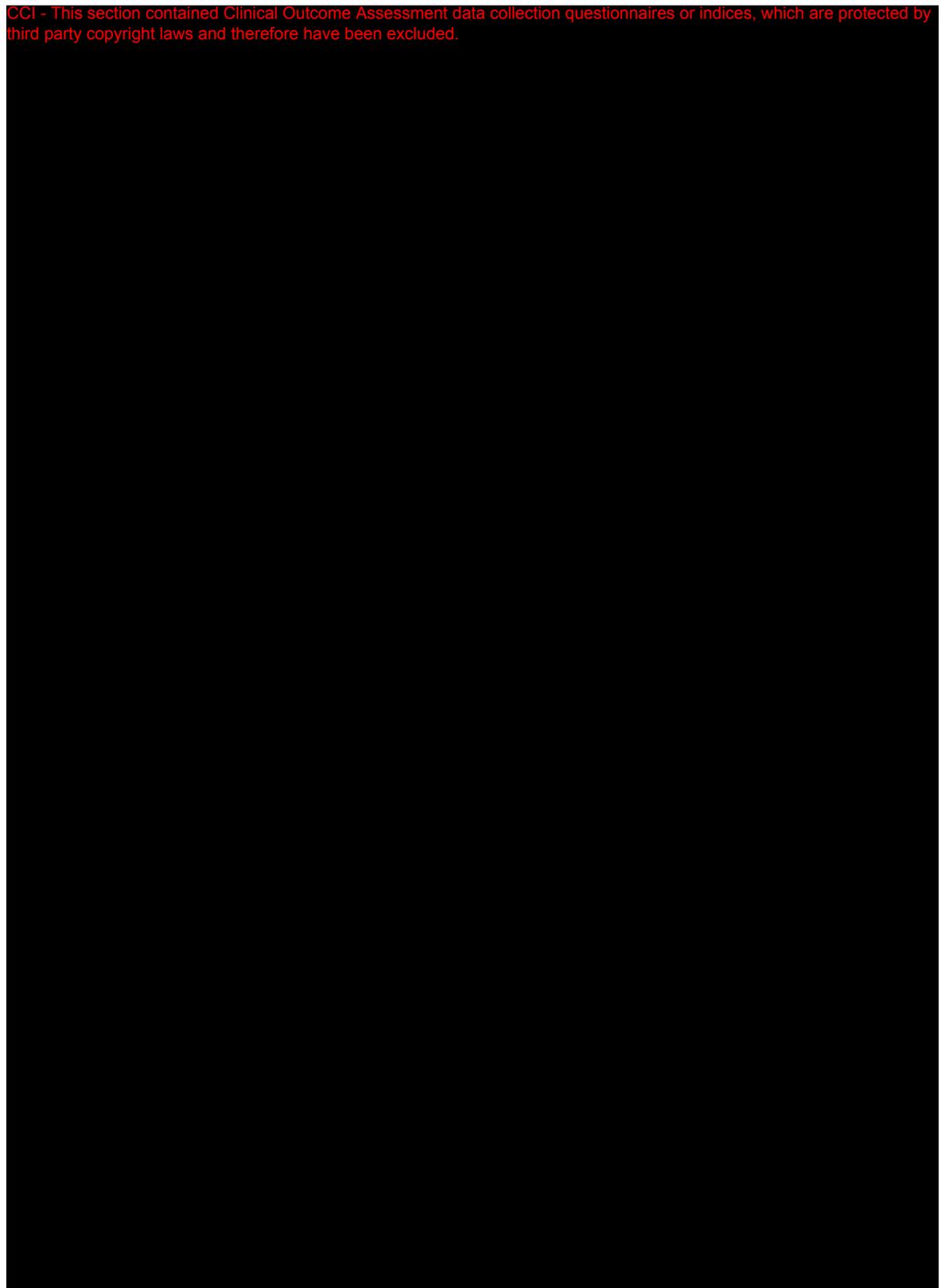
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
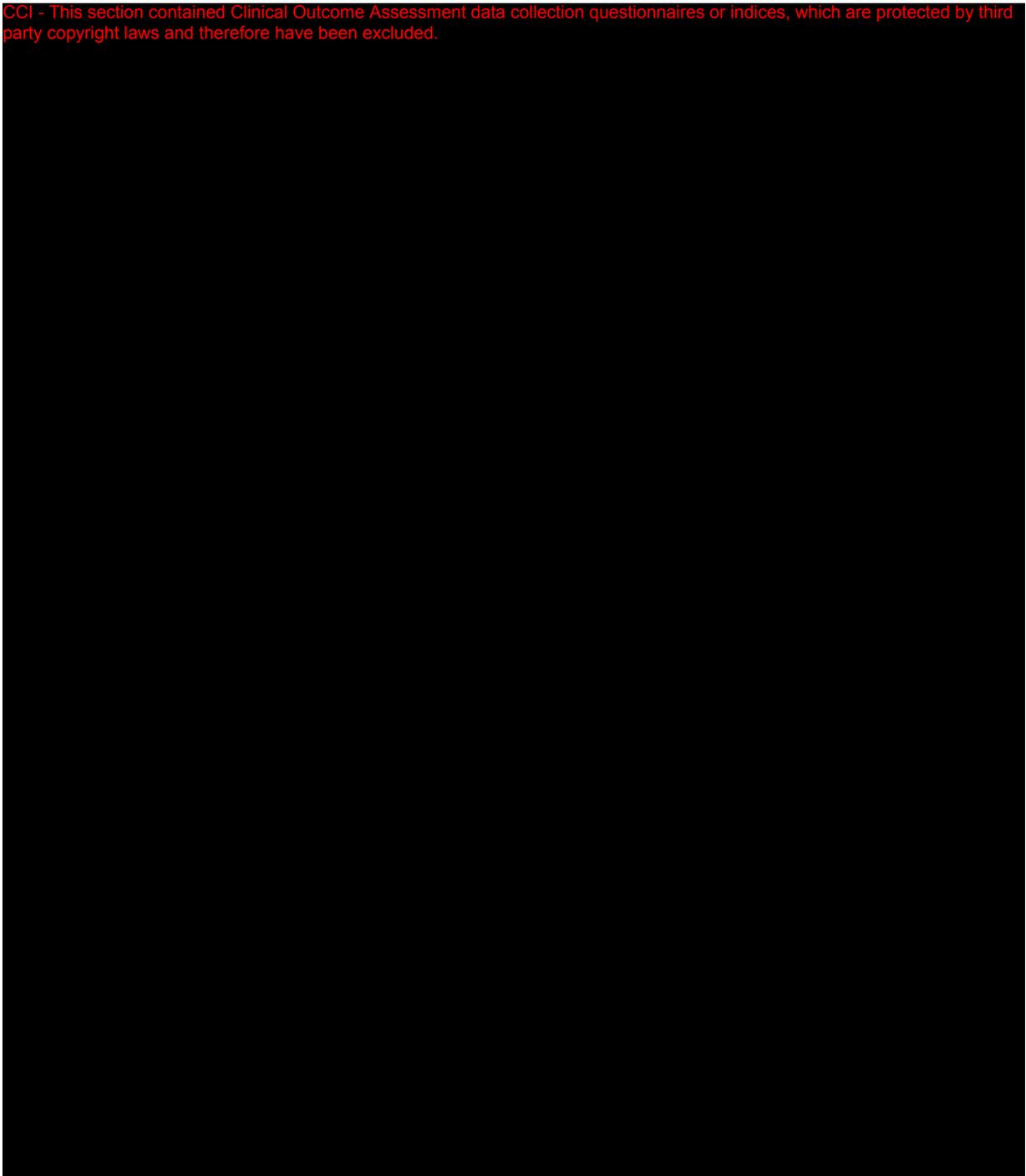
17.12. Appendix 12: SLE Allowable Medication Categories

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) **AND route of administration is not "TOPICAL"**.
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"," BELIMUMAB", "ADALIMUMAB", "ETANERCEPT", "INFLIXIMAB", "CERTILIZUMAB", "TOCILIZUMAB", "GOLIMUMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "IMMUNOGLOBULIN", "CYCLOPHOSPHAMIDE" (IV route), "PLASMAPHERESIS" or "LEUKAPHERSIS".

17.13. Appendix 13 – Prednisone Conversion Factors

- 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. Although not systemic, intra-articular steroids are also identified for treatment failure rules. Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).

- At data base release and in-stream, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor and dosing frequency exist for all terms with a systemic route of administration.

- Similarly, all routes of administration for preferred terms with an ATC code beginning with 'H02'will be reviewed to ensure all systemic routes have been identified in the list above.

- In order to be converted, the frequency and dose of the steroid must be present with the unit dose in milligrams (mg).

- Reported dose for systemic steroid is converted to prednisone equivalent dose using conversion factor for each particular medication (refer to online calculator http://www.globalrph.com/corticocalc.htm).

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

Table 7   Prednisone Conversion Factors (mg)

Preferred term	Conversion factor for converting to a prednisone-equivalent dose
BETAMETHASONE	8.333
BETAMETHASONE DIPROPIONATE	8.333
BETAMETHASONE SODIUM PHOSPHATE	8.333
BETAMETHASONE VAL	8.333
BETROSPAM	8.333
BUDESONIDE	0.333
CELESTONA BIFAS	8.333
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.333
DEFLAZACORT	0.8333
DEPO-MEDROL MED LIDOKAIN	1.25
DEXAMETHASONE	6.667
DEXAMETHASONE ACETATE	6.667
DEXAMETHASONE SODIUM PHOSPHATE	6.667
FLUOCORTOLONE	3
HYDROCORTISONE	0.25

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

Frequency Factors	
Frequency	**Factor**
BID	2
BIW	2/7
OAM	1/30
Once	1
PRN	null
Q2H	12
Q2W	1/14
Q3H	8
Q3MO	1/84
Q3w	1/21
Q4H	6
Q4W	1/28
Q6H	4
Q8H	3
Q12H	2
QAM	1
QD	1
QH	24
QHS	1
QID	4
QM	1
QOD	½
QPM	1

Frequency Factors	
QW	1/7
QWK	1/7
TID	3
TIW	3/7
UNK	Null
2 TIMES PER WEEK	2/7
3 TIMES PER WEEK	3/7
4 TIMES PER WEEK	4/7
5 TIMES PER WEEK	5/7
5 TIMES PER DAY	5
EVERY 2 WEEKS	1/14
EVERY 3 WEEKS	1/21
EVERY 4 WEEKS	1/28
EVERY WEEK	1/7

17.14.   Appendix 14 – Treatment Failure Rules

Subjects considered to be potential treatment failures, per the treatment failure rules defined below, will be outputted to an adjudication spreadsheet for adjudication by an internal adjudication committee comprised of representatives from clinical research, biostatistics, and safety.

For steroids, a list of all indications will first be sent to the clinical team in an Excel spreadsheet to determine whether the indication is considered SLE-related. The programming team will then use this flag to program the steroid rules for SLE and non-SLE indications.

Potential treatment failures will be exported to an Excel spreadsheet and shared with the adjudication committee. The adjudication committee will then use their judgement and the defined rules to flag subjects as either a treatment failure or not a treatment failure. The spreadsheet will then be merged back into the ADTF dataset.

At least one adjudication will take place prior to DBR, with treatment failures finalized prior to SDL.

General Conventions

- Treatment failure date will correspond to the date on which the treatment failure rule is met.

- Assessment of dose is based on analysis dose. Analysis dose is daily dose adjusted for dosing frequency, and in the case of steroid is converted to prednisone equivalents. Exception is intra-articular dose where analysis dose is not populated.

- If a critical visit (Day 113, 169, 309) is missing and the subject has not withdrawn then the date is imputed e.g., date of Day 169 visit is imputed as the target day for Day 169.

- Actual visit date, not target visit date, is used to assess treatment failures. For example, the Day 169 visit can occur on study day 169 ± 7 days. If the subject's Day 169 study visit occurs on Day 171, the date for Day 171 is used when applying the treatment failure rules.

- Prohibited medications/dosages started on the day the subject completes the double blind treatment phase do not result in treatment failure designation.

- Prohibited medications/dosages started on the date of early withdrawal are considered a treatment failure (see clarification below for steroids).   If the prohibited medication/dose starts after the date of withdrawal it will not be part of the treatment failure assessment.

- All potential treatment failure rule violation types are output programmatically. If the first instance is adjudicated as a not being a treatment failure then the clinical adjudicators will review the entirety of the relevant concomitant medication records to assess if the subject subsequently became a treatment failure for the same

violation type (e.g., steroid dose does not return to within 25% or 5mg, whichever is higher, above baseline dose by Day 169 (Week 24) visit).

- Clinical may amend the date of treatment failure during adjudication if, for instance, a subject did not meet the criterion on the date identified by the program (as may be the case if their steroid usage was short term and not SLE-related) but did meet it later.

Total systemic steroid dose is defined as the average daily dose of all steroids taken IV, IM, SC, intradermally and orally for both SLE and non-SLE reasons.

Steroids

- SLE-related steroids are steroids where the Clinical team has adjudicated the reason for medication to be SLE related.

- Total steroids include steroids for SLE and non-SLE reasons.

- Baseline dose is the 7-day average based on the 7 days **prior** to, but not including, treatment start date.

- The Day 309 (Week 44) visit steroid dose is the sum of steroid dose over 7 consecutive days leading up to, and including the Day 309 (Week 44) visit, divided by 7. The Day 309 (Week 44) visit steroid dose is used to determine if there is a new increase in steroids above the Day 1 (Baseline) visit or Day 309 (Week 44) visit within 8 weeks of the Day 365 (Week 52) visit.

- To determine whether a subject shall be classified as a treatment failure due to steroid use within 8 weeks prior to the Week 52 visit, the 8-week window is defined from the day after Day 309 (Week 44) visit to the Day 365 (Week 52) visit. Note there is no check that the Day 309 (Week 44) and Day 365 (Week 52) visits are within 8 weeks of each other.

- In all instances in which the protocol states that a subject's steroid dose must return to a specified level (e.g., within 5 mg or 25% of baseline whichever is higher) by a specific visit day (e.g., Day 169 (Week 24) visit), the calculation of the 7-day average steroid dose to determine whether a subject is a treatment failure will begin on the day after the visit.

- When assessing dose at critical visits the average dose is based on the 7 days after the visit e.g., Day 169 7-day average dose is the average of day 170 -176 (if Day 169 occurred on the actual target date; or 7 days after the date of the Day 169 (Week 24) visit otherwise).

- The final week interval for subjects who complete Part A will be 7 days prior to the exit visit date; [exit visit -7 days] to [exit visit -1 day]. The day of the exit visit will not be included.

- The final interval for subjects who withdraw early from Part A will be the 7 days up to and including the exit visit date; [exit visit/early withdrawal date -6] to [exit visit/ early withdrawal date]. The day of withdrawal will be included.

- If a subject meets the criterion for treatment failure based on a 7-day average, the date of treatment failure will be the **last day** of the 7-day interval.

- The above rules may miss a subject who starts/increases a steroid close to the day of withdrawal. In this situation it is possible that the subject may have withdrawn prior to the end of the interval for computing their 7-day average exceeding the treatment failure threshold. Hence all subjects whose dose of steroid increased within 7 days (including day of withdrawal) of withdrawal, and have not already crossed the dose threshold for treatment failure based on the 7-day average rule after Day 169, will be output for clinical adjudication. If clinical adjudication determines these to be treatment failures the date of treatment failure will be set to the date of withdrawal.

- A subject who is receiving 0mg of steroid at baseline will be allowed to take ≤ 5mg of steroid at critical assessments without being considered a treatment failure.

- Intra-articular steroids are not included in average steroid dose calculations.

- All assessments relating to within 8 weeks of Day 365 (Week 52) are based off the interval from Day 309 (Week 44) visit date to the Day 365 (Week 52) visit date; not Day 365 (Week 52) visit date – 64 days.

- Every other day (QOD) dosing regimens (and regimens with frequency <once/day) will be reviewed to ensure the analysis dose is calculated correctly. Consider an example of a subject taking 5mg QOD and 7.5mg QOD. To calculate an analysis average daily dose for a QOD (every other day) regimen, half of the dose is attributed to each day in the dosing interval. In this example, 2.5mg would be assigned as the analysis dose for each day of the 5mg QOD dosing interval and 3.75mg would be the analysis dose for each day of the 7.5mg QOD dosing interval. The analysis dose for a given day is the sum of all steroid doses for the day. If the 5mg QOD dose is recorded as starting one day prior to the 7.5mg QOD dose and no other steroids were taken on that day, then the analysis dose for the first day of the 5mg QOD will be 2.5mg; for subsequent days when the 5mg and 7.5mg dosing intervals overlap, the analysis dose will be 2.5mg + 3.75mg = 6.25mg.

Systemic Steroids for SLE-related Disease Activity

- A subject who fails to return to within 25% or 5 mg over the baseline (Day 0) dose, whichever is higher, by the Day 169 (Week 24) visit will be considered a treatment failure.

- After the Day 169 (Week 24) visit, an increase >25% or >5 mg over the baseline (Day 1) dose, whichever is higher, for SLE activity will deem the subject a treatment failure.

- Within 8 weeks before the Day 365 (Week 52) visit, no new increase over the baseline (Day 1) or Day 309 (Week 44) visit dose, whichever is higher, is allowed. A new increase would deem the subject a treatment failure.

Intra-articular (IA) injections

- Subjects may receive intra-articular injections between baseline (Day 0) and the Day 309 (Week 44) visit.

- Intra-articular (IA) injections after the Day 309 (Week 44) visit and before the Day 365 (Week 52) visit will be defined as a treatment failure.

Steroids for Reasons Other Than SLE Disease Activity

Inhaled and topical steroids are allowed throughout the course of the study. The following time specific restrictions apply to steroid formulations which are not inhaled or topical.

From Day 1 to the Day 169 (Week 24) Visit:

- Steroids may be given for reasons other than SLE disease activity (such as asthma, contact dermatitis) as clinically indicated until Day 169 (Week 24) visit.

From Day 169 to 309 (Week 24 to 44) Visits:

- Steroids may be given for reasons other than SLE disease activity from the Day 169 (Week 24) visit until the Day 309 (Week 44) visit at any dose/duration that does not result in a total steroid dose (for SLE and non-SLE reasons) >25% or >5 mg, whichever is higher, over the baseline dose. Any total steroid dose exceeding this rule will deem the subject a treatment failure.

- Steroids (prednisone equivalent) for non-SLE reasons may be given at the investigator's discretion short-term at higher doses but not to exceed the maximum doses described below.

  - Up to 750 mg (prednisone equivalent) for 1 day,

    and/or

  - Up to 100 mg/day (prednisone equivalent) for up to 3 days,

    and/or

  - Up to 40 mg/day (prednisone equivalent) for up to 7 days.

- The duration of high dose steroid use for reasons other than SLE **must not exceed 7 days**, after which time, tapering should begin. The total steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, within 30 days of the 1st dose of a course of steroids. In addition, the steroid dose must be tapered to within 25% or 5 mg over the baseline dose, whichever is higher, by the Day 309 (Week 44) visit. Otherwise the subject will be deemed a treatment failure.

From the Day 309 to Day 365 (Week 44 to 52) Visits:

- After the Day 309 (Week 44) visit through the Day 365 (Week 52) visit, no new steroids are allowed for reasons other than SLE activity that result in a total daily steroid dose >25% or >5 mg, whichever is higher, over the baseline total steroid dose. A subject will be considered a treatment failure for any steroid use 8 weeks before the Day 365 (Week 52) visit that does not meet this criterion.

- The above rules may miss a subject who starts / increases a steroid close to the day of withdrawal. In this situation it is possible that the subject may have withdrawn prior to their 7-day average exceeding the TF threshold. Hence all subjects whose dose of steroid increased within 7 days (including day of withdrawal) of withdrawal, and have not already crossed the TF threshold based on the 7-day average rule, will be

output for adjudication. These subjects will be assessed as part of clinical adjudication. If clinical adjudication determines these to be treatment failures the date of treatment failure will be set to the date of withdrawal.

Anti-Malarials

- Dose of anti-malarial at baseline is the dose the subject received on the treatment start date.

- Dose of anti-malarial at Day 113 (Week 16) visit is the dose of received on the Day 113 (Week 16) visit date.

- Treatment failure date will be the anti-malarial start date that resulted in treatment failure.

- Clinical loading dose is permitted for initiation or replacement. Whether or not the dose was a loading dose will be assessed by clinical adjudication.

- A new anti-malarial (eg, hydroxychloroquine, chloroquine, quinacrine) may be started between Day 0 and the Day 113 (Week 16) visit.

- The dose of an anti-malarial may be reduced during the course of the study. The dose of an anti-malarial may be increased as clinically required, up to the Day 113 (Week 16) visit.

- After the Day 113 (Week 16) visit, any increase in dose of an anti-malarial over the baseline (Day 1) or Day 113 (Week 16) visit dose, whichever is higher, will declare the subject a treatment failure.

- Starting any new anti-malarial treatment after the Day 113 (Week 16) visit will declare the subject a treatment failure.

- An antimalarial treatment will be considered new if the subject did not receive an antimalarial at any time during the Day 1 to Day 113 (Week 16) treatment interval.

- An anti-malarial may be replaced by another anti-malarial due to documented toxicity or lack of availability at any time during the study. Replacement due to toxicity/lack of availability will be assessed during clinical adjudication.

- The allowable doses of anti-malarial drugs are:

  - Hydroxychloroquine –up to 400 mg/day.

  - Chloroquine – up to 500 mg/day.

  - Quinacrine – up to 100 mg/day.

  - Compounded anti-malarials – no individual component may exceed the maximum dose above.

Immunosuppressant/Immunomodulatory agents

- Baseline dose is the dose received on the treatment start date.

- Whether or not a dose is a clinical loading dose will be assessed by clinical adjudication.

- Replacement of one immunosuppressant with another due to toxicity/lack of availability will be assessed during clinical adjudication.

- Starting any new immunosuppressive/immunomodulatory agent after Day 1 will cause the subject to be declared a treatment failure. (New topical immunosuppressive agents [e.g., eye drops, topical creams] are allowed after Day 0.)

- The dose of existing immunosuppressive/immunomodulatory agents may be increased, as clinically required, up to the Day 113 (Week 16) visit.

- After the Day 113 (Week 16) visit, any increase in dose over the baseline (Day 1) or Day 113 (Week 16) visit dose, whichever is higher, will cause the subject to be declared a treatment failure.

The allowable doses for immunosuppressives at baseline (Day 1) and during the study:

- Azathioprine – up to 300 mg/day

- 6-mercaptopurine – up to 300 mg/day

- Mycophenolate mofetil (PO)/ mycophenolate mofetil hydrochloride (IV) – up to 4 g/day

- Mycophenolate sodium (PO) – up to 2.88 g/day

- Methotrexate –up to 25 mg/week

- Oral cyclophosphamide – up to 2.5 mg/kg/day

- Cyclosporine – up to 4 mg/kg/day

- Tacrolimus – up to 0.2 mg/kg/day

- Sirolimus – up to 2 mg/day

- Thalidomide – up to 200 mg/day

- Leflunomide – up to 40 mg/day

- Mizoribine – up to 150 mg/day

If a subject receives a higher dose than any of the immunosuppressive doses above, they will be further reviewed as part of clinical adjudication.

NSAIDs and Aspirin

- NSAIDs may be given as clinically indicated until the Day 309 (Week 44) visit.

- For subjects who have received an NSAID between the Day 1 and Day 309 (Week 44) visit, the existing NSAID can continue at a stable dose after the Day 309 (Week 44) visit.

- For subjects who never received an NSAID between the Day 1 and Day 309 (Week 44) visit, starting a new NSAID after the Day 309 (Week 44) visit will declare the subject a treatment failure unless the NSAID is given for <1 week. The programming algorithm will need to check if an NSAID was taken between the Day 0 and Day 309 (Week 44) visit.

- An NSAID may be replaced with another NSAID due to documented toxicity or lack of availability. Replacement due to toxicity/lack of availability will be assessed during clinical adjudication; therefore, programming should identify all unique NSAID terms that were taken after the Day 309 (Week 44) visit that were not present on/before the Day 309 (Week 44) visit.

- Anti-thrombotic doses of aspirin are permitted at any time during the study. Topical or Conjunctival use of NSAIDs and PRN use of NSAIDs are also permitted at any time during the study.

- Baseline is defined as the NSAID/aspirin received on the treatment start date.

- Treatment failure date will be the date the medication/dose was started resulting in treatment failure designation.

Prohibited medications/non-Drug Therapies

- Date of treatment failure is date subject started Prohibited medications/non-Drug Therapy.

The following medications and therapies are prohibited at any time during Part A of the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used. [No check for investigational agents not approved for sale in country is being made.]

- Participation in a study using an investigational agent or non-drug therapy that may interfere with the conduct of this protocol. [No check available for this criterion.]

- Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certilizumab, tocilizumab, golimumab).

- Other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).

- Intravenous immunoglobulin (IVIG).

- IV cyclophosphamide (oral cyclophosphamide is permitted).

- Plasmapheresis, leukapheresis.

Live Vaccines

- Receiving a live vaccine is prohibited due to safety reasons but is not a treatment failure criterion.

17.15. Appendix 15 – PSAP Sections for Adverse Events of Special Interest

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

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

- Just preceding data base release (DBR), allowing time to send queries or update the eCRF/database as necessary prior to DBR.

- After DBR to provide final confirmation of adjudications and ensure there are no new AESI or relevant data changes to adjudicated events since the pre-DBR adjudication. This would be a requirement for declaring database freeze (DBF).

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 since MedDRA v19.1:

- The term "Paraneoplastic glomerulonephritis" has been removed from the SMQ as it is a complication of malignancy.

- The term "Mismatch repair cancer syndrome" has been added as a tumour of unspecified malignancy

- The term "Malignant meningioma metastatic" has been added as a solid tumor type.

- The term "Marginal zone lymphoma recurrent" has been added as a hematological tumor type.

- The term "Skin neoplasm bleeding" has been added as a tumour of unspecified malignancy.

- The term "Astroblastoma" has been added as a solid tumour type.

- The term "Epstein Barr virus positive mucocutaneous ulcer" has been added as a hematological tumour type.

- The term "Langerhans cell sarcoma" has been added as a solid tumour type.

- The term "Naevoid melanoma" has been added as a skin tumour type.

- The term "Nasopharyngeal cancer metastatic" has been added as a solid tumour type.

- The term "Phospaturic mesenchymal tumour" has been added as a solid tumour type.

- The term "Primary gastrointestinal follicular lymphoma" has been added as a hematological tumour type.

- The term "Squamous cell breast carcinoma" has been added as a solid tumour type.

- The term "Transformation to acute myeloid leukaemia" has been added as a hematological tumour type.

- The term "FIP1L1/PDGFR alpha fusion kinase positive" has been added as a hematological tumour type.

- The term "Gleason grading score" has been added as a solid tumour type.

- The term "Oncotype test" has been added as a solid tumour type.

- The term "Intestinal metastasis" has been added as an unspecified tumour type.

- The term "Maternal cancer in pregnancy" has been added as an unspecified tumour type.

- The term "Microsatellite instability cancer" has been added as an unspecified tumour type.

- The term "Pulmonary tumour thrombotic microangiopathy" has been added as an unspecified tumour type.

- The term "Tumour cavitation" has been added as an unspecified tumour type.

- The term "Malignant urinary tract obstruction" has been added as a solid tumour type.

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

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 term: "Fixed eruption". GSK has also removed three terms that are not relevant for an analysis of hypersensitivity reactions to belimumab ("Anaphylactic transfusion reaction", "Dialysis membrane reaction", and "First use syndrome"). Anaphylactic transfusion reaction is an adverse event associated with a blood transfusion, not related to study medication. First use syndrome and dialysis membrane reaction are associated with adverse events related to kidney transplants and dialysis, not related to study medication.

<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:

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

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

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

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

For CSR reporting, all post-infusion/injection systemic reaction AESIs defined via narrow, broad, or algorithmic search, the AEs need to have occurred on the day of an infusion/injection or within 3 days after an infusion/injection. GSK will review all serious events identified via the broad search occurring within 21 days after an infusion/injection, and adjudicate these events as post-infusion/injection systemic reactions or hypersensitivity reactions per the criteria in Section 16.2. Therefore, the window for the

narrow, broad or algorithmic searches for SRT reporting (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. See Section 8.3.2 for the definition of the assessment windows.

Sampson Criteria

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

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

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

j.   Any Infusion/Injection-related Reaction per Anaphylactic Reaction SMQ broad search SAE which occurs on the day of an injection.

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

l.   Any anaphylaxis and hypersensitivity reactions per Anaphylactic Reaction SMQ algorithmic search SAE which occurs on the day 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 prior to database release 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 prior to database release 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 prior to database release 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 (20000035) 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 (20000035) preferred terms (Section 17.1).

Section 15.5: Fatalities

All fatalities 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.

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 at the subject level by the GSK SRT during regular SRT meetings or during quarterly adjudication. The adjudication occurs prior to database release and is performed for reporting purposes, per the criteria described below.

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

- Just preceding data base release (DBR), allowing time to send queries or update the eCRF/database as necessary prior to DBR.

- After DBR to provide final confirmation of adjudications and ensure there are no new AESI or relevant data changes to adjudicated events since the pre-DBR adjudication. This would be a requirement for declaring data a freeze (DBF).

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

Before the data base is released, 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 infusion/injection reaction. Time to onset after an infusion/injection and details provided in the clinical narratives with respect to the nature and likely cause of the events are taken into consideration. Time to onset within 24 hours is generally applied to post infusion/injection reactions. The GSK SRT adjudicates serious hypersensitivity reactions into a category based primarily on time to onset: acute (onset ≤ 1 day), delayed acute (onset 2-3 days), or delayed, non-acute (onset 4-21 days). In addition to time to onset, description of associated symptoms is taken into account for this categorization. In 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 prior to database release to determine if criteria are met for an opportunistic infection. Targeted follow-up is sought for events with insufficient information. In general, potential OIs that are non-serious with insufficient information to adjudicate will be considered non-opportunistic. Potential OI SAEs with insufficient information to adjudicate will be considered opportunistic. See below for a list of agreed upon pathogens and infections considered to be opportunistic for the purpose of adjudication.

Pathogens and Infections Considered Opportunistic:

- Acinetobacter infection
- Aspergillosis
- Blastomycosis, extrapulmonary
- Candidiasis of esophagus, bronchi, trachea or lungs
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis infection, chronic intestinal (greater than 1 month duration)
- CMV disease other than liver, spleen, or nodes
- Herpes simplex – bronchitis, pneumonitis, or esophagitis
- Herpes Zoster (adjudication details are below)
- Histoplasmosis disseminated or extrapulmonary
- Human polyomavirus infection
- Isosporiasis, chronic intestinal (greater than one month duration)
- Listeriosis
- Mycobacterium avium complex or M. Kansasii, disseminated or extrapulmonary
- Nocardiosis
- Other non-tuberculous mycobacterium (NTM) infections (other species or unidentified species), disseminated or extrapulmonary*
- Polyomavirus (JC virus or BK virus) associated nephropathy (including PML)
- Pneumocystis jiroveci infection
- Toxoplasmosis of brain

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

In addition, GSK SRT will review all SAEs, including those coded under preferred terms not 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)

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 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

Adjudicated Category of Death
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 v20.1

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

Section 17.2: MedDRA v20.0

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

Section 17.3: MedDRA v19.1

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

Section 17.4: MedDRA v19.0

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

Section 17.5: MedDRA v18.1

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

Section 17.6: MedDRA v18.0

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

Section 17.7: MedDRA v17.1

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

Section 17.8: MedDRA v17.0

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

Section 17.9: MedDRA v16.1

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

Section 17.10: MedDRA v16.0

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

17.16.   Appendix 16 – B Cells

B Cell Panel (BIMETHCD/ LBMETHCD)	Biomarker Category Code [BICATCD]	Biomarker Category [BICAT]	Lab Test Code (LBTESTCD)	Lab Test Code (LBTESTCD)	Units of Measurement (BIORRESU/ LBORRESU)
FLWTBNK	CD19	CD19	CD19LY	CD19_Percentage	%
FLWTBNK	CD19	CD19	CD19	CD19_Concentration	GI/L
FLWPLSM	CD19	CD19	CD19E	CD19_Number of events	EVENTS
FLWPLSM	CD20	CD20	CD20CD19	CD20_Percentage	%
FLWPLSM	CD20	CD20	CD20E	CD20_Number of events	EVENTS
FLWPLSM	CD20	CD20	CD20	CD20_Concentration	GI/L
FLWPLSM	CDX136	CD20+ CD27-	CDX13619	CD20+ CD27-/CD19+	%
FLWPLSM	CDX136	CD20+ CD27-	CDX136E	CD20+ CD27- Number of Events	EVENTS
FLWPLSM	CDX136	CD20+ CD27-	CDX136	CD20+ CD27-	GI/L
FLWPLSM	CDX137	CD20+ CD27+	CDX13719	CD20+ CD27+/CD19+	%
FLWPLSM	CDX137	CD20+ CD27+	CDX137E	CD20+ CD27+ Number of Events	EVENTS
FLWPLSM	CDX137	CD20+ CD27+	CDX137	CD20+ CD27+	GI/L
FLWPLSM	CDX141	CD20+ CD69+	CDX14119	CD20+ CD69+/CD19+	%
FLWPLSM	CDX141	CD20+ CD69+	CDX141	CD20+ CD69+	GI/L
FLWPLSM	CDX155	CD19+CD20+CD69+	CDX155E	CD19+CD20+CD69+ Number of Events	EVENTS
FLWPLSM	CDX143	CD20- CD138+	CDX14319	CD20- CD138+/CD19+	%
FLWPLSM	CDX143	CD20- CD138+	CDX143E	CD20- CD138+ Number of Events	EVENTS
FLWPLSM	CDX143	CD20- CD138+	CDX143	CD20- CD138+	GI/L
FLWPLSM	CDX145	CD20+ CD138+	CDX14519	CD20+ CD138+/CD19+	%
FLWPLSM	CDX145	CD20+ CD138+	CDX145E	CD20+ CD138+ Number of Events	EVENTS
FLWPLSM	CDX145	CD20+ CD138+	CDX145	CD20+ CD138+	GI/L
FLWPLSM	CDX154	CD27+b CD20-	CDX15419	CD27+b CD20-/CD19+	%
FLWPLSM	CDX154	CD27+b CD20-	CDX154E	CD27+b CD20-+Number of Events	EVENTS
FLWPLSM	CDX154	CD27+b CD20-	CDX154	CD27+b CD20-	GI/L
FLWPLSM	CDX156	CD27+CD38+CD19+	CDX15619	CD27+CD38+CD19+/CD19+	%
FLWPLSM	CDX156	CD27+CD38+CD19+	CDX156E	CD27+CD38+CD19+ Number of Events	EVENTS
FLWPLSM	CDX156	CD27+CD38+CD19+	CDX156	CD27+CD38+CD19+	GI/L

B cell subsets to be reported:

Lab Test Code (LBTESTCD)	Lab Test (LBTEST)	Units of Measurement[1] (LBORRESU)	Display Label for B cell
Common B cells			
CD19	CD19_Concentration	GI/L	CD19 (/uL)
CD20	CD20_Concentration	GI/L	CD20 (/uL)
CDX136	CD20+ CD27-	GI/L	Naive CD19+CD20+CD27- (/uL)
CDX137	CD20+ CD27+	GI/L	Memory CD19+CD20+CD27+ (/uL)
Rare B cells[2]			
CDX141N	CD20+ CD69+	GI/L	Activated CD19+CD20+CD69+ Normalized (COUNT/mL)
CDX143N	CD20- CD138+	GI/L	Plasma CD19+CD20-CD138+ Normalized (COUNT/mL)
CDX145N	CD20+ CD138+	GI/L	Plasmacytoid CD19+CD20+CD138+ Normalized (COUNT/mL)
CDX154N	CD27+b CD20-	GI/L	Short-lived Plasma CD19+CD20-CD27b+ Normalized (COUNT/mL)
CDX156N	CD27+CD38+CD19+	GI/L	SLE Subset CD19+CD38b+CD27b+Lymph Normalized (COUNT/mL)
[1]GI/L=10⁹/L [2]The lab test code for the new record containing the normalized value will be the same as the corresponding absolute B cell concentration record prior to normalization, suffixed with N. The display label corresponds to the normalized value that is to be reported in the displays.			

[1]GI/L=10^9/L

[2]The lab test code for the new record containing the normalized value will be the same as the corresponding absolute B cell concentration record prior to normalization, suffixed with N. The display label corresponds to the normalized value that is to be reported in the displays.

17.17.   Appendix 17 – Study Day for Reporting

Belimumab Study Days	
Protocol	RAP and Reporting
Day 0	Day 1
Day 14	Day 15
Day 28	Day 29
Day 56	Day 57
Day 84	Day 85
Day 112	Day 113
Day 140	Day 141
Day 168	Day 169
Day 196	Day 197
Day 224	Day 225
Day 252	Day 253
Day 280	Day 281
Day 308	Day 309
Day 336	Day 337
Day 364	Day 365

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

17.18. Appendix 18 – Population Pharmacokinetic Analysis

Belimumab serum concentration-time data will be analyzed by population pharmacokinetic methods using a non-linear mixed-effects modelling approach.

The key objectives of this analysis are:

- Develop a population PK model that characterizes the PK disposition of belimumab following intravenous administration in pediatric subjects with SLE and evaluate the potential effect of selected covariates on PK parameters

- Compare belimumab exposure in pediatric SLE patients to exposure in adult SLE Phase 3 patients

17.18.1. Systems

The quantitative analysis will be performed using NONMEM (ICON Solutions) and PsN (Perl Speaks NONMEM) or another software platform deemed appropriate. Graphical displays and, if needed, modifications of the dataset will be produced using R (The R Foundation for Statistical Computing). The analysis will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline using the currently supported versions of all software packages.

17.18.2. Data Assembly

Subject data will be collected in the electronic CRF and will be transmitted into a validated database by GSK data management. Derived/processed variables will be provided by or under the guidance of Clinical Programming. Serum samples will be analyzed under supervision of Department of Bioanalysis, Immunogenicity and Biomarker, IVIVT, GSK, using approved analytical methodology. Data will be transferred electronically to data managers to be processed and stored in the GSK database. GSK or a designated third party will generate the NONMEM input dataset.

Previously generated adult belimumab IV PK data may be merged with the pediatric PK data in order to provide a pooled adult/pediatric NONMEM data set.

17.18.3. Model Development

A population pharmacokinetic model for IV belimumab in adult SLE patients (adult popPK model) was developed [Struemper, 2013] and will be the starting point for the pediatric population PK analysis.

Initially, empirical Bayes estimates will be derived applying the adult popPK model to the pediatric dataset with the MAXEVAL=0 option. If the corresponding model diagnostics indicate that the adult popPK model is appropriate to represent the pediatric belimumab PK data, then comparison with adult popPK parameters may be based upon these empirical Bayes estimates for the pediatric population.

If the parameter set of the adult popPK model applied to the pediatric data set results in substantial bias or if a further exploration of the covariate effect in the pediatric

population is deemed necessary, the parameters of the adult popPK model will be re-estimated for the pediatric PK data alone and/or for a pooled adult/pediatric data set. Certain parameter values may be fixed to the value in the adult popPK model, if they cannot be estimated with sufficient precision within the pediatric PK population. Covariates not available for the pediatric PK population but present in the adult popPK model may be removed from the pediatric popPK model. The set of remaining covariate-parameter relationships of the adult popPK model will be reduced using the full model approach [Gastonguay, 2011]. Different body-size variables may be explored with estimated or fixed allometry-based exponents. Lastly, a model refinement step will include, but may not be limited to, a qualification and possible modification of the models random effect structure.

17.18.4.   Model Qualification

Any model development will be supported and the final model will be qualified using the following criteria where appropriate:

- Scientific plausibility of parameter estimates

- Goodness of fit plots

- Relative standard errors (RSE) of the parameter estimates

- Objective function value

- Distribution and shrinkage of random effects;

- Successful minimization and execution of covariance step

- Condition number (ratio of the largest and smallest eigenvalue of the covariance matrix

- Visual predictive check

- Bootstrap (if deemed necessary/feasible)

17.18.5.   Comparison to Exposure in Adult SLE Phase 3 Subjects

To assess belimumab IV dosing in pediatric subjects with SLE, the pediatric individual PK and exposure parameters will be compared to PK and exposure parameters from the adult IV Phase 3 SLE studies [Struemper 2013]. Simulations may be performed to illustrate the effect of certain covariates on belimumab exposure.

18. ATTACHMENTS

18.1. Table of Contents for Data Display Specifications

Please see document "BEL114055 Mock TFL Shells.doc" for the table of contents of outputs to be presented.

18.2. Data Display Specifications

Please see the Mock TFL Shells document for the data display specifications.

18.3. Headline Results

The following TFLs will be included as headline results:

Table 1.4 Subject Completion Status by Week 52 (Part A)
Table 1.8 Demographic and Baseline Characteristics
Table 1.17 Baseline Disease Activity
Table 1.34 Demographic and Baseline Characteristics by Age Group
Table 1.35 Baseline Disease Activity by Age Group
Table 2.1 SRI Response at Week 52 (Part A)
Table 2.3 SRI Response at Week 52 and the 3 Components (Part A)
Table 2.11 Sustained SRI Response from Week 44 - Week 52 (Part A)
Table 2.13 PRINTO/ACR Juvenile SLE Response by Visit: Definition 1 (DO/TF=NR) (Part A)
Table 2.14 PRINTO/ACR Juvenile SLE Response by Visit: Definition 2 (DO/TF=NR) (Part A)
Table 2.17 Sustained Parent's Global Assessment (ParentGA) Response from Week 44 - Week 52 (Part A)
Table 3.2 Adverse Events Summary (Part A)
Table 3.4 Adverse Events by SOC and PT (Part A)
Table 3.7 Serious Adverse Events by SOC and PT (Part A)
Table 3.28 Adverse Events of Special Interest by Category (Part A)
Table 3.83 Serious Adverse Events by SOC and PT and Age Group (Part A)

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

18.4. Table of Contents for Data Display Specifications for Japanese NDA Subgroups

See separate TOC document for a list of Tables and Figures needed for the Japanese NDA for the subgroup of subjects from Japan. These analyses will only be summarized in the Japan CTD (Common Technical Document) and will not be summarized in the CSR.

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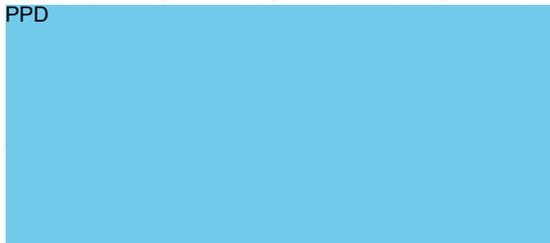Quantitative Clinical Development, PAREXEL
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CPMS

Date

PPD
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Principal Clinical Data Manager
Clinical Data Management

Date _____

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Medical Writing Director
Clinical Development

Date _____

PPD
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Director, Regulatory Affairs
Global Regulatory Affairs

Date _____

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Senior Director, Value Evidence Leader
Value Evidence and Outcomes

FEBRUARY 16, 2018
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Date

PPD
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Senior Director
Quantitative Clinical Development, PAREXEL
On behalf of CPMS

Date _____

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Medical Director
GCSP SERM

Date _____

The GlaxoSmithKline group of companies

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Director, Regulatory Affairs   **Date**
Global Regulatory Affairs

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Senior Director, Value Evidence Leader   **Date**
Value Evidence and Outcomes

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_____ 16-Feb-2018

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Medical Director
GCSP SERM