Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan Addendum
Title	:	Reporting and Analysis Plan Addendum for BEL114054 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis
Compound Number	:	GSK1550188
Effective Date	:	20-Feb-2020

Description:

- This RAP addendum is supplemental to the RAP (Dated: 20/SEP/2019), and based on protocol amendment 07 (Dated: 24/JAN/2019) of study BEL114054 (HGS1006-C1121; GSK Document No.: 2013N179093_06), and eCRF Version 5.0 (Dated: 21/AUG/2017).
- The purpose of this RAP addendum is to document additions/clarifications made after RAP approval but before unblinding.

Author(s)

Author	Date	Approval Method
Lead PPD Director Biostatistics, PAREXEL International	16-MAR-2020	Email
Co-Authors PPD Statistics Leader , GSK Clinical Statistics	16-MAR-2020	Email

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ABBREVIATIONS

ANCOVA	Analysis of Covariance
BLyS	B-Lymphocyte Stimulator
CRF	Case Report Form
CRR	Complete Renal Response
eGFR	Estimated Glomerular Filtration Rate
IP	Investigational Product
IPD	Investigational Product Discontinuation
IPDISCDT	Investigational Product Discontinuation Date
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
PERR	Primary Efficacy Renal Response
RAP	Reporting and Analysis Plan
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-S2K	Systemic Lupus Erythematosus Disease Activity Index using SLEDAI 2000 scoring for proteinuria
TF	Treatment Failure
TR01SDT	Treatment Start Date
uPCR	Urinary Protein:Creatinine Ratio
WD	Withdrawal

1. INTRODUCTION

This RAP addendum is supplemental to the RAP (Dated: 20/SEP/2019), and based on protocol amendment 07 (Dated: 24/JAN/2019) of study BEL114054 (HGS1006-C1121; GSK Document No.: 2013N179093_06), and eCRF Version 5.0 (Dated: 21/AUG/2017).

The purpose of this RAP addendum is to document additions/clarifications made after RAP approval but before unblinding.

2. CHANGES/CLARIFCATIONS TO THE RAP

2.1. BLyS LLOQ (Section 6.7)

Two different assays were used to evaluate BLyS and the assays do not have the same lower limit of quantification (LLOQ), therefore the data is reported as <LLOQ without the numerical value (ie, <0.061 ng/mL) as it depends on the assay.

2.2. Tipping Point Analysis (Section 7.1.6.2)

Replace this paragraph:

> In contrast to the primary analysis, in the event of missing data the tipping point analysis evaluates every possible combination of placebo responder/non-responder with every possible combination of belimumab responder/non-responder. For the treatment policy intercurrent event strategy, all observed data at Week 104 will be used and unobserved (missing) data due to a subject outcome of death, study withdrawal, or lost to follow-up will be assessed using all possible combinations of responder/non-responder by treatment group. For the hybrid treatment policy strategy, a subject experiencing a treatment failure will be considered a non-responder at Week 104, otherwise observed and unobserved data will be managed the same as the treatment policy strategy.

By these three paragraphs for added clarity:

> In contrast to the primary analysis, in the event of missing data the tipping point analysis evaluates every possible combination of placebo responder/non-responder with every possible combination of belimumab responder/non-responder.
>
> For the Treatment Policy (WD=NR) intercurrent event strategy, in the base analysis Missing data and Withdrawal (due to outcome of death, study withdrawal, or lost to follow-up) are set to NR, while IP Discontinuation and Treatment Failure are ignored. In the corresponding Tipping Point analysis, Missing data and Withdrawal will have responses sequentially imputed, and IP Discontinuation and Treatment Failure will continue to be ignored.
>
> For the Hybrid Treatment Policy (TF/WD=NR) strategy, in the base analysis Missing data, Withdrawal, and Treatment Failure are set to NR, while IP Discontinuation is ignored. In the Tipping Point analysis, Missing Data and

> Withdrawal will have responses sequentially imputed, while Treatment Failure will continue to be set to NR and IP Discontinuation will continued to be ignored.

Replace these sentences:

> Reference lines on the hybrid treatment policy heat map will correspond to the response rates for the PERR primary analysis using the IPD/TF/WD=NR imputation. Reference lines on the treatment policy heat map will correspond to the rate using observed Week 104 responders and assuming no subjects with a missing response are responders.

With these sentences:

> For both Treatment Policy and Hybrid Treatment Policy Tipping point plots, reference line for Placebo and Belimumab will be drawn by assuming that the imputed subjects respond at the same rate as the Placebo subjects who are not imputed.

2.3. Time to Death or Renal-related Event (Section 7.2.3)

Additional analyses of Time to Death or Renal-related Event components.

Repeat displays equivalent to the Time to Death or Renal-related Event endpoint, but in each case only for an individual component. When analyzing the individual components, ignore other components instead of censoring, because otherwise event count may become too small for statistical analyses. In addition, to ensure validity of the inference, only report Cox Proportional Hazard model inferences if there are greater than or equal to 5 events per treatment arm. Repeat this for the Treatment Policy version of Time to Death and Renal-related event components, except for the Renal-related Treatment Failure component which is ignored by definition of Treatment Policy.

2.4. Proportion Endpoints (Section 7.3.1)

Add the following under “Statistical Analysis”:

4. No modeling will be performed for the following endpoints since the subgroups are based on a post-randomization characteristic:
   - Proportion of subjects receiving prednisone $\leq$ 5 mg average daily dose since previous visit by Week 104 PERR Response.
   - Proportion of subjects receiving prednisone $\leq$ 7.5 mg average daily dose since previous visit by Week 104 PERR Response.

2.5. Time to Event Endpoints (Section 7.3.3)

- Under "Statistical Analysis," add "For PERR and CRR, in addition the model will be adjusted for baseline uPCR and baseline eGFR."
- Under "Intercurrent Event Strategy" add portion that is underlined "For time to first maintained PERR and CRR, IPD/TF/WD=NR imputation will be used for intercurrent events and will thus be censored."
- Under "Variables" add the following bulleted text:
    - uPCR (at baseline; continuous) [PERR and CRR only]
    - eGFR (at baseline; continuous) [PERR and CRR only]
- Under "Model Results Presentation", add "Only report Cox Proportional Hazard model inferences if there are equal or greater than 5 events per treatment arm."
- To aid in understanding, add the following tables of the censoring and disposition rules

Table 1 Subject Disposition Rules for Time to the first PERR that is maintained through Week 52

Subject Disposition	Event Met	Event Date
Subject has PERR maintained through week 52		
Time to the first PERR that is maintained through Week 52	Yes	Date of first PERR that is maintained through Week 52
Subject does not have PERR maintained through week 52		
Subject completes Week 52	No	Censor at the Week 52 study visit
Subject discontinues IP	No	Censored at IP Discontinuation date (see Section 14.6.1.3.)
Subject is a treatment failure	No	Censored at Treatment failure date
Subject withdraws	No	Censored at earliest of withdrawal date, Lost to Follow-up and death date.
Lost to Follow-up	No	
Subject dies	No	
[1] If a subject belongs in more than one censoring category then the censoring date is the earliest of the dates. **NB:** this implies for subjects with IPD/TF/WD after week 52 they would be censored at their week 52 visit date.		

Table 2 Subject Disposition Rules for Time to the first PERR that is maintained through Week 104

Subject Disposition	Event Met	Event Date
Subject has PERR maintained through week 104		
Time to the first PERR that is maintained through Week 104	Yes	Date of first PERR that is maintained through Week 104
Subject does not have PERR maintained through week 104		
Subject completes Week 104	No	Censored at the Week 104 study visit
Subject discontinues IP	No	Censored at IP Discontinuation date (see Section 14.6.1.3.).
Subject is a treatment failure	No	Censored at Treatment failure date
Subject withdraws	No	Censored at earliest of withdrawal date, Lost to Follow-up and death date.
Lost to Follow-up	No	
Subject dies	No	
[1] If a subject belongs to more than one censoring category then the censoring date is the earliest of the dates.		

2.6. Biomarker Change and Percent Change from Baseline (Section 11.2)

- Analyses for autoantibodies was changed from ANCOVA to rank ANCOVA.
- Analyses for complement was changed from rank ANCOVA to ANCOVA.

2.7. Imputation of missing visit date (Section 14.3.1)

For imputing the visit date of a missing visit, the default method is to compute the missing visit date as the target visit date:

Missing visit date = (missing week * 7) + tr01sdt

However, due to visits shifting relative to the planned visits over time, imputing based on the target visit date can result in an imputed visit being within days of the next observed visit and occasionally even after the next observed visits. Therefore, an alternative method of imputing a missing visit date from a previous non-missing scheduled visit date will be used in Prednisone (ADPRED) and Renal Response (ADRR) datasets. As an example, if a subject missed Week 100 after Week 96, then the imputation will be calculated as:

Week 100: (100-96)*7 + Week 96 visit date.

2.8. Treatment Emergent Flag for Adverse Events (Section 14.4.2)

The definition states that "A treatment-emergent AE is an adverse event that emerges on or after the first treatment dose, having been absent pre-treatment, or that worsens relative to the pre-treatment state. AEs with missing start and/or stop dates will be assumed to be treatment-emergent." Worsening of an event is captured in the eCRF by modifying the severity of the original event; therefore, it should be clarified for the programmers that worsening is accounted for in how the AE is recorded and no programming is required to identify worsening events.

2.9. IP Discontinuation Date (Section 14.6.1.3)

The definition was updated as follows:

> Since the CRF data associated with the IP discontinuation form represents the date the form was completed and not the date the investigator made the decision to discontinue randomized treatment, subjects with a completed IP discontinuation form will have an IP discontinuation date (IPDISCDT) derived based on the following rules:
>
> - If the subject does not have a scheduled visit after the last exposure date and the EXIT Double Blind visit date is non-missing, then IPDISCDT is the earlier of the date of EXIT Double Blind visit or 35 days after the last exposure (35 days is used to include the 28 +7 day visit window).
> - If the subject has a scheduled visit after the last exposure date, then IPDISCDT is the date of the first scheduled visit after the last exposure date.

2.10. Time to First Renal Response Maintained through Week x (Section 14.6.3.3)

- Change "The first renal response maintained to Week x refers the earliest response in a series of consecutive renal responses that extends to and includes Week x. If a subject does not have a renal response at Week x then the Time to First Renal Response that is Maintained to Week x is 0 days. Intercurrent events are incorporated into the renal response endpoints using the IPD/TF/WD=NR strategy."
- To "The first renal response maintained to Week x refers the earliest response in a series of consecutive renal responses that extends to and includes Week x. Subjects without PERR at Week x are censored at the last available visit up through Week x."

2.11. SLE Flare Index (SFI) Scoring (Section 14.6.3.14.1)

SELENA SLEDAI in this section is replaced with SLEDAI-2K in the scoring algorithm.

2.12. Time to First SFI Flare Censoring and Disposition Rules (Section 14.6.3.14.2)

Add underlined text for clarification.

Time to First SFI Flare Censoring and Disposition Rules

The rules described in this section apply to SLE Flares and Severe SLE Flares.
Only post-baseline flares are included in the analysis, therefore flares (not subjects) occurring on the treatment start date should be removed from the analysis set prior to determining the first flare. Subjects with no post-baseline flare assessments will be excluded from the analysis. If a subject is a treatment failure during the period being analyzed, the subject will be considered as having a flare at the time of treatment failure. In the rare situation that a treatment failure occurs on the treatment start date, the treatment failure will be counted as a flare as the assessment of treatment failure is performed post-dose.

Time to first flare is calculated as:

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

After Week 24

For the time to first flare from Week 24 to Week 104, flares (not subjects) occurring on or prior to the Week 24 visit date should be removed from the analysis set prior to determining the first flare. Subjects who withdraw from the study, discontinue IP, or have a treatment failure prior to Week 24 should be excluded from the analysis. Similarly subjects with no flare assessments after Week 24 will be excluded from the analysis. If a subject is a treatment failure on the Week 24 visit date, the treatment failure will be counted as a flare at Week 24. Time to first flare from Week 24 to Week 104 is calculated as:

Time to first flare (days) = Date of first flare – Week 24 visit date + 1.

Table 3 Subject Disposition Rules for SLE Flares (Double-Blind Phase)

Subject Disposition	Event Met	Event Date
Subject has a flare or is a treatment failure, whichever occurs first		
Subject has an SLE flare [1]	Yes	Date of first SFI flare
Subject is a treatment failure [1]	Yes	Treatment failure date
Subject does not have a flare and is not a treatment failure		
Subject discontinues IP	No	Censored at last flare assessment on or prior to IP Discontinuation
Subject withdraws	No	Censored at last flare assessment date
Lost to Follow-up	No	Censored at last flare assessment date

Time to First SFI Flare Censoring and Disposition Rules		
Subject dies	No	Censored at date of death
Subject completes Week 104	No	Censored at the Week 104 study visit
[1] If a subject has a flare and is a treatment failure then the event date is the earliest of the first flare date and the date of treatment failure.		

2.13. SELENA SLEDAI and SLEDAI-S2K Scoring and Endpoint (Section 14.6.3.16)

Add the following paragraph to the end of the section as clarification.

> At baseline, the LOCF and Observed version of the SLEDAI-S2K agree for all organ systems with the exception of Renal because of differences in the cross-referencing with the lab data. For the Observed case, proteinuria lab records within the last 10 days of the SLEDAI visit are cross-referenced, if there are none, then proteinuria is counted as missing and the Renal 2K Total score is summed over the missing. For LOCF, the 10-day limit does not apply and proteinuria lab records can be used as far back as baseline provided the value is within the baseline analysis visit (AVISITN) window. For this reason, baseline presentations of SLEDAI-S2K use the LOCF version of the score.

- To aid in understanding, add the following table to clarify the derivation of the SLEDAI endpoints for different Intercurrent Event strategies.

Situation	Observed	IPD/TF/WD strategy (IPTFOCF)
Missing non-lab parameter	Domain score is the sum of non-missing items	Domain score is the sum of non-missing items
Missing/Unknown lab (including proteinuria) parameter	Sum of non-missing items When cross referencing proteinuria from lab data, use only results that occurred on or in the preceding 10 days.	LOCF will be used
Whole SLE visit missing	Missing	NR (for SLEDAI-S2K < 4, Improvement) LO on or prior to IPD/TF/WD CF (for Worsening, Change from baseline)
IP/TF event	Ignore	IPD/TF/WD=NR (for SLEDAI-

Situation	Observed	IPD/TF/WD strategy (IPTFOCF)
		S2K < 4, Improvement) LO on or prior to IPD/TF/WD CF (for Worsening, Change from baseline)

2.14. SLEDAI-S2K Organ Improvement and Worsening (Section 14.6.3.16.2)

- Remove rows where criterion is "Organ score baseline - missing" under both Improvement and Worsening.
- Under "Worsening," move the equals part of the inequality signs such that criterion "≤ 0" is N and "> 0" is Y.

2.15. Efficacy Tables (Section 14.12.6)

- Population was updated to 'Modified Completers on Study Agent' for Table 2.08 Primary Efficacy Renal Response at Week 104 (Completer Sensitivity Analysis) (IPD/TF/WD=NR)
- For the following tables, change the parenthetical expression in the title from "(WOCF)" to "(Observed with WOCF)"
    - Table 2.80 SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit While on Treatment (Observed with WOCF)
    - Table 2.81 SLICC/ACR Damage Index Change from Baseline by Visit While on Study (Observed with WOCF)
    - Table 2.82 SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit While on Study (Observed with WOCF)
- Delete Table 2.109 SLICC/ACR Damage Index Change from Baseline by Visit While On Study (Observed with WOCF) duplicate of Table 2.81.
- Delete Table 2.110 SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit (Observed) duplicate of Table 2.82.

2.16. Headline Results (Section 14.14)

Table numbers 2.56 and 2.60 should be 2.57 and 2.61, respectively; the table titles are correct as specified analyses for complement was changed from rank ANCOVA to ANCOVA.

2.17. SLE and LN Disease Duration (Section 14.6.2.8)

Variables for SLE disease duration (SLEDUR) and LN disease duration (LNDUR) were not originally defined in the RAP. There was a footnote on the "Baseline Disease Activity" table shell defining the variables as "Screening date – Diagnosis date +1 / 365.25" which was based on the definition in the IV SLE pivotal studies (BLISS-52 and BLISS-76) and BEL112341 (SC). The variables in the ADCOV dataset and presented on the table were programmed consistent with recently reported Benlysta studies using Treatment start date – Diagnosis date + 1 / 365.25; therefore the table footnote is does not match the derivation used.

SLE disease duration (years) = Treatment start date - SLE diagnosis date + 1 / 365.25

LN disease duration (years) = Treatment start date - LN diagnosis date + 1 / 365.25

2.18. Post hoc Analyses

To further understand the results, post hoc analyses were performed and are numbered in accordance with the report sections as 10*n*.*xx* or 20*n*.*xx* where '*n*' is the CSR section (1= Study Population, 2=Efficacy, 3=Safety, etc.) and '*xx*' is a sequential display number.

2.19. Endpoint Naming Updates

Based on FDA feedback, the 'Hybrid Treatment Policy' sensitivity analysis is being referred to as the "Hybrid Estimand" in the clinical study report; the display titles were not updated. Additionally, the key secondary endpoint of 'Time to Death or Renal-related event ' is referred to as 'Time to Renal-related Event or Death' in the clinical study report as renal-related events comprise the large majority of the events; the display titles were not updated.

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- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BEL114054 [HGS1006-C1121].
- This RAP is intended to describe the planned efficacy, safety, pharmacokinetics and biomarker analyses required for the double-blind phase of the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author(s)

Author	Date
Lead PPD Director Biostatistics, PAREXEL International	
Co-Authors PPD Statistics Leader (II Biostatistics)	

RAP Team Review Confirmations
(Method: E-mail)

Reviewer	Date
PPD Medical Monitor	18-SEP-2019
PPD Manager, Clinical Pharmacology	18-SEP-2019

Reviewer	Date
PPD Principal Programmer/Analyst	18-SEP-2019
PPD Statistics Leader (II Biostatistics)	18-SEP-2019

Clinical Statistics & Clinical Programming Line Approvals
(Method: Pharma TMF eSignature)

Approver	Date
PPD Director Statistics	20-SEP-2019
PPD Director Programming	20-SEP-2019

RAP Team Reviewers Not Requiring Confirmation

Reviewer
PPD Medicines Development Leader
PPD Project Physician Lead
PPD Clinical Investigation Lead
PPD Medical Writer
PPD Director Global Regulatory Affairs
PPD Safety Development Lead (SERM)
PPD Director, RD II DPU Mechanistic Medicine Head

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the primary analyses for the double-blind treatment period be included in the Clinical Study Report for Protocol: BEL114054. The open-label extension reporting will be described in a separate RAP.

Protocol Revision Chronology:		
Document Number	Approved	Revision
Global	19-Oct-2011	Original
Global	27-Jan-2012	Amendment 01
Global	08-Mar-2012	Amendment 02
Local	16-Aug-2012	Amendment 02 (Thailand)
2013N179093_00	11-Feb-2014	Amendment 03
2014N205397_00	29-Aug-2014	Amendment 04 (China)
2013N179093_01	16-Mar-2015	Amendment 05
2013N179093_02	17-March-2015	Amendment 05 (France)
2013N179093_03	13-July-2016	Amendment 05 (France-2)
2013N179093_04	25-Apr-2017	Amendment 06
2013N179093_05	26-Apr-2017	Amendment No 06 (France-2)
2013N179093_06	24-Jan-2019	Amendment 07
2013N179093_07	18-Feb-2019	Amendment No 07 (France-2)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	Statistical Analysis Plan	Rationale for Changes
The protocol refers to the first exposure to study agent as Day 0.	The analysis plan refers to the first exposure to treatment as Day 1.	The terminology was changed to be compliant with CDISC standards.
Region subgroup definition is US/Canada Europe/Australia/Israel Asia Americas excluding US/Canada (Protocol Section 8.5.2.3)	Region subgroup definition is US/Canada Europe Asia Americas excluding US/Canada (RAP Section 5.3)	There were no subjects enrolled in Australia or Israel, so these were removed from the subgroup label.
Corticosteroid use endpoints defined as proportion of subjects with prednisone ≤ 5 mg and ≤ 7.5 mg by visit (Protocol Section 8.5.4)	Corticosteroid use endpoints are defined as the proportion of subjects with prednisone average daily dose ≤ 5 mg and ≤ 7.5 mg since previous visit (RAP Section 7.3.1 and Section 14.6.3.17.2)	Provides clarity around the time period used for calculating the average daily prednisone dose.
Calculated GFR (Protocol Section 6.7) references the use of creatinine clearance determined from the mean creatinine value of 2 contiguous 24-hour urine collections and 2 serum creatinine measurements (first serum creatinine collected at initial visit and the second sample taken 3 days later at the follow-up visit).	Calculated GFR (RAP Section 14.6.3.10) defines cGFR as the mean of two contiguous creatinine clearance values adjusted for body surface area each derived from 24-hour urine collections and serum creatinine measurements.	The urine volume data was not available to compute the calculated GFR per the protocol instructions.
Unless otherwise specified, all analyses will be performed on the intention to treat (ITT) population defined as all subjects who are randomized and receive at least 1 dose of study agent. The ITT analysis will be performed according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.	The modified intention to treat population will be used for analysis of the study population, efficacy and biomarker endpoints Safety data will be summarised based on the safety population	An updated modified ITT population was added to exclude the only subject who had an assessment at site PPD for GCP non-compliance and the only subject with an assessment at site PPD due to insufficient source documentation.

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

Objectives	Endpoints
Primary Efficacy Objective	Primary Efficacy Endpoint
To evaluate the efficacy of belimumab in combination with standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 International Society for Nephrology (ISN)/Renal Pathology Society (RPS) criteria.	Primary Efficacy Renal Response (PERR) at Week 104 defined as a reproducible response: <u>Responder</u> • Urinary protein:creatinine ratio ≤0.7; and • Estimated GFR (eGFR) is no more than 20% below the pre-flare value or ≥60 mL/min/1.73m^2; and • Not a Treatment Failure <u>Non-Responder</u> • Not meeting criteria for PERR renal response
Secondary Efficacy Objectives	Secondary Efficacy Endpoints
Assess Major Secondary Objectives	• Complete Renal Response (CRR) at Week 104 defined as a reproducible response: <u>Responder</u> • Urinary protein:creatinine ratio <0.5; and • Estimated eGFR is no more than 10% below the pre-flare value or ≥90 mL/min/1.73m^2; and • Not a Treatment Failure <u>Non-Responder</u> • Not meeting criteria for CRR renal response • PERR at Week 52 (see Section 7.2.2) • Time to Death or Renal-related Event (see Section 7.2.3) • Ordinal Renal Response (ORR) at Week 104 (see Section 7.2.4)
Renal specific measures (supplementary to PERR)	PERR Supplementary Endpoints
Supplementary analyses of PERR	*PERR Individual components* Proportion of subjects with the following by visit: • Urinary protein:creatinine ratio ≤0.7 • eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2 • Not a Treatment Failure *PERR* • Proportion of subjects with PERR by visit. • Time to the first PERR that is maintained through Week 52 • Time to the first PERR that is maintained through Week 104
Renal Specific Measures	CRR Supplementary Endpoints

Objectives	Endpoints
(Supplementary to CRR)	
Provide supplementary analyses of CRR	*CRR individual components* Proportion of subjects with the following by visit: • Urinary protein:creatinine ratio < 0.5 • eGFR no more than 10% below the *pre-flare* value or within the normal range (≥90 mL/min/1.73m^2) *CRR* • Proportion of subjects with CRR by visit. • Time to the first CRR that is maintained through Week 52. • Time to the first CRR that is maintained through Week 104.
SFI Flares	SFI Flare Endpoints
Assess SFI flares	*SFI Flares* • Time to first severe SFI flare. • Time to first severe SFI flare after Week 24.
Other Renal Objectives	Renal Endpoints

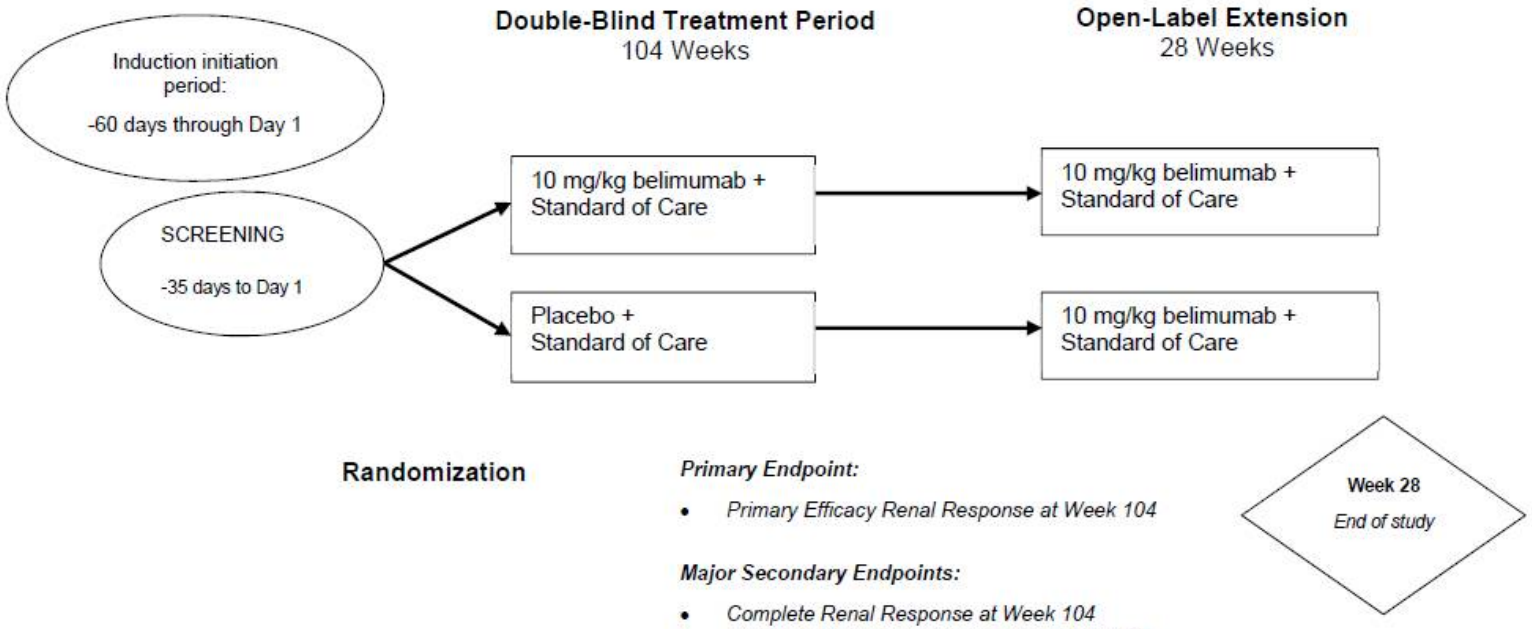
Assess Renal-specific measures	• Percent change in proteinuria by visit.
	• Change in proteinuria by visit.
	• Proportion of subjects with a doubling of the serum creatinine or progression to end stage renal disease (ESRD) as defined below:
	  • Doubling of serum creatinine compared with baseline that is confirmed with a second measurement at least 3 weeks later.
	  • Progression to ESRD defined as the need for chronic dialysis or renal transplantation.

Disease Activity Objectives	SLEDAI-S2K Endpoints
Assess SLEDAI-S2K	• Change from baseline in SLEDAI-S2K score by visit. • Change from baseline in SLEDAI-S2K excluding renal items by visit. • Proportion of subjects with SLEDAI-S2K < 4 by visit • SLEDAI-S2K Organ Worsening by organ system and visit • SLEDAI-S2K Organ Improvement by organ system and visit
Corticosteroid Use Objectives	Corticosteroid Endpoints
Assess Corticosteroid Use	• Proportion of subjects receiving ≤ 5 mg/day prednisone by visit. • Proportion of subjects receiving ≤ 7.5 mg/day

Objectives	Endpoints
	prednisone by visit.
Organ Damage Objectives	SLICC Endpoints
Assess changes in SLICC	• SLICC/ACR Damage Index (SDI) change from baseline by visit. • Percent of patients with any SLICC/ACR Damage Index worsening (change >0) compared with baseline by visit.
Primary Safety Objectives	Primary Safety Endpoints
To assess the safety and tolerability of belimumab plus standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV, or V using the 2003 ISN/RPS criteria.	• Adverse Event frequencies for all AEs, serious AEs, and AEs of Special Interest • Laboratory results by visit, worst laboratory toxicity grades, laboratory toxicity grade worsening of at least 2 grades from baseline, and laboratory reference range shifts from baseline. • C-SSRS
Biomarker Objectives	Biomarker Endpoints
Assess changes in Biomarkers	The change and percent change from baseline by visit of the following variables: • Absolute B cell subsets • Total serum immunoglobulin (IgG and other isotypes: IgM and IgA). • Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q). • Complement (C3, C4) levels. Percent of patients with normalized serological activity at Week 104 and over time • IgG, IgM and IgA (high to normal/low). • Autoantibodies* (anti-dsDNA, ANA, aCL, anti-Sm, and anti-C1q) present to absent. • Complement (C3, C4, and C3 AND C4) levels low to normal/high. * Anti-dsDNA will be collected monthly throughout the double-blind treatment period. Other autoantibodies will be collected from all patients at baseline, then at regular intervals during the study. Data collection and analysis of the exploratory renal biomarkers will be performed independently of the main study and will form the basis of a separate report.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active lupus nephritis. • Subjects must have active, biopsy-proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)] either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria. • This is an induction/maintenance study design. All subjects must start induction therapy within 60 days prior to or on Day 1. • All subjects will receive background therapy consisting of one of the following standard of care regimens: o High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA) for maintenance therapy OR o HDCS + Mycophenolate Mofetil (MMF) for induction therapy followed by MMF for maintenance therapy • Randomized treatment with either belimumab 10 mg/kg or placebo will begin on Day 1 and continue through the 104-week double-blind treatment period. • Renal response will be measured as improvement in proteinuria and estimated GFR without meeting treatment failure criterion. Week 104 renal response will be defined by a response at Week 100 that is confirmed by a repeat measurement at Week 104. • Subjects who receive treatment with study agent through Week 100 and complete Week 104 assessments in the double-blind period may enter a 6-month open-label extension. • The Week 104 visit of the double-blind period will serve as the Day 1 visit for subjects entering the 6-month open-label extension. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the last dose). • All subjects who discontinue treatment with study agent during the double-blind period should return for all scheduled visits through Week 104, unless consent to participate in the study is withdrawn. • Subjects who complete the 104-week double-blind period, but do not enter the open-label extension will be required to return for an additional follow up visit 8 weeks after the last dose of study agent.
Dosing	• In the double-blind treatment period, subjects will be dosed with study agent on Days 1 (baseline), 14, 28 and then every 28 days thereafter through 100 weeks with a final evaluation at Week 104 (4 weeks after the last double-blind dose). • Day 1 of the open-label extension phase is the same date as the Week 104 visit of the double-blind period. Therefore, the first dose of study agent for subjects entering the open-label phase will be at the Week 104/Day 1 visit. In the open-label extension, all subjects will receive 10 mg/kg belimumab every 28 days until Week 24, with a final evaluation at Week 28 (4 weeks after the

	last open-label dose).
Time & Events	• Refer to Appendix 2: Schedule of Activities

Treatment Assignment	• All subjects should start induction therapy within 60 days prior to or on Day 1.
	• All subjects will receive background therapy consisting of one of the following standard of care regimens:
	  • High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA) for maintenance therapy
	OR
	  • HDCS + Mycophenolate Mofetil (MMF) for induction therapy followed by MMF for maintenance therapy
	• At least 400 and up to approximately 464 lupus nephritis subjects will be randomized with a target of at least 200 and up to approximately 232 subjects in each treatment group (belimumab or placebo).
	• The randomization will be stratified by induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black vs non-black). Subjects will be allocated to belimumab or placebo in a 1:1 ratio.
	  • In the event of recruitment challenges, randomization may be stopped if the number randomized is ≥ 400 subjects.
	  • A sample size of N=448 will provide approximately 80% power for the dichotomous endpoints of PERR and CRR assuming the underlying treatment difference is at least 12.0% (20% vs. 32%) to 13.6% (45% vs. 58.6%), depending on where the response rates fall, for placebo plus standard of care compared with belimumab plus standard of care, respectively.
	• During the open-label extension phase, all subjects will receive belimumab 10 mg/kg plus standard of care.

Interim Analysis	• No interim analysis is planned for this study.

2.4. Statistical Hypotheses / Statistical Analyses

- H_o: There is no difference in renal response rates for belimumab plus standard of care vs placebo plus standard of care at Week 104 of the double-blind treatment period.
- H_a: There is a difference in renal response rates for belimumab plus standard of care vs placebo plus standard of care at Week 104 of the double-blind treatment period.

3. PLANNED ANALYSES

3.1. Interim Analyses

- No interim analysis is planned for this study.

3.2. Final Analyses

- There will be two database locks for this study corresponding to the primary analysis (end of double-blind period) and the open-label extension analysis (end of study analysis). The open-label extension analysis and reporting will be described in a separate RAP.
- All subjects and study site personnel (except the unblinded site pharmacist) will remain blinded until the open-label extension data is locked.

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

1. All subjects have completed the Week 104 visit of the double-blind treatment period (or Exit visit for those subjects who withdraw consent during double-blind treatment) or are lost to follow-up. For subjects not entering the open-label extension, data collected during the post-treatment follow-up period will be included if it is available on or before the last subject completes the Week 104 visit, exit visit, or is lost to follow-up.
2. All required database cleaning activities have been completed and final database release (DBR) has been declared by Data Management.
3. Adjudication of protocol deviations, adverse events of special interest, treatment failures, and cases of progression to end stage renal disease has been completed.
4. All criteria for unblinding the randomization codes have been met.
5. Randomization codes have been distributed per GSK procedures.
6. Database freeze (DBF) has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for the trial, irrespective of whether they were randomized.	• Study Population
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment to which the participant was randomized.	• Study Population
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the randomized treatment.	• Safety

Population	Definition / Criteria	Analyses Evaluated
	• If more than 15% of the subjects received a treatment other than their randomized treatment for >50% of infusions, the subject will be classified based on the actual treatment received for >50% of the infusions. • Note: Participants who were not randomized but received at least one dose of study treatment will be listed.	
Modified Intent-To-Treat (MITT)	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment to which the subject was randomized. • Any subject who receives a treatment randomization number in ALMAC will be considered to have been randomized. • Excludes the one subject at site PPD due to GCP non-compliance issues and the one subject at site PPD due to insufficient source documentation..	• Study Population • Efficacy • Biomarkers
Per-Protocol (PP)	• A subset of the MITT population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in Appendix 1. • The PP set will only be analysed if this population excludes more than 15% of the MITT population.	• Efficacy
Completers on Study Agent	• Subjects from the MITT population who completed through Week 104 and were not permanently discontinued from treatment prior to Week 104.	• Efficacy
Completers on Study	• Subjects from the MITT population who completed through Week 104 including subjects both on and off treatment	• Efficacy
Pharmacokinetic (PK)	• All belimumab-treated subjects in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

Refer to Appendix 13 which details the population used for each display.

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [Version 3, 13Aug19].

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting	
Code	Description	Description	Order in TFL
0	Placebo	Placebo	1
1	Belimumab 10 mg/kg	Belimumab 10 mg/kg	2

On some safety displays, belimumab is presented without the dose and unit due to space restrictions.

Treatment comparisons will be displayed as follows using the descriptors as specified:

- Bel 10 mg/kg vs Placebo

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

For Study Population tables presenting baseline demographics and characteristics described in Section 6, a total column for both treatment groups combined will also be presented for subjects in the double-blind phase. Other subgroup descriptors will be described in more detail in Section 5.4.2.

5.2. Baseline Definitions

The baseline value of a variable will be defined as the value of the variable measured at Day 1 (treatment start date) 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. For ECGs where timing is collected, the date and time will be compared to the infusion date and time to determine baseline; in the event of a missing time, the ECG will be assumed to be prior to dosing.

If there are multiple results on Day 1 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.

For concomitant medications and adverse events, these are considered present at baseline if the start date is prior to Day 1 and the end date is on or after Day 1. Medications or events with a start date on Day 1 are considered as being on-treatment and treatment-emergent, respectively.

Baseline flares are flares that occur on or prior to the treatment start date.

Baseline values occurring on Day 1 will not be considered on-treatment unless explicitly defined as such.

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

The protocol specifies Day 0 as Baseline/Treatment Start date, but the CDISC standard is to refer to the Baseline/Treatment Start date as Day 1; therefore Baseline/Treatment Start date will appear as Day 1 in the displays and will be referenced as Day 1 in this document. A table indicating the target study day for each planned visit starting at Day 1 (instead of Day 0) is in Section 14.3.1.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be carried out in the following Regions and Countries:

Region	Countries
Asia	China, Hong Kong, Korea, Philippines, Taiwan, Thailand
US/Canada	United States, Canada
Americas excluding US/Canada	Argentina, Brazil, Colombia, Mexico
Europe	Belgium, Czech Republic, France, Germany, Hungary, Netherlands, Russian Federation, Spain, United Kingdom

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details

Strata	Randomization Stratification Factors
	• Induction Regimen
	  • CYC
	  • MMF
	• Race
	  • Black
	  • Non-Black

Covariates	• Baseline uPCR

Category	Details
	• Baseline eGFR

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

If the percentage of subjects is small within a subgroup, then the subgroup categories may be refined prior to unblinding the trial or a subgroup may be eliminated.

If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the subgroup.

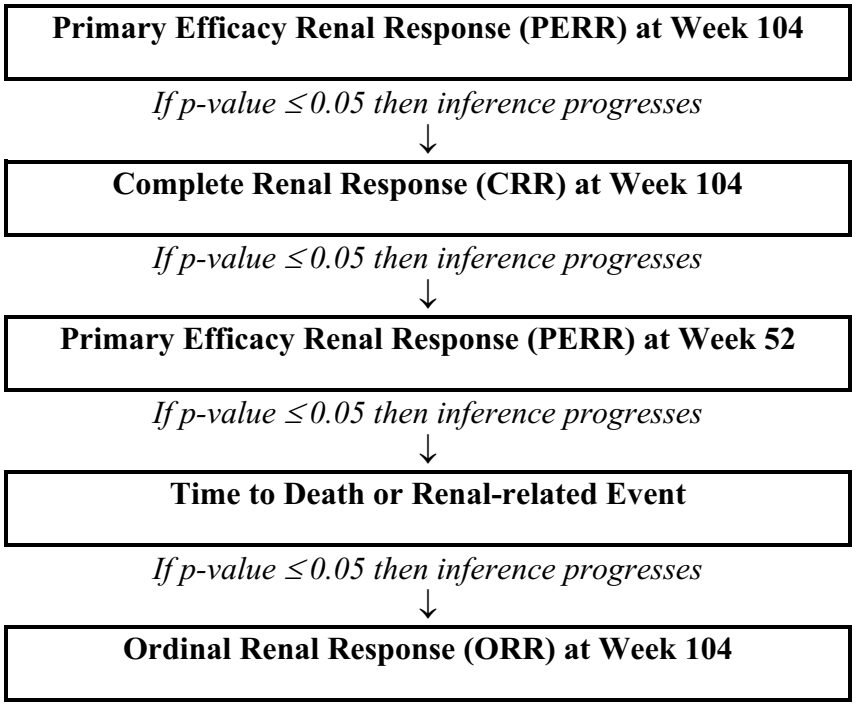
Subgroup	Categories
Induction Regimen	CYC vs. MMF
Race Stratification Factor	Black vs. Non-Black
Region	Asia, US/Canada, Americas excluding US/Canada, Europe
Baseline anti-dsDNA	Positive (≥30 IU/mL) vs. Negative (<30 IU/mL)
Baseline Complement	At least one C3/C4 Low vs. No C3/C4 Low where Low C3 is <90 mg/dL and Low C4 is <10 mg/dL
Baseline C3/C4 levels & anti-dsDNA	At least one C3/C4 low and anti-dsDNA ≥30 IU/mL vs. Not (At least one C3/C4 low and anti-dsDNA ≥30 IU/mL)
Baseline Renal Biopsy Class (local reader assessment)	Class III or Class IV Class III+V or IV+V Class V
Gender	Female vs. Male
Baseline Body Weight Quartile	1st Quartile < q1 kg 2nd Quartile q1 - < q2 kg 3rd Quartile q2 - < q3 kg 4th Quartile ≥ q3 kg Where q1, q2, and q3 are the observed values from the data.

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interest is the comparison between Belimumab 10mg/kg and Placebo for the primary endpoint in the MITT population. This analysis will be adjusted for the stratification factors applied at randomization.

An overview of the multiplicity control is provided in Figure 1.

Figure 1 Step-down, Sequential Testing Procedure



For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure will be used to control the overall type 1 error. With this procedure, the primary and 4 major secondary efficacy endpoints will be evaluated for statistical significance based on the pre-specified sequence for interpretation shown in Figure 1.Specifically, endpoints will be tested in the sequence above (2-sided alpha=0.05) provided statistical significance is achieved by all prior tests. If at any point in the sequence statistical significance is not met, then subsequent endpoints in the sequence cannot be deemed statistically significant, although nominal p-values and 95% confidence intervals may be reported and considered descriptive. Analyses of other efficacy endpoints will not be subject to any multiplicity adjustment. All statistical tests will be two-sided and performed at an overall significance level of 0.05.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
14.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
14.2	Appendix 2: Schedule of Activities
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events

Section	Component
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Laboratory Toxicity Grades
14.9	Appendix 9: Population Pharmacokinetic (PopPK) Analyses
14.10	Appendix 10: B cells
14.11	Appendix 11: Abbreviations & Trade Marks
14.12	Appendix 12: List of Data Displays
14.13	Appendix 13: Example Mock Shells for Data Displays
14.14	Appendix 14: Headline Results

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards and Benlysta program standards, where applicable. Details of the planned displays are presented in Section 6.7: Summary of Study Population Analyses and in Appendix 12: List of Data Displays. With few exceptions, displays will be presented by treatment arm for the overall modified Intent-to-Treat population and within induction regimen.

6.2. Disposition of Subjects

Using the Randomized population, the number and percentage of subjects randomized by country and site will be summarized by treatment group and for the combined treatment groups.

Using the Screened population, the number of subjects in each population (Screened, Randomized, Safety, modified Intent-to-Treat, Per Protocol, Completers on Study Agent, Completers on Study, and PK) will be summarized by treatment group and for the combined treatment groups. Using 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.

The subject's status by Week 104 will be assessed to evaluate percentages of subjects who completed the study and treatment or withdrew from the study and/or discontinued treatment prematurely. The summary will be presented by treatment group for the overall modified Intent-to-Treat population and within induction regimen.

The subject's completion status will be presented as percentage of withdrawals from the study as well as the reasons for withdrawal. The number and percentage of subjects who completed through Week 104 and who withdrew, including the primary reasons for withdrawal, will be displayed by treatment group for the overall modified Intent-to-Treat population and within induction regimen. The cumulative number and percentage of subjects who withdrew from the study by study visit will also be displayed by treatment group for the overall modified Intent-to-Treat population and within induction regimen. Additionally, a figure for the cumulative proportion of subjects withdrawn from the study by visit, derived using assessment windows defined in Appendix 3, will be generated to evaluate the pattern of dropouts over time.

The subject's investigational product status and reason for investigational product (IP) discontinuation will be assessed. The number and percentage of subjects who completed treatment through Week 104 and who prematurely discontinued IP, including primary reason for IP discontinuation, will be displayed by treatment group for the overall modified Intent-to-Treat population and within induction regimen. Additionally, the cumulative number and percentage of subjects who discontinued IP by study visit, derived using assessment windows defined in Appendix 3, will be displayed by treatment group for the overall modified Intent-to-Treat population and within induction regimen. A figure for the cumulative proportion of subjects who discontinued IP will be generated to evaluate the pattern of IP discontinuations over time. Subjects that discontinue IP prematurely will be counted as discontinued at the first visit without a treatment infusion. A listing of subject disposition will be provided showing completion status and inclusion in each population. A listing of subjects who withdrew from the study, including reason for and date of withdrawal will also be provided. Both listings will be displayed by induction regimen and treatment group.

An additional listing will be provided of subjects who discontinued IP, including reason and date of discontinuation. Subjects for whom the treatment blind was broken during the study will be listed. These listings will be displayed by induction regimen and treatment group.

A listing of planned and actual treatments will be provided for each subject by Country, Site ID, and Investigator name.

6.3. Protocol Deviations

- Please refer to the Protocol Deviation Management Plan (PDMP): Dated: 13Aug2019 (Version 3.0) 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 for the overall modified Intent-to-Treat population and within induction regimen. Deviations which result in exclusion from the PP population will be summarized by treatment group for the overall modified Intent-to-Treat population and within induction regimen.

A listing of subjects experiencing an important protocol deviation, including PP population exclusions, will be provided by induction regimen and treatment group (see Appendix 1). A listing of subjects excluded from the PP population will also be provided by induction regimen and treatment group.

- The number and percentage of subjects who deviated from any inclusion or exclusion criteria and each inclusion/exclusion criteria type will be displayed by treatment group for the overall modified Intent-to-Treat population and within induction regimen. A listing of subjects who had a deviation from the inclusion or exclusion criteria will be provided by induction regimen and treatment group.

Additional protocol deviations may be identified during the study and will be documented in Protocol Deviation Adjudication Meeting minutes prior to the first database lock and unblinding. A final list of subjects that have an important protocol deviation will be agreed after database release, prior to unblinding.

6.4. Demographic and Baseline Characteristics

Continuous parameters will be summarized using descriptive statistics (mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum). Categorical parameters will be summarized using counts and percentages.

Demographic and baseline characteristics including region and country, sex, ethnicity, age, age group, height, weight, and body mass index (BMI) will be summarized by induction regimen, treatment group and overall. A summary of age ranges by treatment group for the overall modified Intent-to-Treat population and within induction regimen will also be provided. A listing of demographic and baseline characteristics will be displayed by induction regimen and treatment group.

Vital signs at baseline, including diastolic and systolic blood pressure, heart rate, and temperature will be summarized by treatment group for the overall modified Intent-to-Treat population and within induction regimen.

A listing of ECG findings, including clinically significant abnormalities, will be presented by induction regimen and treatment group.

Current and past medical conditions will be summarized separately by any medical history, and also by body system or organ class and preferred term, by treatment group for the overall modified Intent-to-Treat population and within induction regimen. A listing of subjects with current and past medical conditions will be displayed by induction regimen and treatment group.

A summary of race and racial combination details will be presented by treatment group for the overall modified Intent-to-Treat population and within induction regimen. Subjects who check more than one race category are counted under the Multiple category. The following minority rule will be applied to all analyses related to race (except for stratification):

If a subject checks multiple race categories on the eCRF, the subject will be assigned to a unique race group according to the following priority order:

- Native Hawaiian or Other Pacific Islander
- Alaska Native or American Indian from North/Central/South America
- Asian
- Black
- White/Caucasian

Race will be listed for all subjects by induction regimen and treatment group.

Baseline stratification factors, induction regimen (CYC, MMF) and race (Black, Non-Black), will be presented by treatment group and the combined treatment groups for the modified Intent-to-Treat population. A shift table of differences between stratification factors at Screening and as Randomized (data entered into the ALMAC system) will be produced for the combined treatment groups.

Stratification factors (randomized and actual strata) will be listed for all subjects by induction regimen and treatment group.

A summary of baseline disease activity, including SLE and LN (Lupus Nephritis) disease duration, renal biopsy class (local and central reader) renal biopsy category (local and central reader), urine protein-creatinine ratio (uPCR), estimated GFR (eGFR), SLEDAI-S2K score, physician's global assessment (PGA), and SLICC/ACR Damage Index (SDI) will be presented by treatment group for the overall modified Intent-to-Treat population and within induction regimen.

The following indicators of baseline disease activity will be summarized by treatment group for the overall modified Intent-to-Treat population and within induction regimen:

- Pre-flare serum creatinine and estimated GFR values
- Lupus Nephritis therapy history (previous CYC or MMF therapy and response [responded/failed] to therapy)
- ACR classification criteria at baseline
- SLEDAI-S2K organ and item involvement at baseline
- Baseline immunoglobulin levels (IgA, IgG, and IgM)
- Baseline autoantibody levels (Anti-dsDNA, ANA, Anti-cardiolipin, Anti-dsDNA and/or ANA positive, Anti-c1q, and Anti-Sm)
- Baseline levels of complement and other biomarkers (C3, C4, and BLyS Protein)
- Baseline B cells (CD19, CD20, Naïve CD19+CD20+CD27-, Memory CD19+CD20+CD27+, Activated CD19+CD20+CD69+ Normalized, Plasma CD19+CD20-CD138+ Normalized, Plasmacytoid CD19+CD20+CD138+ Normalized, Short-lived Plasma CD19+CD20-CD27b+ Normalized, SLE subset CD19+CD38b+CD27b+ Normalized, Transitional CD19+CD24b+CD38b+CD27- Normalized
- Pre-treatment Columbia Suicide Severity Rating Scale (C-SSRS) responses by behavior and ideation components

- Allowable SLE and LN medication usage at baseline

Listings for pre-flare serum creatinine and eGFR, Lupus Nephritis therapy history, and renal biopsy results at Screening will be provided for each subject by induction regimen and treatment group.

The demographic and baseline characteristics, baseline disease activity, and allowable SLE and LN medication at baseline summaries will be repeated for the subgroups defined in Section 5.4.2.

6.5. 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 are defined as (1) medications that start on or before the first dose date of study treatment and end on or after the first dose date of study treatment, or (2) medications that start after the first dose date of study treatment and before the open-label 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 study treatment and if the month and year are the same or later, then the medication will be considered concomitant.

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 by induction regimen, treatment group and overall. A further summary of concomitant medications by ATC level 4 term and preferred term will be provided by induction regimen, treatment group and overall. A listing of all concomitant medication data for subjects will be displayed by induction regimen and treatment group. A listing of the relationship between ATC Level 1, ingredient, and verbatim text will also be provided.

Protocol-prohibited medication and allowable medication that results in treatment failure designation (see protocol Section 5.5 and Section 5.6) will be summarized by induction regimen, treatment group and overall. A listing of protocol-prohibited medication and allowable medications that result in treatment failure designation will be displayed for subjects by induction regimen and treatment group.

6.6. Extent of Exposure

The extent of exposure to study treatment through Week 104 will be assessed by examining the duration of exposure to belimumab/placebo in days and the total number of infusions a subject receives. Duration of exposure in days will be calculated as:

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

If a subject dies <28 days after the last infusion, then exposure will be calculated as (Death date – First Infusion Date + 1). Only complete dates will be used when calculating duration of exposure. First and last infusion dates will be used, regardless of any missed

doses. Subjects who were randomized but did not report a treatment start date will be categorized as having zero days of exposure.

The duration of exposure and the total number of infusions will be summarized using descriptive statistics. The duration of exposure will also be summarized using counts and percentages for the following categories: <24 weeks, 24 – 52 Weeks, >52 – 76 weeks, >76 weeks where weeks are based on the visit week of the last infusion received. The total number of infusions will be summarized using counts and percentages for the following categories: 1 – 9 doses, 10 – 18 doses, 19 – 27 doses, and ≥28 doses. These summaries will be presented by induction regimen, treatment group and overall.

Exposure data will be listed for all subjects by induction regimen and treatment group.

6.7. Summary of Study Population Analyses

The following Study Population parameters will be summarized:

PARAMETER	SUMMARY TYPE
Randomization by Country and Site	
Country, Site, and Investigator Name	Categorical
Populations	
Populations	Categorical
Reasons for Failing Screening	
Screening Status and Reason for Failed Screening	Categorical
Subject Status by Week 104	
Completion / Withdrawal Status	Categorical
Subject Completion Status by End of Double-Blind Phase Week 104	
Week 104 Completion and Withdrawn Prior to Week 104; Includes Reasons for Withdrawal	Categorical
Time to Withdrawal from Study	
Completions Through Week 104 and Subjects Withdrawn by Week	Categorical
Investigational Product Status and Reasons for Discontinuation	
Investigational Product Status and Primary Reason for Premature Discontinuation	Categorical
Investigational Product Discontinuation by Visit	
Investigational Product Completion Through Week 104 and Discontinuation by Visit	Categorical
Inclusion/Exclusion Criteria Deviations	
Any Criteria Deviations and Specific Inclusion/Exclusion Criteria Not Met	Categorical: Presented if Yes
Important Protocol Deviations	
Any Important Protocol Deviations and Deviations Presented by Category and Coded Term	Categorical: Presented if Yes
Exclusions from the Per Protocol Population	
Exclusion Category and Coded Term	Categorical: Presented if Yes
Shifts in Differences Between Stratification Factors at Screening and as Randomized	
Displays induction regimen and race categories at screening and as randomized	Induction Regimen (CYC vs. MMF) Race (Black, Non-Black)
Demographic and Baseline Characteristics (table is also displayed by Subgroups)	

PARAMETER	SUMMARY TYPE
Region and Country	Categorical: Asia, Europe, US/Canada, Americas excluding US/Canada
Sex	Categorical: Female, Male
Ethnicity	Categorical: Hispanic or Latino, Not Hispanic or Latino
Age (years)	Continuous Categorical: ≤45 years, >45 – <65 years ≥65 years ≥65 – <75 years ≥75 years
Height (cm)	Continuous
Weight (kg)	Continuous
Body Mass Index (BMI) (kg/m^2)	Continuous
Summary of Age Ranges	
Age Ranges	Categorical: Adult (18-64 years) ≥65-84 years ≥85 years
Race and Racial Combination Details	
Race	Categorical: White/Caucasian White/Caucasian/European Heritage Arabic/North African Heritage Mixed Caucasian Asian Central/South Asian Heritage Japanese/East Asian/South East Asian Heritage Mixed Asian Black or African American American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Multiple
Vital Signs at Baseline	
Systolic Blood Pressure	Continuous
Diastolic Blood Pressure	Continuous
Heart Rate	Continuous
Temperature	Continuous
Current and Past Medical Conditions	
Current Medical Conditions by Body System or Organ Class and Preferred Term	Categorical: present if current medical condition exists
Past Medical Conditions by Body System or Organ Class and Preferred Term	Categorical: present if past medical condition exists
Stratification Factors	
Induction Regimen	Categorical: - CYC - MMF

PARAMETER	SUMMARY TYPE
Race	Categorical: -Black -Non-Black
Induction Regimen and Race Strata	Categorical: CYC and Black CYC and Non-Black MMF and Black MMF and Non-Black
Baseline Disease Activity (table is also displayed by Subgroups)	
SLE disease duration (years)	Continuous
LN disease duration (years)	Continuous
Renal Biopsy Class (local reader and central reader results will be displayed separately)	Categorical: Class I Class II Class III (A) Class III (A/C) Class III (C) Class IV-S (A) Class IV-G (A) Class IV-S (A/C) Class IV-G (A/C) Class IV-S (C) Class IV-G (C) Class V Class VI Categorical (Subgroup): Class III or Class IV Class V Class III+V or Class IV+V
Urine Protein-Creatinine Ratio (uPCR)	Continuous Categorical: <0.5, 0.5-<3, ≥3 <=0.7
Estimated GFR (mL/min/1.73m2)	Continuous Categorical: <30, 30-<60, 60-<90, ≥90 ≥60
SLEDAI-S2K score	Continuous Categorical: <8, 8 - <12, 12 - <16, ≥ 16
PGA	Continuous Categorical: 0-1, >1 – 2.5, >2.5, Missing
SLICC/ACR Damage Index score	Continuous Categorical: 0, 1, >1
Pre-Flare Serum Creatinine and eGFR Values	
Pre-Flare Serum Creatinine and Pre-Flare Estimated GFR Values (pre-flare estimated GFR values are calculated from pre-flare serum creatinine)	Continuous: Serum Creatinine and eGFR Categorical: eGFR <30, 30-<60, 60-<90, ≥90 ≥60
Lupus Nephritis Therapy History	

PARAMETER	SUMMARY TYPE
Previous CYC or MMF Therapy and whether subject responded or failed therapy	Categorical
ACR Classification Criteria at Baseline	
ACR classification criteria by symptom	Categorical: Presented if Yes
SLEDAI-S2K Organ and Item Involvement at Baseline	
SLEDAI-S2K by organ and item at baseline	Categorical: presented if Yes
Immunoglobulin Levels at Baseline	
Baseline immunoglobulin levels (g/L): IgA, IgG, and IgM	Continuous Categorical: -below the lower limit of normal (LLN) -above upper limit of normal (ULN)
Autoantibody Levels at Baseline	
anti-dsDNA [IU/mL]	Continuous Categorical: -positive (≥ 30 IU/mL) -negative (< 30 IU/mL)
ANA [Titer]	Continuous Categorical: -positive (≥ 80 Titer) -negative (< 80 Titer)
anti-cardiolipin (aCL)	Categorical: -positive (if any of the three isotypes IgG, IgA or IgM are above the lower limit of quantification) -negative (if at least one is non-missing and none of the isotypes above the limit of quantification)
anti-dsDNA and/or ANA positive	Categorical: Yes, No
Anti-c1q (U/mL)	Continuous Categorical: -positive (≥22.2 U/mL) -negative (<22.2 U/mL)
Anti-Sm (KU/L)	Continuous Categorical: -positive (≥15 KU/L) -negative (<15 KU/L)
Complement Levels and Other Biomarkers at Baseline	
Baseline levels of complement: C3 (mg/dL)	Continuous Categorical: -high (>180 mg/dL), -normal (90 -180 mg/dL), -low (<90 mg/dL)
Baseline levels of complement: C4 (mg/dL)	Continuous Categorical: -high (>40 mg/dL), -normal (10 -40 mg/dL), -low (<10 mg/dL)
Complement Level	At least one C3/C4 Low No C3/C4 Low

PARAMETER	SUMMARY TYPE
Complement and anti-dsDNA Level	At Least One C3/C4 Low and anti-dsDNA ≥30 IU/mL Not(At Least One C3/C4 Low and anti-dsDNA ≥30 IU/mL)
BLyS Protein (ng/mL)	Continuous Categorical: -below limit of quantification [LOQ] (<0.061 ng/mL), -above LOQ - ≥ 2 ng/mL
B cells at Baseline	
CD19 CD20 Naïve CD19+CD20+CD27– Memory CD19+CD20+CD27+ Activated CD19+CD20+CD69+ Normalized Plasma CD19+CD20-CD138+ Normalized Plasmacytoid CD19+CD20+CD138+ Normalized Short-lived Plasma CD19+CD20-CD27b+ Normalized SLE subset CD19+CD38b+CD27b+Lymph Normalized Transitional CD19+CD24b+CD38b+CD27- Normalized	Continuous
Columbia Suicide Severity Rating Scale (C-SSRS) Responses by Behavior and ideation Components – Pre-treatment	
C-SSRS responses by behavior and ideation components for lifetime, current (over the last two months) and Baseline (since last visit)	Categorical: -Ideation: categories 1-5 with corresponding text -Behavior: categories 6-11 with corresponding text
Allowable SLE and LN Medication Usage at Baseline (table is also displayed by Subgroups)	
Average daily prednisone dose (mg/day) at baseline	Continuous
Allowable SLE and LN medications by class and drug at baseline	Categorical: -Steroids -Anti-malarials -Immunosuppressants -ACE/ARBs
Concomitant Medications by ATC Level 1 and ATC Level 4 Term	
ATC Level 1 and ATC Level 4	Categorical: Presented if Yes
Concomitant Medications by ATC Level 4 and Preferred Term	
ATC Level 4 and Preferred Term	Categorical: Presented if Yes
SLE and LN Medication Usage Resulting in Treatment Failure Designation Through Week 104	
Medication Category	Categorical: -Subjects with Treatment Failure -Steroids -Anti-malarials -Immunosuppressives -ACE/ARBs -Prohibited Medications
Exposure to Study Treatment through Week 104	
Duration of Exposure	Continuous (Days) Categorical: <24 weeks, 24 – 52 weeks, >52 - 76 weeks, >76 weeks

PARAMETER	SUMMARY TYPE
Total Number of Infusions	Continuous Categorical: 1-9,10-18, 19-27, ≥28

7. EFFICACY ANALYSES

Unless otherwise stated, all analyses will be limited to the double-blind treatment period while subjects are on investigational product (IP) defined as on or after the treatment start date up through and including the IP discontinuation date . Analyses of data after subjects have discontinued IP are described as sensitivity analyses and will be clearly identified.

For the purposes of the analysis plan, the period from Day 1 through Week 24 will be referred to as 'the induction phase' and the period from Week 24 visit date +1 through the Week 104 visit will be referred to as 'the maintenance phase.'

7.1. Primary Efficacy Analyses

7.1.1. Endpoint

The primary efficacy endpoint is the Primary Efficacy Renal Response (PERR) at Week 104 measured as a dichotomous response (Responder vs Non-Responder).

PERR is determined by reproducible changes in proteinuria and renal function. The PERR at Week 104 is defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit.

Primary Efficacy Renal Response (PERR)
Responder -uPCR ≤ 0.7; and - eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2; and -Not a Treatment Failure [1] **Non-Responder** -Not meeting criteria for PERR renal response

[1] Treatment failure is defined in Section 5.5 and Section 5.6 of the protocol with further detail in RAP Section 14.6.3.3

Further detail on the endpoint derivation can be found in Section 14.6.3.

7.1.2. Summary Measure

An odds ratio will measure the treatment effect for the odds of being a responder on belimumab vs. placebo.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the modified Intent-to-Treat population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

There are five types of intercurrent events (IEs):

1. Treatment Failure (TF)
2. Investigational Product (IP) Discontinuation
3. Study Withdrawal
4. Lost to Follow-up
5. Death

Intercurrent events of TF and IP discontinuation may have data observed after the event unless it coincides with a withdrawal event (Death, lost to follow-up, or study withdrawal) while withdrawal events have no data observed after the event.

The composite strategy is used for intercurrent events where renal response is imputed as a non-responder from the date of the earliest intercurrent event and all timepoints thereafter through Week 104. This imputation strategy is referred to as IP discontinuation, treatment failure, or withdrawal equals a non-responder and is written as IPD/TF/WD=NR.

7.1.4.1. Handling of Missing Data

7.1.4.1.1. Imputation for Missing Visits

Per the PERR definition, a Week 104 response is defined as a response at Week 100 confirmed at Week 104. If a subject misses the Week 100 or Week 104 visit (or is missing data for both eGFR and uPCR at the visit), the Week 96 renal response will be used to derive the primary endpoint as follows:

- If the Week 104 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 100 visits.
- If the Week 100 visit is missing, the primary endpoint will be determined using data from the Week 96 and the Week 104 visits.
- If subject misses both the Week 100 and the Week 104 visit, the subject's response will be imputed as a non-responder.
- If the subject has only one non-missing visit among Week 96, 100, and 104, the subject's response will be imputed as a non-responder.

Imputation for missing visits is limited to the current visit and two previous visits therefore limiting reproducibility to three visits. This three-visit rule is used for determining renal response at all visits renal response is derived.

7.1.4.1.2. Imputation if Missing a Single Lab Component within a Visit

At a given visit, eGFR and uPCR are required to assess whether a subject is a responder for the visit, assuming the subject has not had an intercurrent event on or before the visit.

An indicator variable for whether the lab criteria were met (Y or N) will be created for each lab component.

If either lab component (eGFR or uPCR) is missing for the Week 100 or 104 visits, the indicator variable for the missing lab component will be imputed based on the value for the non-missing visit (Week 100 or Week 104) and the Week 96 visit. Two values are required for the imputation to confirm the result. If both lab components are missing at the same visit, then the rules for a missing visit (Section 7.1.4.1.1) will be used to impute the visit response.

The following imputation method will be used for the missing response:

- If a lab component is missing at the Week 104 visit, the missing component will be determined using data on the component from the Week 96 and the Week 100 visits.
- If a lab component is missing at the Week 100 visit, the missing component will be determined using data on the component from the Week 96 and the Week 104 visits.
- If a lab component is missing at both the Week 100 and the Week 104 visits, then the subject's lab criterion indicator flag will be set to 'N' at each visit resulting in the subject being a non-responder for the PERR endpoint at Week 104.

Table 2 Imputation for Lab Component Indicator Variables When a Lab Component is Missing

Component Indicator Variable (Imputed Value)		
Week 96 Visit Lab Criterion Met	**Week 100 Visit Lab Criterion Met**	**Week 104 Visit Lab Criterion Met**
Y	Y	Missing (Y)
Y	N	Missing (N)
N	Y	Missing (N)
N	N	Missing (N)
Y	Missing (Y)	Y
Y	Missing (N)	N
N	Missing (N)	Y
N	Missing (N)	N
Y	Missing (N)	Missing (N)
N	Missing (N)	Missing (N)

Note: This will apply to the eGFR or uPCR criterion separately.

7.1.4.1.3. Example of the Renal Response Endpoint Derivation with Missing Data

The example in Table 3 illustrates the following:

- Imputation of a missing lab component at a single visit (i.e., missing uPCR at Week 104)

- Indicator variables for response criterion met within a visit (Y or N; shown in rows for each renal response component)
- Renal response at the visit (Y or N; shown in the last row for each visit column)
- Primary renal response at Week 104 (Y or N; shown in the last row/last column)

Table 3 Example of Renal Response Endpoint Derivation including Imputation due to Missing uPCR at Week 104

Responder	Week 96	Week 100	Week 104	Primary Renal Response
uPCR component	Y	N	Missing (N)	
eGFR component	Y	Y	Y	
Not a Treatment Failure	Y	Y	Y	
Renal Response*	Y	N	N	N

*Requires a 'Y' indicating criterion met for each component to achieve a response.

7.1.5. Statistical Analyses / Methods

PERR (Responder vs. Non-Responder) at Week 104 will be compared between belimumab and placebo using logistic regression controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.

Variables
• PERR (Responder vs. Non-Responder) • Treatment (belimumab=1, placebo=0) • Induction (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0) • uPCR (at baseline; continuous) • eGFR (at baseline; continuous)
Model Specification
The model will be specified as: PERR = Treatment Induction Race uPCR eGFR. Reference cell coding will be used.
Model Checking & Diagnostics
The data will be evaluated by two independent statisticians to determine if the model assumptions and fit are reasonably met. If either is deemed unacceptable, additional sensitivity analysis using an alternative method may be performed.
Model Results Presentation
The primary table will present Week 104 results as the percentage of responders by treatment group, SE for the percentage of responders by treatment group, the observed treatment difference

(belimumab – placebo), Cochran-Mantel-Haenzel estimates of the treatment difference and associated 95% confidence interval adjusted for induction regimen and race, odds ratio (OR) for the treatment effect (belimumab/placebo), 95% confidence interval (CI) for the odds ratio, and p-value. Additionally, a table for the model parameters (intercept and main effects: treatment, induction, race, uPCR, and eGFR) will display the parameter estimate, standard error, odds ratio (95% CI), and p-value for each parameter.

For the proportions of responders in each treatment group the 95% CI for the proportion will be produced using the Wald method (simple asymptotic) without continuity correction. For the difference in proportions the 2 binary covariates will be consolidated to give 4 strata levels and the Cochran-Mantel-Haenszel strata-adjusted proportion difference and stratified Wald 95% confidence intervals will be produced (Kim, 2013).

Subgroup Analyses

Subgroup analysis of the PERR endpoint at Week 104 will be performed in the following subgroups:

- Induction Regimen (CYC, MMF)
- Race (Black, Non-Black)
- Region (Asia, US/Canada, Americas excluding US/Canada, Europe)
- Baseline anti-dsDNA (Anti-dsDNA≥30 IU/mL, Not [anti-dsDNA≥30IU/mL])
- Baseline Complement (At least one C3/C4 Low, No C3/C4 Low)
- Baseline C3/C4 levels & anti-dsDNA (At least one C3/C4 low and anti-dsDNA ≥30 IU/mL, Not [At least one C3/C4 low and anti-dsDNA ≥30 IU/mL])
- Baseline Renal Biopsy Class (Class III or Class IV, Class V, Class III+V or Class IV+V)

To assess the treatment effect within a subgroup, the data will be modelled using BY-group processing where the subgroup is the BY-group. The independent variables in the model will be treatment group, induction regimen, race, baseline uPCR, baseline GFR. If the subgroup variable is one of the covariates, then the corresponding covariate will be removed (i.e., for the induction regimen subgroup, induction regimen will not be a covariate in the model.

The treatment-by-subgroup interaction will be assessed in a separate model, without BY-group processing, and with covariates as described above plus the subgroup variable and the treatment-by-subgroup interaction term. If the subgroup of interest is one of the independent variables defined for the model, then only the interaction term will be added.

Statistical significance will be declared for main effects with $p \leq 0.05$ and interaction term with $p \leq 0.10$.

7.1.6. Sensitivity Analyses

Sensitivity analyses will be performed to evaluate the robustness of the primary efficacy results if the primary endpoint is statistically significant. The sensitivity analyses will use the same estimand parameters described in Section 7.1.1 through Section 7.1.5 unless

otherwise stated. Sensitivity analyses will include comparing PERR at Week 104 between treatment groups for:

Sensitivity analysis	Summary Measure	Population	Intercurrent Event Strategy (Imputation [1])
Completer	Adjusted Odds Ratio	Completer	Composite (IPD/TF/WD=NR)
Per Protocol [2]	Adjusted Odds Ratio	Per Protocol	Composite (IPD/TF/WD=NR)
Hybrid Treatment Policy [3]	Adjusted Odds Ratio	MITT	Hybrid Treatment Policy (TF/WD=NR)
Treatment Policy [3]	Adjusted Odds Ratio	MITT	Treatment Policy (WD=NR)
Unadjusted	Unadjusted Odds Ratio	MITT	Composite (IPD/TF/WD=NR)

[1] IPD=Investigational Product Discontinuation, TF=Treatment Failure, WD=Withdrawal, NR=Non-responder. The terminology indicates the intercurrent events in the list result in a non-responder imputation from the date of the earliest intercurrent event through the Week 104 visit.
[2] Performed only if ≥15% of subjects are excluded from the Per Protocol population.
[3] See Section 7.1.6.1.

7.1.6.1. Treatment Policy Sensitivity Analyses

Two treatment policy analyses will be performed. One analysis, referred to as the Treatment Policy analysis, ignores intercurrent events of IP discontinuation and treatment failure such that all data observed after these events will be used in the analysis. Additionally, a hybrid treatment policy analysis implements the composite strategy for treatment failure since it is a component of the primary endpoint, and a treatment policy strategy for intercurrent events of IP discontinuation. In this hybrid treatment policy analysis, treatment failures are treated as non-responders from the date of treatment failure onward and IP discontinuations are ignored such that all observed data after IP discontinuation is used in the analysis.

Missing data due to study withdrawal, loss to follow-up, or death will be treated as non-responders from the date of the intercurrent event onward (see Section 7.1.4.1.). Table 4 provides a comparison of the management of TF and IP discontinuation between the primary endpoint and treatment policy analyses.

Table 4 Management of Intercurrent events in Primary Analysis vs. Treatment Policy Sensitivity Analyses

Analysis	TF retained as part of Endpoint?	Observed Data post-TF used?	Observed Data Post IP Discontinuation Used?
Primary [1]	Y	N	N
Hybrid Treatment Policy [2]	Y	N	Y
Treatment Policy [3]	N	Y	Y
[1] IPD/TF/WD=NR imputation. [2] TF/WD=NR imputation. [3] WD=NR imputation.			

7.1.6.2. Tipping Point Analysis

Tipping point analyses will be performed for the primary endpoint (PERR) and the complete renal response (CRR) endpoint if either endpoint is statistically significant per the pre-specified testing hierarchy and it is plausible that the imputation strategy for missing data could alter the conclusions of the analysis. Plausible occurs when the endpoint p-value is ≤ 0.05 and > 0.001. The tipping point analysis will be based on the modified Intent-to-treat population using both the hybrid treatment policy and treatment policy intercurrent event strategies described in Section 7.1.6.1.

In the primary analysis, subjects for whom the Week 104 PERR response status cannot be determined due to missing data, either due to intercurrent events that preclude observation of data (study withdrawal, lost to follow-up, or death; Section 7.1.4) or due to missing visit data (see Section 7.1.4.1), are imputed as non-responders. This imputation will be referred to as IPD/TF/WD=NR imputation.

In contrast to the primary analysis, in the event of missing data the tipping point analysis evaluates every possible combination of placebo responder/non-responder with every possible combination of belimumab responder/non-responder. For the treatment policy intercurrent event strategy, all observed data at Week 104 will be used and unobserved (missing) data due to a subject outcome of death, study withdrawal, or lost to follow-up will be assessed using all possible combinations of responder/non-responder by treatment group. For the hybrid treatment policy strategy, a subject experiencing a treatment failure will be considered a non-responder at Week 104, otherwise observed and unobserved data will be managed the same as the treatment policy strategy.

Each possible combination of responder/non-responder outcome by treatment will be tested using a Mantel-Haenszel chi-square test. Table 5 provides an example for illustrative purposes.

Table 5 Example of Responders, Non-Responders, and Missing Data

PERR	Placebo (N=10)	Belimumab (N=10)
Responders, n (%)	3 (30%)	5 (50%)
Non-Responders, n (%)	3 (30%)	2 (20%)
Missing Data, n (%)	4 (40%)	3 (30%)

Table 6 provides all possible combinations of imputation of responders among the 4 placebo subjects and 3 belimumab subjects with missing data due to missed visits or an intercurrent event.

Table 6 All Possible Combinations of Responders Among Subjects with Missing Data

Combination Number	Placebo Responders	Belimumab Responders
1.	0/4 (0%)	0/3 (0%)
2.	0/4 (0%)	1/3 (33%)
3.	0/4 (0%)	2/3 (67%)
4.	0/4 (0%)	3/3 (100%)
5.	1/4 (25%)	0/3 (0%)
6.	1/4 (25%)	1/3 (33%)
7.	1/4 (25%)	2/3 (67%)
8.	1/4 (25%)	3/3 (100%)
9.	2/4 (50%)	0/3 (0%)
10.	2/4 50%)	1/3 (33%)
11.	2/4 (50%)	2/3 (67%)
12.	2/4 (50%)	3/3 (100%)
13.	3/4 (75%)	0/3 (0%)
14.	3/4 (75%)	1/3 (33%)
15.	3/4 (75%)	2/3 (67%)
16.	3/4 (75%)	3/3 (100%)
17.	4/4 (100%)	0/3 0%)
18.	4/4 (100%)	1/3 (33%)
19.	4/4 (100%)	2/3 (66%)
20.	4/4 (100%)	3/3 (100%)
Belimumab and placebo percentages will be graphed on the x-axis and y-axis, respectively.		

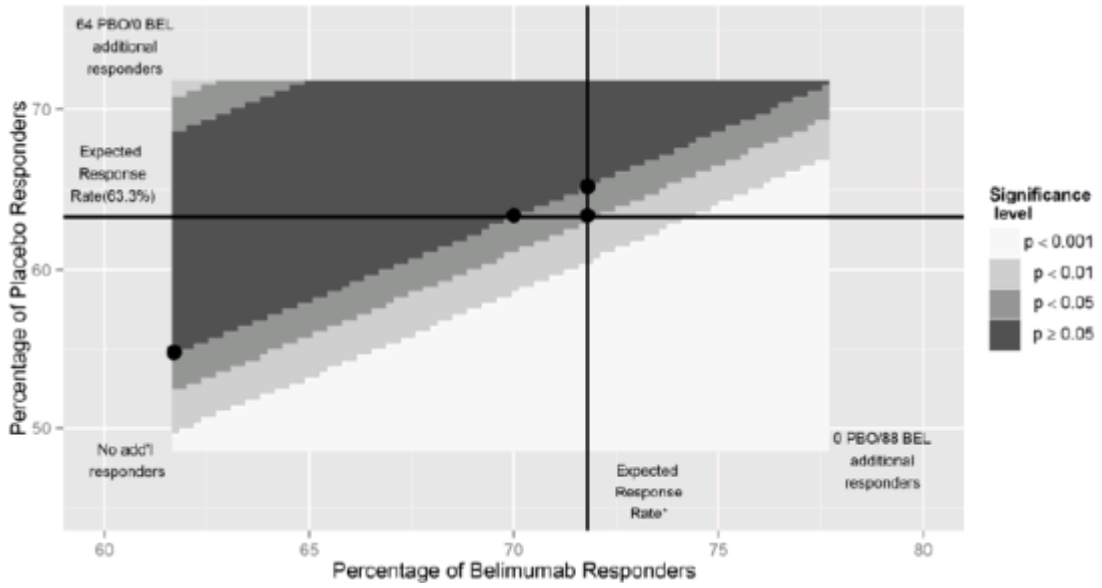
Table 7 provides an example of the results for the placebo/belimumab responder combination in row 2 of Table 5. In this example, if there is one additional responder in each treatment arm among subjects with missing data, then the overall response rate becomes 40% Placebo and 60% Belimumab.

Table 7 Example of Imputation of Responders Among Subjects with Missing Data

PERR		Placebo (N=10)	Belimumab (N=10)
Responders, n		**3**	**5**
Non-Responders, n		3	2
Missing Data	**Responders**	**1**	**1**
	Non-Responders	3	2
Overall Responders		(3+1)/10 or 40%	(5+1)/10 or 60%

No covariates will be used in the tipping point analysis; this simplifies the analysis and interpretation by removing the impact of response within stratum on the overall analysis. Additionally, removing the covariates allows for the outcomes of all possible combinations of responders/non-responders by treatment to be presented on a single heat map graph which aids the interpretation. The heat map (Figure 2) will display the percentage of placebo responders on the Y-axis and belimumab responders on the X-axis for each of the possible combinations of responders/non-responders for missing data. Each incremental step will represent a difference in the overall percentage of responders for each additional subject assumed to respond, up to the maximum percentage which assumes all missing data were classified as responders. Reference lines on the hybrid treatment policy heat map will correspond to the response rates for the PERR primary analysis using the IPD/TF/WD=NR imputation. Reference lines on the treatment policy heat map will correspond to the rate using observed Week 104 responders and assuming no subjects with a missing response are responders. The statistical significance of the treatment difference under each response scenario will be assessed by a Mantel-Haenszel chi-square test. A table presenting all response scenarios and associated Mantel-Haenszel test will be produced for each treatment policy approach.

Figure 2 Tipping Point for PERR at Week 104



7.1.7. Supplementary Analyses

The following endpoints are described in greater detail in Section 7.3 and are considered as supplementary analyses of the PERR:

PERR Individual components
Proportion of subjects with the following by visit:

- Urinary protein:creatinine ratio ≤0.7 (IPD/TF/WD=NR)
- eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2 (IPD/TF/WD=NR)
- Not a Treatment Failure

- PERR and the individual components at Week 104 using the Treatment Policy Strategy (WD=NR)

Other Supplementary PERR Analyses

- Proportion of subjects with PERR by visit.
- Time to the first PERR that is maintained through Week 52
- Time to the first PERR that is maintained through Week 104

Analyses of these endpoints are described in Section 7.3.

Additionally, a table providing the disposition of subjects for the PERR endpoint will be provided to understand the reasons for not being a PERR responder. The categories will be arranged hierarchically such that a subject is only presented in one category in the following order:

Intercurrent event without treatment failure
    Study withdrawal without prior study drug discontinuation
    Study drug discontinuation
Insufficient Renal Response due to:
    Urine protein:creatinine ratio (uPCR) only
    Estimated Glomerular Filtration Rate (eGFR) Only
    Treatment Failure (TF) Only
    uPCR and eGFR
    uPCR and TF
    eGFR and TF
    uPCR and eGFR and TF

A table of the first criterion met to deem a subject a treatment failure will also be provided for all treatment failures while on treatment and renal event-related treatment failures while on treatment. If more than one criterion is met on the earliest treatment failure date, all criteria met on the earliest treatment failure date will be presented. To support the treatment policy analysis, an additional table will be provided that includes the number and percentage of subjects experiencing each unique treatment failure criterion, including criterion met after IP discontinuation.

7.2. Secondary Efficacy Analyses

7.2.1. Complete Renal Response at Week 104

Endpoint
Complete Renal Response (CRR)
Defined as reproducible changes
Responder • uPCR < 0.5; and • eGFR no more than 10% below pre-flare GFR or within normal range; and • Not a Treatment Failure [1] **Non-Responder** • Not meeting criteria for a responder
[1] Treatment failure is defined in Section 5.5 and Section 5.6 of the protocol and further described in Section 14.6.3.3 of this RAP.
Statistical Analysis
CRR (Responder vs. Non-Responder) at Week 104 will be compared between belimumab and placebo using logistic regression with covariates for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.
Summary Measure
An odds ratio will measure the treatment effect for the odds of being a responder on belimumab vs. placebo.
Population of Interest
The analyses will be based on the modified Intent-To-Treat population.
Intercurrent Event Strategy
The intercurrent events strategy is the IPD/TF/WD=NR strategy as defined in Section 7.1.4.
Variables
• CRR (Responder vs. Non-Responder) • Treatment (belimumab=1, placebo=0) • Induction regimen (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0) • uPCR (at baseline; continuous) • eGFR (at baseline; continuous)
Model Specification
model CRR = Treatment Induction Race uPCR eGFR
Model Checking & Diagnostics
See Section 7.1.5.
Model Results Presentation
See Section 7.1.5.
Subgroup Analyses

See Section 7.1.5.

Sensitivity Analyses

Sensitivity analyses analogous to the sensitivity analyses described for the PERR endpoint in Section 7.1.6 will be performed for CRR if the endpoint is statistically significant per the testing hierarchy and includes:

- Hybrid Treatment Policy and Treatment Policy analyses (see Section 7.1.6.1)
- Completer Population
- Per Protocol Population (will be performed only if ≥15% of subjects are excluded from the Per Protocol population)
- Modified Intent-to-Treat population unadjusted for covariates to complement the tipping point analysis which is also unadjusted for covariates
- Tipping point analysis (see Section 7.1.6.2).

Supplementary Analyses

The following endpoints are supplementary analyses of the CRR endpoint. These will be analysed and presented as described in Section 7.3. Derivations of these endpoints are found in Section 14.6.3. The Not a Treatment Failure component is identical to the PERR component and is presented with the PERR supplementary analyses.

CRR individual components
Proportion of subjects with the following by visit:

- Urinary protein:creatinine ratio < 0.5.(IPD/TF/WD=NR)
- eGFR no more than 10% below the pre-flare value or within the normal range .(IPD/TF/WD=NR)

- CRR and the individual components at Week 104 using the Treatment Policy Strategy (WD=NR)

CRR

- Proportion of subjects with CRR by visit.
- Time to the first CRR that is maintained through Week 52.
- Time to the first CRR that is maintained through Week 104.

Additionally, a table providing the disposition of subjects for the CRR endpoint will be provided to understand the reasons for not being a CRR responder. The categories will be arranged hierarchically such that a subject is only presented in one category in the following order:

Intercurrent event without treatment failure
    Study withdrawal without prior study drug discontinuation
    Study drug discontinuation
Insufficient Renal Response due to:
    Urine protein:creatinine ratio (uPCR) only
    Estimated Glomerular Filtration Rate (eGFR) Only
    Treatment Failure (TF) Only
    uPCR and eGFR
    uPCR and TF
    eGFR and TF

uPCR and eGFR and TF

7.2.2. Primary Efficacy Renal Response (PERR) at Week 52

Endpoint
Primary Efficacy Renal Response at Week 52 is defined in the same manner as PERR at Week 104 defined in Section 7.1.1. only using a response at the Week 48 visit that is confirmed by a repeat measurement at the Week 52 visit to derive the endpoint.
Statistical Analysis
PERR (Responder vs. Non-Responder) at Week 52 will be compared between the belimumab plus standard of care treatment group and placebo plus standard of care group using logistic regression with covariates for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.
Summary Measure
An odds ratio will measure the treatment effect for the odds of being a responder on belimumab vs. placebo.
Population of Interest
The analyses will be based on the modified Intent-To-Treat population.
Intercurrent Event Strategy
The intercurrent events strategy will be analogous to that described in Section 7.1.4.
Variables
• PERR at Week 52 (Responder vs. Non-Responder) • Treatment (belimumab=1, placebo=0) • Induction (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0) • uPCR (at baseline; continuous) • eGFR (at baseline; continuous)
Model Specification
model PERR at Week 52 = Treatment Induction Race uPCR eGFR
Model Checking & Diagnostics
See Section 7.1.5.
Model Results Presentation
See Section 7.1.5.
Subgroup Analyses
Subgroup analysis of the PERR endpoint at Week 52 will be done for • Induction Regimen (CYC, MMF), and • Baseline C3/C4 levels & anti-dsDNA (At least one C3/C4 low and anti-dsDNA ≥30 IU/mL,

Not [At least one C3/C4 low and anti-dsDNA ≥30 IU/mL]). See Section 7.1.5. for more details.
Sensitivity Analyses
Sensitivity analysis using the treatment policy strategy described in Section 7.1.6.1 may be performed if PERR at Week 52 is statistically significant per the testing hierarchy. If required, this sensitivity analysis will be carried out after SAC.
Supplementary Analyses
A table providing the disposition of subjects for the PERR endpoint at Week 52 will be provided to understand the reasons for not being a Week 52 PERR responder. The categories will be arranged hierarchically such that a subject is only presented in one category in the following order: Intercurrent event without treatment failure Study withdrawal without prior study drug discontinuation Study drug discontinuation Insufficient Renal Response due to: Urine protein:creatinine ratio (uPCR) only Estimated Glomerular Filtration Rate (eGFR) Only Treatment Failure (TF) Only uPCR and eGFR uPCR and TF eGFR and TF uPCR and eGFR and TF

7.2.3. Time to Death or Renal-related Event

Endpoint
Time to Death or Renal-related event is defined as the first event occurring among the following: i) Death ii) End stage renal disease (ESRD), iii) Doubling of serum creatinine, iv) Renal worsening as evidenced by increased proteinuria and/or impaired renal function, or v) Renal event-related treatment failure. Events are only counted if they occur on or before IP discontinuation and treatment failure not related to renal disease. A subject will be classified as having an event or being censored based on the earliest occurrence of endpoint and censoring events in Table 8.

Table 8 Disposition of Events and Censoring (IPD/TF not related to renal disease/WD=Censor)

Endpoint Event	**Disposition**
Death	Event at date of death
End stage renal disease	Event at date of progression to end stage renal disease
Doubling of serum creatinine	Event at date of first doubling of serum creatinine relative to baseline
Renal worsening	Event at date of renal worsening
Renal event- related treatment failure	Event at renal event-related treatment failure date
The following events will result in censoring if an endpoint event has not occurred:	
Censoring Event	**Disposition**
Discontinue investigational product (IP)	Censor at IP discontinuation date.
Treatment Failure not related to Renal Event	Censor at treatment failure date not related to renal event
Withdraw (WD) from Study	Censor at double blind withdrawal date
Lost to Follow-up	Censor at lost to follow-up date (i.e., last visit in double blind period)
Completes Week 104	Censor at Week 104 visit date
Continues to open-label extension but missing Week 104 visit	Censor at the last visit in the double-blind period

Statistical Analysis
A Cox proportional hazards model controlling for induction regimen (CYC, MMF), race (Black, Non-Black), baseline uPCR, and baseline eGFR will be used to evaluate time to death or renal-related event.
Summary Measure
A hazard ratio will measure the treatment effect for belimumab vs. placebo.
Population of Interest
The analyses will be based on the modified Intent-To-Treat population.
Intercurrent Event Strategy
Intercurrent events are defined in Section 7.1.4. Intercurrent events of IP discontinuation, treatment failure not related to renal event, lost to follow-up, and study withdrawal will result in censoring unless they occur after a renal-related event. The intercurrent events of death and treatment failure related to renal event are counted as an event if they occur on or before the intercurrent events that result in censoring. This strategy is referred to as IPD/TF not related to renal disease/WD=Censor.

Variables
• Time (time to first event in days) • Censor (Yes=1, No=0) • Treatment (belimumab=1, placebo=0) • Induction (CYC=1, MMF=0) • Race (Black=1, Non-Black=0) • uPCR (at baseline; continuous) • eGFR (at baseline; continuous) The endpoint derivations are described in Section 14.6.3.
Model Specification
model Time*Censor = Treatment Induction Race uPCR eGFR Ties will be managed using Efron's approximation.
Model Checking & Diagnostics
The data will be evaluated by two independent statisticians to determine if the model assumptions and fit are reasonably met. If either is deemed unacceptable, additional sensitivity analysis using an alternative method may be performed
Model Results Presentation
The following results will be displayed by treatment group: number and percentage of subjects with an event and the median, 25th percentile, and 75th percentile of days to first event, hazard ratio, 95% CI, and p-value be presented for the effect of belimumab vs. placebo for proportional hazards models. For subjects with an event, the median, 25th percentile, 75th percentile, minimum, and maximum values of the study day of the first event will be presented.
Subgroup Analyses
Subgroup analysis of Time to Death or Renal-related Event will be done for • Induction regimen (CYC, MMF), and • Baseline C3/C4 levels & anti-dsDNA (At least one C3/C4 low and anti-dsDNA ≥30 IU/mL, Not [At least one C3/C4 low and anti-dsDNA ≥30 IU/mL]). See Section 7.1.5. for more details.
Supplementary Analyses
A Kaplan-Meier (KM) plot of time to event will be produced to evaluate the pattern of events over time as well as a supporting table of Kaplan-Meier estimates. Each component of the composite endpoint will be assessed individually for time to 'component' using the 'IPD/TF not related to renal disease/WD=Censor' strategy for intercurrent events. To assess the impact of the component independent of the other events, a subject's follow-up time will not be censored if another component event occurs. Censoring will be applied as described in Table 8. Additionally, a table displaying the number and percentage of subjects with a first event by event type, induction regimen, and induction regimens combined will be provided.

7.2.3.1. Treatment Policy Analysis

For the treatment policy analysis of Time to Death or Renal-related Event, the renal event-related treatment failure will not be one of the components of the composite endpoint as this is also an intercurrent event. A subject will be classified as having an event based on the earliest occurrence of one of the four endpoint events in Table 9.

Table 9 Disposition of Events and Censoring (Treatment Policy)

Endpoint Event	**Disposition**
Death	Event at date of death
End stage renal disease	Event at date of progression to end stage renal disease
Doubling of serum creatinine	Event at date of first doubling of serum creatinine relative to baseline
Renal worsening	Event at date of renal worsening
The following will result in censoring if an endpoint event has not occurred:	
Censoring Event	**Disposition**
Withdraw (WD) from Study	Censor at double blind withdrawal date
Lost to Follow-up	Censor at lost to follow-up date (i.e., last visit in double blind period)
Completes Week 104	Censor at Week 104 visit date
Continues to open-label extension but missing Week 104 visit	Censor at the last visit in the double-blind period

Analyses of the components will be managed as described in Section 7.2.3. under Supplementary Analyses using censoring rules in Table 9.

7.2.3.2. Tipping Point Analysis

To assess the sensitivity to the censoring-at-random assumption, the missing event times for subjects who dropped out or died will be imputed under the censoring-not-at-random assumption implemented using a range of values for the true event rate for these subjects [Jackson, 2014; Zhao, 2014].

The following methods and assumptions will be applied:

The assumed event rates for censored subjects will be varied independently for each treatment group, and range from assuming that all prematurely censored subjects on a particular treatment arm experienced an endpoint event at the time of censoring (worst case scenario corresponding to an infinite event rate for subjects who dropped out/lost to follow-up) to assuming that all prematurely censored subjects on a particular treatment arm had completed the study without experiencing an event (best case scenario

corresponding to zero event rate for subjects who dropped out/died). Assumed event rates for each arm will be varied incrementally between these two extreme scenarios.

A multiple imputation approach will be used to account for uncertainty about imputed event times. The multiple imputation process will follow Jackson et al [Jackson, 2014]. For a particular assumption about the post-censoring step-change in the event rate for censored subjects on each arm, this will involve the following steps:

1. Bootstrap (i.e. sample with replacement the subjects in the original dataset). This accounts for uncertainty in the estimated baseline hazard function used to impute the event times for censored subjects. The seed to be used for the bootstrap will be 114054. The number of replications will be at least 50.

2. Fit a Cox proportional hazards model (unadjusted for covariates) to the bootstrapped dataset. To inform on the validity of the adjusted Cox proportional hazards model, the proportional hazards assumption will be assessed by plotting the logarithm of the negative logarithm of the estimated survivor function against the logarithm of time, for each treatment group. If the hazards are proportional, the lines should be approximately parallel. With the fitted model

   - Extract the baseline cumulative hazard function.
   - Predict the hazard risk for subjects who discontinued prematurely.
   - Increase or decrease the predicted hazard of the subject by the pre-specified step-change amount relative to those in the same arm who stay longer in the trial. The hazard rate of subjects will be increased/decreased multiplicatively with separate multiplying factors for experimental and control.

3. Impute time-to-event for subjects who dropped out or died. For a given subject, if the imputed time was below the maximum follow-up time (taken here to be 729 days), the subject will be considered to have experienced an endpoint at the imputed event time. Otherwise the subject was administratively censored at 729 days (i.e., assumed to have completed the study event-free). The resulting imputed dataset assumes that all subjects have been followed until the end of the study.

4. Repeat steps 1 to 3 m times to obtain m imputed datasets.

5. Fit a Cox proportional hazards model to each imputed dataset to estimate the hazard ratio for time to Death or Renal-related event for belimumab versus placebo. The proportional hazards assumption will be assessed for a random subset of the fitted models. The analysis will allude to an average hazard ratio for interpretation of result if appropriate.

6. Combine the results of the m imputed datasets using Rubin's rules [Rubin, 1987].

These analyses assume a step change in the hazard even though there could be a more gradual change after dropout. The sensitivity analyses will not distinguish between

reasons for dropout, i.e., they assume dropouts for any reason have the same step change in the event rate.

The results will be displayed in a heat map.

7.2.4. Ordinal Renal Response at Week 104

Endpoint
Complete Renal Response (CRR) • uPCR < 0.5; and • eGFR no more than 10% below *pre-flare* GFR or within normal range; and • Not a Treatment Failure [1] **Partial Renal Response (PRR)** • ≥ 50% decrease from baseline in uPCR and one of the following: value <1 if baseline ≤3, or value <3 if the baseline was >3; and • eGFR no more than 10% below *baseline* GFR or within normal range; and • Not a Treatment Failure [1] **No Response** • Not meeting criteria for either complete or partial renal response
[1] Treatment failure is defined in Section 5.5 and Section 5.6 of the protocol and further described in Section 14.6.3.3 of this RAP. See Section 14.6.3.10 for more details on the endpoint derivation.
Statistical Analysis
A rank analysis of covariance model controlling for induction regimen (CYC, MMF), race (Black, Non-Black), baseline uPCR, and baseline eGFR will be used to evaluate the treatment effect for ORR.
Summary Measure
A treatment difference for the proportion of subjects in each response category (CRR, PRR, and NR) will measure the treatment effect for belimumab vs. placebo.
Population of Interest
The analyses will be based on the modified Intent-To-Treat population.
Intercurrent Event Strategy
The intercurrent events strategy is the IPD/TF/WD=NR strategy as defined in Section 7.1.4. Handling of missing data is defined in Section 7.1.4.1.
Variables
• Ordinal Renal Response (Complete=2, Partial=1, Non-Responder=0) • Treatment (belimumab=1, placebo=0) • Induction (CYC=1 vs. MMF=0)

• Race (Black=1 vs. Non-Black=0) • uPCR (at baseline; continuous) • eGFR (at baseline; continuous)
•
Model Specification
model ORR = Treatment Induction Race uPCR eGFR
Model Checking & Diagnostics
Not applicable.
Model Results Presentation
At Week 104, each response category (complete, partial, no response) will have the number, percentage, standard error of the percentage and treatment difference displayed along with the p-value from the rank ANCOVA analysis.
Subgroup Analyses
Subgroup analysis of the ORR endpoint at Week 104 will be done for • Induction Regimen (CYC, MMF), and • Baseline C3/C4 levels & anti-dsDNA (At least one C3/C4 low and anti-dsDNA ≥30 IU/mL, Not [At least one C3/C4 low and anti-dsDNA ≥30 IU/mL]). The subgroup analysis for induction regimen will be provided on the by-visit table for the Week 104 visit only. To assess the treatment effect within a subgroup, the data will be modelled using BY-group processing where the subgroup is the BY-group. The independent variables in the model will be treatment group, induction, race, baseline uPCR, baseline GFR. If the subgroup variable is one of the covariates, then the corresponding covariate will be removed (i.e., for the induction regimen subgroup, induction regimen will not be a covariate in the model).
Sensitivity Analyses
Sensitivity analysis using the treatment policy strategy described in Section 7.1.6.1 may be performed if the endpoint is statistically significant per the testing hierarchy. If required, this sensitivity analysis will be carried out after SAC.
Supplementary Analyses
The following endpoints are supplementary analyses of the ORR endpoint. Derivations of these endpoints are found in Section 14.6.3. • Proportion of subjects with ORR by visit. • ORR including Urinary Sediment at Week 104 which will be analysed with a rank ANCOVA. • ORR including Urinary Sediment and using calculated GFR at Week 104 which will be analysed using a Van Elteren test.

7.3. Other Efficacy Analyses

Other Efficacy endpoints and supplementary efficacy endpoints identified in Section 2.2 have been grouped by endpoint type (proportion; change/percent change from baseline;

and time to flare) to provide a blanket explanation of the estimands and analysis methods for each endpoint type.

7.3.1. Proportion Endpoints

Endpoints

Individual Components of PERR
• Urinary protein:creatinine ratio ≤0.7
• eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2
• Not a Treatment Failure
 	
PERR
• Proportion of subjects with PERR by visit.
 	
CRR individual components
Proportion of subjects with the following by visit:
• Urinary protein:creatinine ratio < 0.5.
• eGFR no more than 10% below the pre-flare value or within the normal range (≥90 mL/min/1.73m2).
 	
CRR
• Proportion of subjects with CRR by visit.
 	
Renal-Specific Measures
• Proportion of subjects with a doubling of the serum creatinine or progression to end stage renal disease (ESRD) as defined below:
  ○ Doubling of serum creatinine compared with baseline that is confirmed with a second measurement at least 3 weeks later.
  ○ Progression to ESRD defined as the need for chronic dialysis or renal transplantation.
 	
SLEDAI-S2K
• Proportion of subjects with SLEDAI-S2K <4 by visit
• Proportion of subjects with improvement in SLEDAI-S2K organ systems by visit among subjects with organ system involvement at baseline.
• Proportion of subjects with worsening in SLEDAI-S2K organ systems by visit among subjects with no organ system involvement at baseline.
 	
Corticosteroids
• Proportion of subjects receiving prednisone $\leq$ 5 mg average daily dose since previous visit
• Proportion of subjects receiving prednisone $\leq$ 7.5 mg average daily dose since previous visit
Supplementary Analyses
• Proportion of subjects receiving prednisone $\leq$ 5 mg average daily dose since previous visit by Week 104 PERR Response.
• Proportion of subjects receiving prednisone $\leq$ 7.5 mg average daily dose since previous visit by Week 104 PERR Response.
 	
SLICC Damage Index

- Percent of patients with any SLICC Damage Index worsening (change >0) compared with baseline by visit.

The endpoint derivations are described in Section 14.6.3.

Statistical Analysis

Each proportion endpoint will be compared between belimumab and placebo using logistic regression controlling for baseline value, induction regimen (CYC vs. MMF) and race (Black vs. Non-Black).

Exceptions:

1. Endpoints without a baseline value (treatment failures, PERR by visit, and CRR by visit) will be evaluated using logistic regression controlling for induction regimen (CYC vs. MMF) and race (Black vs. Non-Black).
2. Renal Specific Measures is a composite endpoint but only serum creatinine has a baseline value, therefore this endpoint will be evaluated using logistic regression controlling for baseline serum creatinine, induction regimen (CYC vs. MMF) and race (Black vs. Non-Black).
3. SLEDAI-S2K organ worsening and organ improvement endpoints will not have statistical analysis performed.

Summary Measure

An odds ratio will measure the treatment effect for the odds of being a responder on belimumab vs. placebo at Week 104 only.

Population of Interest

The analyses will be based on the modified Intent-To-Treat population.

Intercurrent Event Strategy

Intercurrent events are defined in Section 7.1.4.

- PERR- and CRR-based endpoints, prednisone endpoints, and SLEDAI-S2K < 4 will impute a Non-Responder for all planned time points after the first intercurrent event occurs (IPD/TF/WD=NR strategy).
- Endpoints for Renal-Specific measures, SLEDAI-S2K organ worsening, serum creatinine doubling/ESRD will use a LO on or prior to IPD/TF CF strategy for timepoints post an intercurrent event in which the last observed value on or before the intercurrent event will be carried forward for all subsequent time points through Week 104.
- SLEDAI-S2K organ improvement will use an IPD/TF/WD=No improvement imputation strategy in which the last observed post-baseline value on or prior to the intercurrent event will be carried forward for all subsequent time points through Week 104.
- SLICC Damage Index will use a Worst Observation Carried Forward (WOCF) imputation and will be presented for data for both on-treatment and on-study analyses.

Variables

- Endpoint (Responder vs. Non-Responder or Yes vs. No)
- Baseline_Value (Continuous)*

- Treatment (belimumab=1, placebo=0)
- Induction regimen (CYC=1 vs. MMF=0)
- Race (Black=1 vs. Non-Black=0)

*Note: For Renal Specific Measures Baseline_Value is the baseline serum creatinine.

Model Specification

For endpoints with a baseline value:
model Endpoint = Treatment Baseline_Value Induction Race

For endpoints without a baseline value:
model Endpoint = Treatment Induction Race

Model Checking & Diagnostics

See Section 7.1.5.

Model Results Presentation

See Section 7.1.5.

For SLEDAI-S2K organ worsening and organ improvement endpoints, the number and percentage of subjects who experience worsening or improvement will be presented within induction regimen and overall for combined induction regimens by organ domain and visit.

Subgroup Analyses

Analyses will be performed within induction regimen (CYC, MMF). The independent variables in the model will be treatment group and race. Model results will be presented as defined in Section 7.1.5 with the exception of the p-value.

Sensitivity Analyses

Sensitivity analyses of the endpoints based on observed data ignoring intercurrent events will be performed for the following:

Renal Response

- PERR and its components at Week 104
- CRR and its components at Week 104

Renal-Specific Measures

- Proportion of subjects with a doubling of the serum creatinine or progression to end stage renal disease (ESRD)

SLEDAI-S2K

- Proportion of subjects with SLEDAI-S2K <4 by visit
- Proportion of subjects with improvement in SLEDAI-S2K organ systems by visit among subjects with organ system involvement at baseline.
- Proportion of subjects with worsening in SLEDAI-S2K organ systems by visit among subjects with no organ system involvement at baseline.

Corticosteroids

- Proportion of subjects receiving prednisone $\leq$ 5 mg average daily dose since previous visit

- Proportion of subjects receiving prednisone ≤ 7.5 mg average daily dose since previous visit

SLICC Damage Index

- Percent of patients with any SLICC Damage Index worsening (change >0) compared with baseline by visit.

(Note: The WOCF is used for SLICC in the observed case to ensure the highest score for an individual item is carried forward to subsequent observed visits, it does not impute missing visits.)

7.3.2. Continuous Endpoints (Change/Percent Change from Baseline)

Endpoints
Renal Endpoints • Percent change in proteinuria by visit. • Change in proteinuria by visit. *SLEDAI-S2K* • Change from baseline in SLEDAI-S2K score by visit. • Change from baseline in SLEDAI-S2K excluding renal items by visit. *SLICC Damage Index* SLICC Damage Index (SDI) change from baseline by visit.
Statistical Analysis
An ANCOVA will be used to evaluate SLEDAI-S2K change from baseline endpoints for the treatment effect controlling for baseline value, induction regimen (CYC, MMF) and race (Black, Non-Black). A rank ANCOVA will be used to evaluate proteinuria and SLICC Damage Index change from baseline endpoints for the treatment effect controlling for baseline value, induction regimen (CYC, MMF) and race (Black, Non-Black).
Summary Measure
The difference in the Least Square (LS) means (belimumab – placebo) will be used to assess the treatment effect for the ANCOVA analyses.
Population of Interest
The modified Intent-to-Treat population will be used for the analysis.
Strategy for Intercurrent Events
Intercurrent events are defined in Section 7.1.4. • Data will be presented as 'While on Treatment (Observed)' meaning only data collected while the subject is on IP is presented, intercurrent events of treatment failure are ignored, and there is no imputation for unobserved data (e.g., after withdrawal events). • For SLICC change from baseline, data will be presented as 'While on Treatment (Observed with WOCF) meaning only data collected while the subject is on IP is presented, intercurrent events of treatment failure are ignored, for observed visits only a Worst Carried Forward (WOCF) imputation (see Section 14.6.3.18 for more detail). will be applied at the item level but will not carry forward to missed visits, and there is no

imputation for unobserved data (e.g., after withdrawal events.
Variables
• Endpoint (defined in Section 14.6.3) • Treatment (belimumab=1, placebo=0) • Baseline Value (continuous) • Induction (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0)
Model Specification
model Endpoint = Treatment Baseline_Value Induction Race
Model Checking & Diagnostics
The data will be evaluated by two independent statisticians to determine if the model assumptions and fit are reasonably met. If either is deemed unacceptable, additional sensitivity analysis using an alternative method may be performed
Model Results Presentation
The following results will be displayed by treatment group: mean, standard deviation, standard error, median, 25th percentile, 75th percentile, minimum, and maximum. The following will also be presented at Week 104: LS mean and its standard error, the difference (belimumab – placebo) in LS Means, 95% CI, and p-value from ANCOVA for difference in LS Means will be presented. For rank ANCOVA, the following results will be displayed by induction regimen and treatment group: mean, standard deviation, standard error, median, 25th percentile, 75th percentile, minimum, maximum. The p-value for the rank ANCOVA will be presented for the treatment comparison for the combined induction regimens at Week 104 only.
Subgroup Analyses
Subgroup analysis will be performed within each induction regimen (CYC, MMF) using the model Endpoint = Treatment Baseline_Value Race. Model results as defined above will be presented with the exception of the p-value.
Sensitivity Analyses
Sensitivity analyses of the endpoints based 'While on Study (Observed)' uses all observed data whether on or off IP, ignores intercurrent events of treatment failure, and does not impute values for unobserved data (e.g., after withdrawal events) for the following: *Renal Endpoints* • Percent change in proteinuria by visit. • Change in proteinuria by visit. *SLEDAI-S2K* • Change from baseline in SLEDAI-S2K score by visit. • Change from baseline in SLEDAI-S2K excluding renal items by visit. For SLICC, sensitivity analyses will be based on 'While on Study (Observed with WOCF) which follows the same intercurrent event strategy as the 'While on Study (Observed)' and applies WOCF on the observed visits only. *SLICC Damage Index* SLICC Damage Index (SDI) change from baseline by visit.

Further exploration of the impact of missing data on these endpoints may be undertaken post-SAC. These analyses will use multiple imputation methodology.

7.3.3. Time to Event Endpoints

Endpoint
PERR Supplementary Endpoints • Time to the first PERR that is maintained through Week 52 (see Section 14.6.3.3) • Time to the first PERR that is maintained through Week 104 (see Section 14.6.3.3) *CRR Supplementary Endpoints* • Time to the first CRR that is maintained through Week 52 (see Section 14.6.3.3) • Time to the first CRR that is maintained through Week 104 (see Section 14.6.3.3) *SFI Flares* • Time to first severe SFI flare. (see Section 14.6.3.14) • Time to first severe SFI flare from Week 24. (see Section 14.6.3.14)
Statistical Analysis
A cox proportional hazards model controlling for induction regimen (CYC, MMF) and race (Black, Non-Black) will be used to evaluate time to event endpoints.
Summary Measure
A hazard ratio will measure the treatment effect for belimumab vs. placebo.
Population of Interest
The analyses will be based on the modified Intent-To-Treat population.
Intercurrent Event Strategy
Intercurrent events are defined in Section 7.1.4. For time to first maintained PERR and CRR, IPD/TF/WD=NR imputation will be used for intercurrent events. For severe SFI flares, a treatment failure is imputed as an event while IP discontinuation and study withdrawal are censoring events (TF=Flare, IPD/WD=Censor).
Variables
• Time (time to first event in days) • Censor (Yes=1, No=0) • Treatment (belimumab=1, placebo=0) • Induction (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0) The endpoint derivations are described in Section 14.6.3.

Model Specification
model Time*Censor = Treatment Induction Race Ties will be managed using Efron's approximation.
Model Checking & Diagnostics
The data will be evaluated by two independent statisticians to determine if the model assumptions and fit are reasonably met.
Model Results Presentation
The following results will be displayed by treatment group: number and percentage of subjects with an event and the median, 25th percentile, and 75th percentile of days to first response, hazard ratio, 95% CI, and p-value be presented for the effect of belimumab vs. placebo for proportional hazards models.
Subgroup Analyses
Time to event analyses will be performed within each Induction Regimen (CYC, MMF). The independent variables in the model will be treatment group and race. Model results will be presented as defined above with the exception of the p-value.
Supplementary Analyses
A Kaplan-Meier (KM) plot of time to event will be produced to evaluate the pattern of events over time as well as a supporting table of Kaplan-Meier estimates.

8. SAFETY ANALYSES

Unless otherwise stated, all analyses will be limited to the double-blind treatment period while subjects are on investigational product (IP). For safety analyses this is defined as the period of exposure defined in Section 14.6.2.4. Safety will be evaluated by adverse events (AEs), changes in laboratory parameters, vital signs and immunogenicity. The safety analyses will be based on the safety population, unless otherwise specified. The safety population is defined in Section 4 as all randomized subjects who received at least one dose of investigational product and includes the subject enrolled at site PPD and the subject at site PPD who are excluded from the efficacy analyses. Analyses of the safety population is based on the randomized treatment; however, if there are more than 15% of subjects who receive a study treatment that is different from the randomized treatment for > 50% of infusions, safety analysis will be performed based on the actual treatment received. Unless otherwise specified, the safety tables and listings will be presented by induction regimen and treatment group; an overall summary by treatment group will also be presented on the tables.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious Adverse Events (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

1. All subjects will be followed for safety through the end of the double-blind treatment period including data through the post-treatment follow-up period per Section 3.2 (unless continuing treatment in the open-label phase of the study).
2. A table summarizing AEs that occurred prior to treatment start date will be presented, for each system organ class (SOC) and preferred term (PT).
3. All AEs will be classified using the standard GSK Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by SOC and 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 per the Adverse Event Severity Grade Tables Appendix 7 of the Protocol, if a grade is defined for the AE of interest.
4. All treatment-emergent AEs will be summarized for both the double-blind phase.
5. 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, AE resulting in study agent discontinuation, AE resulting in study withdrawal, and deaths.
6. The number and percentage of subjects experiencing an AE and the total number of AEs will be summarized for each of the following AE categories:
    - All AEs (by SOC; by SOC and PT; by PT)
    - Serious AEs (by SOC; by SOC and PT; by PT)
    - Severe AEs (by SOC; by SOC and PT; by PT)
    - Related AEs (by SOC; by SOC and PT; by PT)

- AEs leading to discontinuation of study agent (by SOC; by SOC and PT; by PT)
- Deaths (by Category and PT)
- Common Non-Serious AEs (by SOC and PT)
- Related Serious AEs (by SOC and PT)
- Related Fatal Serious AEs (by SOC and PT)
- Non-Fatal Serious AEs (by SOC and PT)
- Related Non-Fatal Serious AEs (by SOC and PT)
- Pre-Treatment AEs (by SOC and PT)
- Post-Treatment AEs for Serious AEs (by SOC and PT)
- AEs Through Week 24 for AEs (by SOC and PT) and SAEs (by SOC and PT)
- AEs Post Week 24 for AEs (by SOC and PT) and SAEs (by SOC and PT)

7. The tabular summary for each category of AE listed above will include the number of events, number of subjects who reported at least one event, and percentage of subjects who reported at least one AE (incidence) for each SOC (where applicable), each PT, and overall. By default, adverse events will be sorted by MedDRA SOCs, in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any adverse event within the class, to the SOC with the lowest total incidence. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. Only SOCs with observed AE PTs will be presented. Repeat sort order for MedDRA PTs within each SOC.
8. Common AEs will be defined as ≥ 5% incidence in any treatment group.
9. The table for all AEs by SOC and PT will be repeated for the age, gender, race, region, baseline C3/C4 levels & anti-dsDNA categories, and body weight quartile subgroups. See Section 5.4.2 for details on the subgroup categories.
10. A summary of study agent related AEs by SOC, PT, and maximum intensity will be provided by induction regimen. For this display, the number and percentage of subjects will be summarized as mild, moderate, or severe for each treatment group based on the maximum severity observed within each PT, and within each SOC.
11. A summary of AEs by SOC, PT and maximum intensity will also be provided by induction regimen. The number and percentage of subjects will be summarized as mild, moderate, or severe for each treatment group based on the maximum severity observed within each PT, and within each SOC.
12. A summary of serious AEs by SOC and PT will be presented. The number of SAEs will be summarized for each of the following categories:
    - Subjects with SAEs
    - SAEs
    - Drug-related SAEs
    - Fatal SAEs
    - Drug-related Fatal SAEs
13. The hierarchical relationship between MedDRA SOCs, PTs, and verbatim text will be displayed in a listing for all AEs.

14. Drug-related AEs will be summarized by seriousness (serious and Non-serious) by overall frequency

15. A listing that displays which subjects reported each AE will be produced by SOC and PT. AEs will be grouped and sorted by SOC and PT. Listings of all AEs, and Post-Treatment Serious and Non-Serious AEs will be presented, including duration and study day of onset/resolution.

16. A listing of all AEs for subjects who participated in the study from Mexico, and a listing of SAEs for subjects in countries other than Mexico will be presented.

8.2. Deaths, Serious Adverse Events, and Survival Status

In addition to the tabular summaries of AEs described in Section 8.1, listings for all SAEs, all deaths, all non-fatal SAEs, and reasons for considering an AE a serious AE will be produced. The categorization of the cause of death will be adjudicated by GSK.

Survival status will also be summarized at Week 104. The number and percentage of subjects will be summarized for each of the following categories:

1. Alive
2. Consent Withdrawn
3. Lost to Follow-up
4. All Deaths
    - Deaths on Treatment
    - Deaths Post-Treatment

A listing of survival status will also be presented.

8.3. Adverse Events Leading to Discontinuation of Investigational Product

In addition to the tabular summaries described in Section 8.1, a listing of all AEs leading to discontinuation of study treatment will be produced.

8.4. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. The details of the planned displays are provided in Appendix 12: List of Data Displays.

The Benlysta Program Safety Analysis Plan (PSAP) has been developed to include an adverse event of special interest (AESI) analysis for consistent reporting across belimumab studies. Categorizations for the AESIs will be defined in the PSAP (PSAP,

2018) and reporting of AESIs for these analyses is defined in Section 8.4. An overall summary of AESIs will be presented and each specific category of AESI will be presented separately by PT. The number and percentage of subjects with at least one occurrence and the number of events of the following AESIs will be provided. The following AESIs will be identified using the list of preferred terms in the PSAP (PSAP, 2018) and adjudicated by GSK to further categorize the events as follows:

Adverse Events

Adverse Events of Special Interest (AESI)

AESI will be defined per the version of the PSAP/MedDRA in effect at the time of DBR.

Malignant Neoplasms

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

Post-Infusion Systemic Reactions (PISR)

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

All Infections of Special Interest (Opportunistic Infections (OI), Herpes Zoster (HZ), Tuberculosis (TB), And Sepsis; All and Serious, separately)

- All opportunistic infections (OI) per GSK adjudication
- OI per GSK adjudication excluding Tuberculosis and Herpes Zoster
- Active Tuberculosis
  - Non-Opportunistic
  - Opportunistic
- Herpes Zoster
  - Non-Opportunistic
  - Opportunistic
    - Recurrent
    - Disseminated
- Sepsis

Depression (including mood disorders and anxiety)/suicide/self-injury (All and Serious, separately)

- Depression (including mood disorders and anxiety) (excluding suicide and self-injury)
- Suicide/self-injury
- Serous suicide/self-injury per GSK adjudication
  - Suicidal Behaviour

Adverse Events
Adverse Events of Special Interest (AESI)
▪ Completed Suicide – Suicidal Ideation – Self-injurious Behaviour without Suicidal Intent • Deaths

Malignant neoplasm events identified as "tumours of unspecified malignancy" will be reviewed for classification as malignant per GSK adjudication and will be presented by category and PT.

Post-infusion systemic reactions and serious post-infusion systemic reactions will be presented using nine different definitions as indicated above. These will be presented by category and PT.

Post-infusion systemic reactions per Anaphylactic Reaction CMQ narrow search are defined as at least one event from the list of preferred terms in Category A as listed in the PSAP (PSAP, 2018).

Post-infusion systemic reactions per Anaphylactic Reaction CMQ broad search are defined as at least one event from the list of preferred terms in either Category A, B, C or D as listed in the PSAP (PSAP, 2018). The SAEs that are identified by the Anaphylactic Reaction CMQ broad search will be reviewed further for potential classification as serious post-infusion systemic reactions per GSK adjudication.

The post-infusion systemic reactions per Anaphylactic Reaction CMQ algorithmic search are defined in the PSAP (PSAP, 2018). The SAEs that are identified by the algorithmic search will be reviewed further for potential classification as serious post-infusion systemic reactions per GSK adjudication. For all post-infusion, systemic reaction AESIs defined via narrow, broad, or algorithmic search, the AEs need to have occurred on the day of an infusion or within 3 days after an infusion. GSK will adjudicate serious events identified via the broad search occurring within 21 days after an infusion, and these will be divided into a category based on time to onset: acute (onset $\leq$ 1 day), delayed acute (onset 2-3 days), or delayed non-acute (onset 4-21 days). Adverse events with partial or missing start dates will be included unless there is evidence through comparison of partial dates to suggest otherwise.

Possible cases of serious anaphylaxis per Sampson criteria will be identified as defined in the PSAP (PSAP, 2018).

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

A summary table of AESIs by Category will be presented for AESIs during the induction phase (through Week 24) and maintenance phase (post Week 24).

Post-Treatment AESIs will be summarized and presented by Category. A listing of Post-Treatment AESIs will also be presented.

Depression, suicide and self-injury are defined using terms from the 'Depression (excluding suicide and self-injury)' CMQ plus additional terms added by Marketing Authorization Holder (MAH) and 'Suicide/self-injury' CMQ. Depression, suicide, and self-injury AESIs will be presented by Category and PT.

A listing of all adverse events of special interest will be presented.

8.4.1. Post-Infusion Systemic Reactions by Infusion

Summaries of post-infusion systemic reactions will be presented by treatment group, by the first six infusions and over all infusions, and PT for the following:

- Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion)
- Serious Post-Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the infusion or within 3 days after the infusion)
- Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK adjudication (onset within 24 hours of infusion)
- Serious Delayed Acute Hypersensitivity Reactions per GSK adjudication (onset 2-3 days post-infusion)
- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK adjudication (onset 4-21 days post-infusion)
- Post-Infusion Systemic Reactions Adverse Events of Special Interest by Category and PT (on the day of the infusion or within 3 days after the infusion)
- Serious Post-Infusion Systemic Reactions Adverse Events of Special Interest by Category and PT (on the day of the infusion or within 3 days after the infusion)

The first six infusions represent the first 6 dosings for each subject and is not based on a defined set of scheduled visits.

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

Suicidality assessments are completed at every visit during the double-blind phase. Assessments are done using the investigator-administered C-SSRS. If a "yes" response is given to any suicidal behavior or a "yes" response is given 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). A listing of the PSRQ will be presented.

Listings will be generated for the following:

- Suicidal ideation and behavior data for subjects who have any suicidal ideation or behavior recorded at any point on the study (including screening)

- 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).

8.5.1. C-SSRS Suicidal Ideation or Behavior Post-Baseline

- The number and percentage of subjects with each category of suicidal ideation or behavior post-baseline (starting after Day 1 assessment onwards including data collected post-IP discontinuation) will be presented for the double-blind phase, 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 is presented. Subjects may have more than one type of behavior.
- For the rows pertaining to suicidal ideation, the number of subjects whose maximum ideation on-treatment is the specified ideation is presented. Subjects will be counted once for the maximum ideation.

8.5.2. Subjects may be counted for ideation and behavior C-SSRS Suicidal Ideation or Behavior Relative to Pre-Treatment

The number and percentage of subjects with treatment-emergent suicidal ideation or behavior post-baseline (starting after Day 1 assessment onwards) will be presented. A subject must have at least one pre-treatment assessment and at least one post-baseline assessment in order to be included in this display. A subject may have more than one treatment-emergent suicidal ideation and/or behavior.

8.5.3. C-SSRS Shift Changes in Categories from Pre-Treatment to Post-Baseline

A summary of the shift from maximum pre-treatment C-SSRS category to maximum post-baseline (up to and including Week 104 including any data collected after IP discontinuation) category will be produced by treatment group. 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 post-baseline assessment to be included in this display. The table will display the number and percentage of subjects within the specific shift categories: No suicidal ideation or behavior, suicidal ideation, and suicidal behavior.

8.6. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of hematology, liver function, electrolytes, other chemistries, urinalysis and immunoglobulin data will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays. Laboratory analyses will be presented for data while subjects are on randomized treatment. Analyses of laboratories for worst toxicity grade and toxicity with a ≥2 grade shift will also be presented for all data collected after IP discontinuation.

For laboratory analyses, the following will be analyzed: (1) analytes with a numeric normal range, and (2) urinalysis analytes with categorical results (i.e., positive/negative and present/absent). Summaries and analyses will be performed based on the observed data for planned assessment visits per the study calendar (Section 14.2.1) for the given analytes; time points corresponding to unscheduled visits or exit visits which fall at an unplanned time for an analyte will not be presented in the tables or figures but will be reported in the listings. No imputation will be done for missing data. Baseline is defined as described in Section 5.6. See Protocol Appendix 5 for a list of laboratory parameters and RAP Appendix 8 for a definition of the laboratory toxicity grades.

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

8.6.1. Laboratory Descriptive Statistics by Visit

Descriptive statistics for each analyte will be displayed for each visit. The tables will display the mean value, standard deviation, median, 25th and 75th percentiles, minimum and maximum. No statistical tests will be performed.

A line graph will be produced for each analyte which displays the mean value by visit and treatment group by induction regimen and overall.

8.6.2. 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 treatment for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries, urinalysis and immunoglobulins) will be presented. Data for both scheduled and unscheduled visits will be included throughout the double-blind phase (including follow-up). Additionally, these toxicity tables will be repeated using all data collected after IP discontinuation.

8.6.3. Laboratory Toxicity ≥ 2 Grade Shift Post-Baseline

Toxicity grade shifts from baseline of ≥ 2 grades will be summarized during treatment 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. Data for both scheduled and unscheduled visits will be included throughout the double-blind phase. Additionally, these shift tables will be repeated using all collected after IP discontinuation.

8.6.4. Laboratory Reference Range Shifts from Baseline by Visit

For laboratory tests without toxicity grades, shifts relative to the normal range will be summarized for each analyte as shifts ‘to low’ and shifts ‘to normal/high.’ For the ‘to low’ category the percentage of subjects with at least one low post-baseline value relative to the baseline will be displayed using the categories: remained low and normal/high to

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

8.6.5. Immunoglobulin Reference Range Shifts from Baseline by Visit

For immunoglobulins (IgG, IgA, and IgM) reference range shifts will be summarized across all visits 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.

8.6.6. Immunoglobulin Below LLN by Visit

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

8.6.7. Immunoglobulin Relative to LLN by Visit

The number and percentage of subjects with immunoglobulin values (IgG, IgA, and IgM) greater than or equal to the LLN at each visit will also be presented for all subjects and then repeated for subjects < LLN at baseline. No statistical test will be performed.

8.6.8. Immunogenicity

Immunogenicity will be assessed in 3 basic steps utilizing a binding assay (screening and confirming), titration assay, and neutralizing assay. Step 1 is a screening assessment (positive/negative) of the binding assay. If the screening result is negative the sample is deemed negative and no further steps are performed. If the screening result is positive, then Step 2 is to run a confirming assay (positive/negative) on the sample. If the confirming assay is negative the sample is deemed negative and no further steps are performed. If the confirming assay is positive, the sample is deemed positive and Step 3 is performed to obtain a titer value to quantify the degree of binding and to run a neutralizing assay.

Binding assay results are categorized and presented as negative, persistent positive (defined as a positive immunogenic response that occurs at least 2 consecutive assessments or a single result at the final assessment) or transient positive (defined as a single positive immunogenic response that does not occur at the final assessment). A result is unknown if the confirmatory result is missing when the screening result is positive.

A table displaying the proportion of subjects within each immunogenic category will be presented by visit and anytime post-baseline where anytime post-baseline summarizes the highest category obtained for each subject (lowest to highest result is Negative, Transient Positive, Persistent Positive). A listing will also be presented.

8.7. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

8.7.1. Vital Signs

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

8.7.2. Concomitant Medical/Surgical Procedures

A listing of all concomitant medical/surgical procedures will be presented.

8.7.3. Liver Monitoring/Stopping Criteria

If any liver monitoring or stopping criteria events occur, a listing will be provided along with a listing of substance use reported with liver event. Any medical conditions reported associated with the liver event will be included in the Current and Past Medical Conditions listing.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

Pharmacokinetic analyses will be based on the PK population. PK samples erroneously collected more than 8-weeks post IP discontinuation will be excluded from all analyses and displays and can be identified due to no corresponding visit and date recorded in the eCRF. Descriptive statistics for serum belimumab concentrations will be displayed for each visit for the double-blind phase. The tables will display the mean value, standard deviation, 95% confidence interval, geometric mean, geometric standard deviation, geometric 95% confidence interval, coefficient of variation (%), median, 25th and 75th percentiles, minimum, and maximum. No statistical tests will be performed.

A line graph will be produced which displays the median belimumab concentration values along with 25th and 75th percentiles by visit for the double-blind phase.

To assess the effect of body size, proteinuria, and immunogenicity on belimumab exposure, the table and line graph described above will also be repeated for the subgroups of baseline body weight quartiles, baseline BMI categories (Underweight <18.5, Normal 18.5 - <25, Overweight 25 - <30, Obese ≥ 30), and baseline proteinuria categories (<0.5, 0.5-<3, ≥3) and may be repeated for immunogenicity status (persistent positive vs.

transient persistent vs. negative) if the number of subjects with a positive status warrants it.

A listing of serum belimumab PK concentration-time data will be presented.

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.2 Reporting Standards for Pharmacokinetic).

9.1.2. Population of Interest

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

9.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

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

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

10.1. Strategy

The objective of this analysis is to explore the relationship between proteinuria, PK and PD response. The analysis will be split into two parts:

- An exploratory analysis to assess overall trends and variability in the observed data.
- A population PK analysis to link proteinuria levels to exposure and to compare individual predicted exposure parameters with the observed PD response.

A relationship between proteinuria levels and the PK or PD response would support the recommendation of a dose adjustment to correct for the effects of proteinuria, and any proposed change in dosing regimen will be investigated. A more complex population PK analysis, treating proteinuria as a time dependent model predicted variable, may also be carried out time permitting.

10.2. Statistical Analyses / Methods

Belimumab serum concentration-time data will be analyzed by population pharmacokinetic (popPK) methods using a non-linear mixed-effects modelling approach. Pharmacokinetic data will be presented in graphical and/or tabular form and will be

summarized descriptively. A summary of study PK and PD parameters will be reported with respect to the mean, standard deviation, median and range (median and maximum). All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Details for the PopPK methodology are provided in Appendix 9.

10.3. Exploratory Analysis

The exploratory analysis is intended to be a straight forward comparison between the observed proteinuria levels, PK and PD response, and will not include more in-depth modelling or data manipulation. The PK will be specified by the pre-dose (Cmin) and post-infusion (Cmax) concentrations at weeks 2, 4, 8, 24, 52 and 104. The proteinuria and PD biomarkers will be specified by their observed values, change from baseline and percent change from baseline, at the weeks the samples were taken (which is different for each biomarker). The analysis may include:

- **Response over time**
  Plot and summary table of the proteinuria levels, PK (Cmin, Cmax) and PD response over time.

- **Effect of proteinuria on PK**
  Plot of observed Cmin and Cmax values versus proteinuria levels measured at the same week.

- **Effect of PK on PD biomarker response**
  Plot of the biomarker response at week N against the PK (Cmin and Cmax) at the same or earlier time points.

- **Effect of proteinuria on PD biomarker response**
  Plot of biomarker response at each week versus baseline proteinuria levels.

10.4. Population PK Analysis

The proteinuria/PK and the PK/PD exposure response relationships will be explored in more detail through a population PK analysis. A population PK model will be constructed from the observed data. The effect of body size (for example, body weight, body-mass index, fat-free mass) and proteinuria will be evaluated and included in the model if shown to be a pharmacokinetically relevant covariate or the fit to the data is substantially improved. Additional covariates of potential clinical importance, such as age, gender, race and co-medication, may also be tested.

10.4.1. Individual Analysis

The population PK model will be used to derive the post-hoc belimumab concentration-time profiles for each subject, based on the observed changes in proteinuria during the study. The analysis may include:

- **Response over time**
  Plot of the individual predicted time course profiles for belimumab.

Plot and summary table of the post-hoc exposure parameters (Cmin, Cavg, Cmax) at selected time points throughout the study.

- **Effect of proteinuria on PK**
  Plot of the individual predicted post-hoc exposure parameters (Cmin, Cavg, Cmax) versus the observed proteinuria level measured at the same week.

- **Effect of PK on PD biomarker response**
  Plot of the observed biomarker response at week N versus the average exposure from week 0 to week N, calculated as the area under the concentration-time curve to week N divided by this time period.

10.4.2. Population Analysis

The population PK model will be used to simulate the PK over an adult lupus-nephritis population. All covariate information required by the model (for example, proteinuria and body weight) will be sampled from an appropriate distribution, consistent with the variability in the study population, or sampled with replacement from the study dataset itself. The results from the simulation will be used to explore the time course of the PK, and the effects of body weight and proteinuria on the PK. The PK will be expressed by its median, inter-quartile range and 95% prediction, as a function of time or any other covariate. The analysis may include:

- **Effect of proteinuria on PK**
  Plot of average concentration at steady state versus proteinuria level.

- **Effect of body weight on PK**
  Plot of average concentration at steady state versus body weight.

For all simulation-based plots the individual predicted post-hoc values will also be superimposed to verify consistency with the simulated population results.

10.5. Population PK Analysis with Proteinuria as a Time-Dependent Model Variable

Time permitting, proteinuria levels will be treated as a time-dependent model variable, as opposed to a covariate parameter of the model, and a population PK model fitted to the observed PK and proteinuria data simultaneously. The population PK analysis described above may be updated using this alternative model, which has the advantage that proteinuria levels in response to drug can be predicted over time. This more detailed level of analysis will be strictly optional, dependent on time available, the requirement to predict the proteinuria response over time, and the likelihood of a successful outcome following assessment of the data.

10.6. Dose Adjustment

Based on the exposure-proteinuria relationship derived from the population PK analysis, a decision may be made to increase the dose if proteinuria is above a chosen threshold

with the aim of maintaining exposures at or close to the target value (Cavg of approximately 100 µg/mL). The exposure-proteinuria relationship incorporating any proposed change in dosing frequency will be calculated and characterised accordingly.

11. BIOMARKER ANALYSES

Unless otherwise stated, all analyses will be limited to the double-blind treatment period while subjects are on investigational product (IP).

11.1. Biomarker Endpoints

Autoantibodies, complement, and peripheral B lymphocytes (referred to as B cells) will be collected per the study calendar (Appendix 2, Section 14.2). In geographies where feasible, the peripheral B lymphocytes will be measured (using FACS analysis). The specific biomarkers collected and analyzed are listed in Table 10:

Table 10 Biomarkers for Analysis

Autoantibodies	**B cells**
aCL	CD19
ANA	CD20
anti-Sm	Naïve CD19+CD20+CD27- *
anti-C1q	Memory CD19+CD20+CD27+ *
Anti-dsDNA	Activated CD19+CD20+CD69+ Normalised
BLyS (only collected at baseline)	Plasma CD19+CD20-CD138+ Normalised
Complement	Plasmacytoid CD19+CD20+CD138+ Normalised
C3	Short-lived Plasma CD19+CD20-CD27b+ Normalised
C4	SLE Subset CD19+CD38b+CD27b+Lymph Normalised
Immunoglobulin	Transitional CD19+CD24b+CD38b+CD27- Normalised
IgG, IgM, and IgA	*Naïve and Memory B cell subsets will also be expressed as a percentage of CD19.

For the duration of the study, biomarker data (serum immunoglobulin isotypes IgA and IgM and B cell results) that have the potential to unblind the study team 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. 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.

11.2. Biomarker Change and Percent Change from Baseline Analyses

Endpoints
The change from baseline and percent change from baseline will be evaluated for each of the biomarkers listed in Table 10.
Statistical Analysis
For immunoglobulins an ANCOVA will be used to evaluate the treatment effect controlling for baseline value, induction regimen (CYC, MMF) and race (Black, Non-Black).

For autoantibodies and complement a rank ANCOVA will be used to evaluate the treatment effect controlling for baseline value, induction regimen (CYC, MMF) and race (Black, Non-Black).
Summary Measure
The difference in the Least Square (LS) means (belimumab – placebo) will be used to assess the treatment effect.
Population of Interest
The modified Intent-to-Treat population will be used for the analysis.
Intercurrent Event Strategy
These analyses will be performed on the observed data up to IP discontinuation. No imputation will be done for missing data.
Variables
• Biomarker (B cells defined in Appendix 10) • Treatment (belimumab=1, placebo=0) • Baseline_Value (continuous)* • Induction (CYC=1 vs. MMF=0) • Race (Black=1 vs. Non-Black=0)
Model Specification
model Endpoint = Treatment Baseline_Value Induction Race
Model Checking & Diagnostics
The data will be evaluated by two independent statisticians to determine if the model assumptions and fit are reasonably met. If either is deemed unacceptable, additional sensitivity analysis using an alternative method may be performed. Model checking diagnostics are not applicable for rank ANCOVA.
Model Results Presentation
For the baseline visit, the table will display the number, mean, standard deviation of the mean, median, 25th and 75th percentiles, minimum and maximum. At each post-baseline visit, the tables will display the number, mean percent change from baseline, standard deviation of the mean, median, 25th and 75th percentiles, minimum and maximum. Additionally, at Week 104 the LS mean and associated standard error, treatment difference versus placebo in LS means, 95% CI for the LS means treatment difference, and p-value from the ANCOVA model will be presented. For rank ANCOVA, the following results will be displayed by induction regimen and treatment group: mean, standard deviation, standard error, median, 25th percentile, 75th percentile, minimum, maximum. The p-value for the rank ANCOVA will be presented for the treatment comparison for the combined induction regimens at Week 104 only. A line graph for the observed median change from baseline in each of these biomarkers will be presented by treatment group (overall and by induction regimen) for both the double-blind phase.
Subgroup Analyses
• For autoantibodies (anti-dsDNA, ANA, aCL, Anti-C1q, and Anti-Sm), analyses will be

performed on subjects who were positive at baseline.

- For complement (C3 and C4), analyses will be performed on subjects with low values at baseline (C3 <90 mg/dL and C4 <10 mg/dL).

11.2.1. Adjustment for IgG Loss

For IgG and autoantibodies (anti-dsDNA, aCL, Anti-C1q, and Anti-Sm) analyses which adjust the results for IgG loss due to proteinuria will be performed to reduce confounding of the treatment effect.

Specifically, for each autoantibody listed above,

- Log(IgG) and Log(Autoantibody) will be fitted jointly in a multivariate ANCOVA model with terms for "Autoantibody x Treatment x Time", "Autoantibody x Baseline x Time", "Autoantibody x Induction Regimen", “Autoantibody x Race Stratification Factor”, Autoantibody x Baseline uPCR”, and "Autoantibody x Baseline eGFR”.
- Models will be fitted using restricted maximum likelihood (REML) methods and have an un-structured variance-covariance matrix for both treatments.
- Model adjusted mean estimates with associated 95% CIs will be produced for both the autoantibody and IgG by treatment at each timepoint (by exponentiation of Least Square Means estimates) with a corresponding plot by treatment over time.
- Model adjusted ratio of mean estimates (Autoantibody/IgG) with associated 95% CIs will be produced by treatment at each timepoint with a corresponding plot by treatment over time.

11.3. Shifts in Immunoglobulins, Autoantibodies, and Complement by Visit

Endpoints

Shift tables will be used to summarize the changes in immunoglobulins, autoantibodies, and complement by induction regimen and overall for each treatment group and visit.

Autoantibody	**Positive**	**Negative**
Anti-dsDNA	≥30 IU/mL	<30 IU/mL
ANA	≥80 Titer	<80 Titer
aCL	If any of the three aCL parameters, IgG (≥14 U/mL), IgA (≥11 U/mL) or IgM (≥12 U/mL), is positive.	If at least 1 is non-missing then aCL is negative; otherwise aCL is missing.
Anti-C1q	≥22.2 U/mL	<22.2 U/mL
Anti-Sm	≥15 KU/L	<15 KU/L
Ig	**High**	**Normal/Low**
IgG	> 16.18 g/L	≤16.18 g/L
IgA	> 4.63 g/L	≤ 4.63 g/L
IgM	> 2.71 g/L	≤ 2.71 g/L
Complement	**Low**	**Normal/High**

C3	<90 mg/dL	≥90 mg/dL
C4	<10 mg/dL	≥10 mg/dL

Statistical Analysis

Fisher's exact test will be performed within each baseline category to evaluate the treatment effect.

Population of Interest

The modified Intent-to-Treat population will be used for the analysis.

Intercurrent Event Strategy

These analyses will be performed on the observed data up to IP discontinuation. No imputation will be done for missing data.

Variables

- Immunoglobulins, autoantibodies, and complement endpoints evaluated one at a time.
- Treatment (belimumab=1, placebo=0)

Results Presentation

For IgG, IgA, IgM, C3 and C4 baseline data will be summarized as the number and percent of subjects who are high or normal/low at baseline. For post-baseline visits the data will be summarized by baseline status defined as high or normal/low. Among subjects high at baseline the shifts presented will be high or normal/low and high to high. Among subjects normal/low at baseline, the shifts presented will be normal/low to high and normal/low to normal/low.

For anti-dsDNA, ANA, aCL, Anti-C1q, and Anti-Sm, 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 or negative. Among subjects positive at baseline the shifts presented will be positive to negative and positive to positive (no change). Among subjects negative at baseline, the shifts presented will be negative to negative (no change) and negative to positive. Anti-C1q and anti-SM are only analyzed post-baseline for subjects positive at baseline, therefore shifts for subjects negative at baseline will not be presented.

Subgroup Analyses

Subgroup analysis will be performed by Induction Regimen (CYC, MMF).

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Pharmacokinetic/Pharmacodynamic (PD) analyses are not prospectively planned for this study. Based on the results obtained, exploratory analyses may be performed on an ad hoc basis.

12.1. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/SupportingDocumentation.aspx):
  - 4.03 to 4.24: General Principles

- 5.01 to 5.08: Principles Related to Data Listings
- 6.01 to 6.11: Principles Related to Summary Tables
- 7.01 to 7.13: Principles Related to Graphics

- Subject level listings will not be included in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings.
  - All data summaries and analyses will be performed using the latest available version of SAS software (as available at GSK). R may be used to quality check statistical analyses. The latest available version of R will be used and the version will be documented in the CSR.
  - Data displays will follow the shells as outlined in Section 14.13 which follow the Benlysta program standards and, as far as possible, follow the GSK Integrated Data Standards Library (IDSL).

Formats

- All data will be reported per the actual treatment the subject received unless otherwise stated.
- GSK IDSL Statistical Principles (4.24) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Unless otherwise stated, the following will apply:

- Continuous variables will be summarized with the statistics mean, median, standard deviation (SD), 25th and 75th percentiles, minimum and maximum.
- Categorical variables will be summarized with frequency counts and percentages, or proportions where specified. A 'Missing' category will be added to frequency counts if there is at least one missing record.
- Percentages will be calculated using the number of non-missing observations as the denominator. If the unit of measurement is a subject, the percentage will be based on the total N for the population that are still in the study at the respective visit
- 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 for any statistics displayed.
- The same decimal point rules described above 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.
- For statistical analyses, all tests will be two-sided and p-values will be presented to a maximum of 4 decimal places.
- When the data are summarized by visit, only scheduled visits at which the data was to be collected will be presented. Unscheduled visits will be included in patient listings
- Listings will be sorted by induction regimen, treatment group, site ID, unique subject ID, and visit (where appropriate).
- Figures displaying means or medians also will include standard error bars or interquartile ranges, respectively.
- 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.

Planned and Actual Time

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

Unscheduled Visits

- Unscheduled visits will not be included in summary tables and/or figures displaying data By Visit.
  - Data collected at unscheduled visits will be used in summaries that present the most extreme values on treatment such as laboratory shift tables or maximum toxicity grades.
- All unscheduled visits will be included in listings.

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to IDSL Statistical Principals 7.01 to 7.13.

13. REFERENCES

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

Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Tables, May 2001.http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/Documents/dmidadulttox.doc

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

From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996

Gastonguay M. Full covariate models as an alternative to methods relying on statistical significance for inferences about covariate effects: a review of methodology and 42 case studies. PAGE Conference, June 2011, Athens, Greece. Available at http://www.page-meeting.org/?abstract=2229 (last accessed 12 Apr 2018).

Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39(3):363-9.

Gladman D, Ibañez D, Urowitz, M. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol 2002, 29 (2) 288-291.

Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation 2001;71(2):242-6.

Jackson D, White IR, Seemain S, et al. Relaxing the independent censoring assumptions in the Cox proportional hazards model using multiple imputation. Stat Med. 2014;33:4681-94.

Kim Y, Won S “Adjusted proportion difference and confidence interval in stratified randomized trials” PharamSUG 2013 Paper SP04

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–54.

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

PSAP, Program Safety Analysis Plan for Belimumab, GSK1550188, Effective Date: 02-OCT-2018.

Rubin DB. Multiple Imputations for Nonresponse in Surveys. John Wiley & Sons. 1987.

Struemper, H., Cai, W., Chen, C. Population pharmacokinetics of belimumab following intravenous administration in patients with systemic lupus erythematosus. J Clin Pharmacol 2013; 53(7):711-20.

Yamani MH, Avery RK, Mawhorter SD, et al. Hypogammaglobulinemia following cardiac transplantation: a link between rejection and infection. J Heart Lung Transplant 2001;20(4):425-30.

Zhao Y, Herring AH, Zhou H, et al. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. J Biopharm Stat. 2014;24:229-53.

14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

14.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Did not have a clinical diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria (Inclusion 2)
02	Did not have active, biopsy-proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)] either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria (Inclusion 3)
03	Did not have unequivocally positive anti-nuclear antibody (ANA titer ≥ 1:80) test results and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results. (Inclusion 4)
04	Did not have documentation of active renal disease at screening requiring induction. (Inclusion 5)
05	Did not have active renal disease defined as above which requires induction therapy with high dose corticosteroids (HDCS) with either intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) or other oral forms of mycophenolate. (Inclusion 6)
06	Previously failed both CYC and MMF (or other forms of mycophenolate) induction therapies based on the investigator's opinion. (Exclusion 1)
07	Received an induction therapy with CYC within 3 months prior to the planned initiation of the current induction for the study. (Exclusion 2)
08	Received treatment with belimumab within 364 days of baseline (Day 1). (Exclusion 6)
09	Received treatment with one of the excluded therapies within 364 days of baseline (Day 1). (Exclusion 7)
10	Received treatment with one of the excluded therapies within 90 days of baseline (Day 1). (Exclusion 8)
11	Received a non-biological investigational agent within 60 days of baseline (Day 1). (Exclusion 9)
12	Subjects who had been on dialysis within 364 days of baseline (Day 1). (Exclusion 13)
13	Had an estimated glomerular filtration rate < 30 mL/min/1.73 m2 at the screening visit (using the simplified Modification of Diet in Renal Disease [MDRD] equation). (Exclusion 14)
14	Received an incorrect treatment most of the time (>50% of the time).
15	Missed 3 or more consecutive study agent infusions.
16	Study blind/unblind procedures: Investigator/site staff/GSK Clinical team did not remain blinded to treatment assignment through Week 104/Exit visit efficacy evaluation, includes emergency unblinding for medical reasons.
17	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.

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Table 11 Study Calendar - Double-Blind Treatment Period (Screening to Week 52)

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-35 days**	**Day 0**	**Day 3**	**14 ± 3 days**	**28 ± 3 days**	**56 ± 7 days**	**84 ± 7 days**	**112 ±7 days**	**140 ± 7 days**	**168 ± 7 days**		**196 ± 7 days**	**224 ± 7days**	**252 ± 7days**	**280 ± 7days**	**308 ± 7days**	**336 ± 7days**		**364 ± 7days**	
Study Week	**Wk -5**			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Written Informed Consent	x																			
Demographics (including race)	x																			
Medical History	x																			
SLE History	x																			
Therapy History	x																			
Eligibility Criteria	x																			
Biopsy Report[A]	x																			
Pre-flare GFR[B]	x																			
Biopsy sample shipment for central evaluation		After Day 0																		
Clinical Assessments																				
SELENA SLEDAI, SLE Flare Index and PGA		x					x			x				x					x	
SLICC Damage		x								x									x	
C-SSRS Screening/Baseline	x																			
C-SSRS Since Last Visit[C]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-35 days**	**Day 0**	**Day 3**	**14 ± 3 days**	**28 ± 3 days**	**56 ± 7 days**	**84 ± 7 days**	**112 ±7 days**	**140 ± 7 days**	**168 ± 7 days**		**196 ± 7 days**	**224 ± 7days**	**252 ± 7days**	**280 ± 7days**	**308 ± 7days**	**336 ± 7days**		**364 ± 7days**	
Study Week	**Wk -5**			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Record Concurrent Medications	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Complete Physical Exam	x																			
Symptom-driven Physical Exam		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Weight[D]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Vital signs[P]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
12-lead ECG		x																		
Record/Assess Adverse Events[E]	x[R]	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Laboratory Assessments																				
Hematology and chemistry (non-fasting)[F]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum Creatinine[G]			x								x							x		x
Urinalysis[H]	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Urinary Microscopy[H]	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
Spot urine	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
24-hour Urine[G]		X								x							x		x	
Urine Biomarkers		x					x			x									x	
BLyS protein (baseline only)		x																		
Pregnancy Test[I]	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
ANA	x	x								x									x	
Complement (C3/C4), anti-dsDNA	x	x			x	x	x	x	x	x		x	x	x	x	x	x		x	
aCL (IgA, IgG, IgM isotypes)		x								x									x	
Anti-Sm, anti-C1q[J]		x								x									x	

	Screening	Baseline	Double-Blind Treatment Period																	
Study Day	**-35 days**	**Day 0**	**Day 3**	**14 ± 3 days**	**28 ± 3 days**	**56 ± 7 days**	**84 ± 7 days**	**112 ±7 days**	**140 ± 7 days**	**168 ± 7 days**		**196 ± 7 days**	**224 ± 7days**	**252 ± 7days**	**280 ± 7days**	**308 ± 7days**	**336 ± 7days**		**364 ± 7days**	
Study Week	**Wk -5**			**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**WK 20**	**Wk 24**	**Wk 24 + 3d**	**Wk 28**	**Wk 32**	**Wk 36**	**WK40**	**Wk 44**	**Wk 48**	**Wk 48 + 3d**	**Wk 52**	**Wk 52 + 3d**
Serum IgG	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Serum IgA & IgM	x	x				x				x									x	
PT/PTT	x	x				x				x									x	
HIV, Hep B and Hep C serology, and HBV DNA[Q]	x																			
Pharmacokinetic Sampling[K]		x	x	x	x	x				x	x								x	
Immunogenicity (anti-belimumab antibody)		x				x				x									x	
Peripheral B lymphocytes		x				x				x									x	
Pharmacogenetics Sampling (consenting subjects only)[L]		x																		
Protocol Treatments																				
Study Agent Administration (Belimumab/Placebo)[M,N]		x		x	x	x	x	x	x	x		x	x	x	x	x	x		x	
Induction/Maintenance Therapy[O]	Throughout the Study																			

[A]Biopsy report indicating proliferative lupus nephritis. Should be from a renal biopsy obtained in the 6 months prior to the screening visit or during the screening period. A tissue sample from the renal biopsy used to qualify the subject for randomization needs to be sent to a central reading center after Day 0 (baseline).

[B]Most recent GFR prior to the current renal flare.

[C] The Columbia-Suicidality Severity Rating Scale (C-SSRS) Since Last Visit form (see Protocol Appendix 9) will be used at Day 0 and all subsequent visits. The C-SSRS Baseline/Screening form (see Protocol Appendix 8) is only used at Screening.

[D]The weight at the current visit should be used to calculate dose.

[E]For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all adverse events will be collected through 8 weeks following the administration of the last dose of study agent. After this time, SAEs, regardless of relationship to study drug, will be collected through Week 104.

[F] Refer to Protocol Appendix 5 for a listing of laboratory assessments to be completed.

[G]Two 24 hour urine and serum creatinine collections will be performed for each of the following visits: baseline, Weeks 24, 48 and 52. Serum creatinine for these visits will be collected at the initial visit which will take place within 3 days prior to or on the day of the scheduled visit, and then 3 days after the initial visit. For urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at time of urinalysis or anytime during the 24 hour urine collection.

[H]Routine urinalysis and urinary microscopy will be performed locally.

[I]For women of child-bearing potential, serum pregnancy test is required at screening. At subsequent visits, a urine pregnancy test is required. Results of the pregnancy test must be available prior to dosing.

[J]Samples will only be analyzed in subjects with positive results at baseline.

[K]For PK sampling times, see Protocol Section 6.7.1.

[L]Pharmacogenetic sampling informed consent must be obtained prior to any blood being taken for PGx research. Sample should be drawn prior to dosing.

[M]Subjects who are withdrawn from treatment with study agent prior to Week 100 (for reasons other than withdrawal of consent) should continue to follow the study calendar and have all assessments completed through Week 104 (with the exception of study agent administration).

[N] Subjects should remain under clinical supervision for 3 hours after completion of the first 2 study agent infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment.

[O]Induction therapy may begin before Screening but should be initiated within 60 days prior to or on Day 0 (baseline).

[P] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate. On days on which study agent is administered, vital signs are to be performed prior to dosing.

[Q]Note: if anti-HBc result is reactive, the sample drawn for HBV DNA will be tested for viral DNA; otherwise, the sample will be destroyed. Subjects in China with positive hepatitis C screening results will be excluded without confirmatory hepatitis C RNA-PCR testing.

[R]Note: For subjects in China, SAEs will be collected from the time a subject consents to participate in the study (see Protocol Section 7.2).

Table 12 Study Calendar - Double-Blind Treatment Period (Week 56 to 104)

	Double-Blind Treatment Period																	
Study Day	**392 ± 7days**	**420 ± 7days**	**448 ± 7days**	**476 ± 7days**	**504 ± 7days**	**532 ± 7days**		**560 ± 7days**	**588 ± 7days**	**616 ± 7days**	**644 ± 7days**	**672 ± 7days**	**700 ± 7days**		**Day 728/ Exit [A] ± 7days (4 weeks after last dose)**		**Follow-up visit[B] (8 week after last dose) +7 days**	**Unscheduled Visit[C]**
Study Week	**Wk 56**	**Wk60**	**Wk64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 76 + 3 d**	**Wk 80**	**Wk 84**	**Wk88**	**Wk92**	**Wk 96**	**Wk 100**	**Wk 100 + 3 d**	**Wk 104**	**Wk 104 + 3 d**		
Clinical Assessments																		
SELENA SLEDAI, SLE Flare Index and PGA			x			x				x					x			x
SLICC Damage						x									x			
C-SSRS Since Last Visit	x	x	x	x	x	x		x	x	x	x	x	x		x			
Record Concurrent Medications	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Symptom-driven Physical Examination	x	x	x	x	x	x		x	x	x	x	x	x		x			
Weight[D]	x	x	x	x	x	x		x	x	x	x	x	x		x			
Vital signs[N]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Record/Assess Adverse Events[E]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Survival Assessment[F]															x			
Laboratory Assessments																		
Hematology and chemistry (non-fasting)[G]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Serum Creatinine[H]							x							x		x		
Urinalysis[I]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Urinary Microscopy[I]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
Spot urine	x	x	x	x	x	x		x	x	x	x	x	x		x		x	x
24-hour Urine[H]						x							x		x			
Urine Biomarkers															x			
Pregnancy Test[J]	x	x	x	x	x	x		x	x	x	x	x	x		x		x	
Complement (C3/C4), anti-dsDNA	x	x	x	x	x	x		x	x	x	x	x	x		x			x
ANA, aCL (IgA, IgG, IgM isotypes)						x									x			
Anti-Sm, anti-C1q[K]						x									x			
Serum IgG			x			x				x			x		x			
Serum IgA & IgM						x									x			
PT/PTT						x									x			

	Double-Blind Treatment Period																	
Study Day	**392 ± 7days**	**420 ± 7days**	**448 ± 7days**	**476 ± 7days**	**504 ± 7days**	**532 ± 7days**		**560 ± 7days**	**588 ± 7days**	**616 ± 7days**	**644 ± 7days**	**672 ± 7days**	**700 ± 7days**		**Day 728/ Exit [A] ± 7days (4 weeks after last dose)**		**Follow-up visit[B] (8 week after last dose) +7 days**	**Unscheduled Visit[C]**
Study Week	**Wk 56**	**Wk60**	**Wk64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 76 + 3 d**	**Wk 80**	**Wk 84**	**Wk88**	**Wk92**	**Wk 96**	**Wk 100**	**Wk 100 + 3 d**	**Wk 104**	**Wk 104 + 3 d**		
Pharmacokinetic Sampling[L]															x		x	
Immunogenicity (anti-belimumab antibody)						x									x		x	
Peripheral B lymphocytes						x									x			
Protocol Treatments																		
Study Agent Administration (Belimumab/Placebo)[M]	x	x	x	x	x	x		x	x	x	x	x	x		**If entering extension**			
Induction/Maintenance Therapy	Throughout the Study																	

[A]For subjects completing 100 weeks of treatment with study agent and continuing into the 6-month open-label extension, the Week 104 visit will also serve as the Day 0 visit of the 6-month open-label extension. Only subjects who continue in the open-label extension study will have study agent (belimumab) administered at the Week 104 visit after the completion of Week 104 assessments. Subjects who are withdrawn from treatment with study agent prior to Week 100 (for reasons other than withdrawl of consent) should continue to follow the study calendar and have all assessments perfomed through Week 104 (with the exception of study agent administration). For subjects who withdrew consent and agreed to have follow-up safety data collected or subjects who are not continuing into the open label extension, the Week 104/Exit visit will occur approximately 4 weeks after the last dose of study agent.

[B]The 8-week follow-up visit is not required for subjects entering the open-label extension.

[C]Adverse events and concurrent medications should be assessed at each unscheduled visit. When a subject has worsening nephritis or SLE, a complete disease activity assessment (SELENA SLEDAI, SLE Flare Index, and PGA), and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and complement) should be performed to document disease activity worsening (eg, renal flare/relapse) prior to instituting treatment that results in treatment failure designation as defined in Protocol Section 5.5 and Protocol Section 5.6. Other assessments should be performed as clinically indicated.

[D]The weight at the current visit should be used to calculate dose.

[E]For subjects who discontinue treatment with study agent during the double-blind period (for reasons other than withdrawal of consent), all adverse events will be collected through 8 weeks following the administration of the last dose of study agent. After this time, SAEs, regardless of relationship to study drug, will be collected through Week 104.

[F]In the event that a subject withdraws consent from the study, an attempt should be made at the time of consent withdrawal to obtain consent to collect survival status at Week 104.

[G]Refer to Protocol Appendix 5 for a listing of laboratory assessments to be completed.
[H]Two 24 hour urine and serum creatinine collections will be performed for each of the following visits: Weeks 76, 100 and 104. The serum creatinine for these visits will be collected on the day of the initial visit and then 3 days after the initial visit. For urinary sediment assessments, both menstrual cycles and genitourinary tract infections may be confounders. Urine collection may be postponed up to 14 days at the investigators discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24 hour urine collection.
[I] Routine urinalysis and urinary microscopy will be performed locally.
[J]For women of child-bearing potential, a urine pregnancy test is required. Results of the urine pregnancy test must be available prior to dosing.
[K]Samples will only be analyzed in subjects with positive results at baseline.
[L]For PK sampling times, see Protocol Section 6.7.1.
[M]Subjects who are withdrawn from treatment with study agent prior to Week 100 (for reasons other than withdrawl of consent) should continue to follow the study calendar and have all assessments completed through Week 104 (with the exception of study agent administration).
[N] Vital signs include temperature, sitting blood pressure (systolic and diastolic) and heart rate. On days on which study agent is administred, vital signs are to be performed prior to dosing.

14.3. Appendix 3: Assessment Windows

14.3.1. Definitions of Assessment Windows for Analyses

Analysis Visit and Analysis Visit Number

The Analysis Visit and Analysis Number are assigned based on the VISIT and VISITNUM for the planned visits. Exit, withdrawal, and unscheduled visits which are not associated with a specific planned time are slotted into one of the planned times based on the interval in which the Study Day falls per the intervals (inclusive) provided below. For completeness, the table also includes visit intervals representing planned study times for which no visits are not slotted; these visits will have 'na' for 'not applicable' listed for the Interval Start and End Day. Since baseline values are defined as the most recent value prior to the first infusion, the baseline value could correspond to a screening visit, Week 0 visit, or an unscheduled visit prior to first infusion; therefore, the analysis visit is labeled 'Baseline' while the analysis visit number (AVISITN) equals the original visit number (VISITNUM). Similarly, a subject's final visit in the double-blind period will be 'Week 104' if the subjected completed all 104 weeks of the study but did not enter the open-label extension phase. Subjects who completed the study and entered the open-label extension phase will have their final visit labeled 'Week 104/EXT Week 0'. Subjects who withdrew from the study prior to Week 104 will have their final visit labeled 'EXIT DOUBLE BLIND'. Each of these categories is mutually exclusive. The Week 104 and 'Week 104/EXT Week 0' will both have an analysis visit of 'Week 104' and an analysis visit number of 350. EXIT DOUBLE BLIND visits will be slotted based on the visit widows.

Visit	Visit Number	Target Study Day	Interval Start Day	Interval End Day
Screening	10	**-35**	na	na
Week 0	20	**1**	-35	1
Week 0 +3 days	30	**4**	na	na
Week 2	40	**15**	2	21
Week 4	50	**29**	22	42
Week 8	60	**57**	43	70
Week 12	70	**85**	71	98
Week 16	80	**113**	99	126
Week 20	90	**141**	127	154
Week 24	100	**169**	155	182
Week 24 + 3 days	110	**172**	na	na
Week 28	120	**197**	183	210
Week 32	130	**225**	211	238
Week 36	140	**253**	239	266
Week 40	150	**281**	267	294
Week 44	160	**309**	295	322
Week 48	170	**337**	323	350
Week 48 + 3 days	180	**340**	na	na
Week 52	190	**365**	351	378
Week 52 + 3 days	200	**368**	na	na
Week 56	210	**393**	379	406
Week 60	220	**421**	407	434

Analysis Visit and Analysis Visit Number				
Week 64	230	**449**	435	462
Week 68	240	**477**	463	490
Week 72	250	**505**	491	518
Week 76	260	**533**	519	546
Week 76 + 3 days	270	**536**	na	na
Week 80	280	**561**	547	574
Week 84	290	**589**	575	602
Week 88	300	**617**	603	630
Week 92	310	**645**	631	658
Week 96	320	**673**	659	686
Week 100	330	**701**	687	714
Week 100 + 3 days	340	**704**	na	na
Week 104	350	**729**	715	742
Week 104 + 3 days	360	**732**	na	na
IP DISC	365	**na**	na	na
EXIT DOUBLE BLIND	366	**SLOT**		
EOS DOUBLE BLIND	368	**na**	na	na
FOLLOW-UP	370	**757**	na	na
Survival	372	**729**	na	na
Week 104/EXT Week 0	375	**729**	715	742
UNSCHEDULED	901	**SLOT**		
UNSCHEDULED	902	**SLOT**		
UNSCHEDULED	903	**SLOT**		
LIVER EVENT 1	8100	**na**		
LIVER EVENT 2	8200	**na**		

14.3.1.1. Exit/Withdrawal and Unscheduled Visits

Exit/Withdrawal and Unscheduled Visits

The data is analyzed per the planned visit assignment.

Exit/withdrawal visit (listed below) must be slotted to the appropriate planned visit for subjects who withdraw prior to the end of the double-blind treatment phase. If the Exit visit is slotted into the same visit as the visit prior to withdrawal, slot the Exit visit to the next scheduled visit. For example, if the subject's last visit prior to the Exit visit was Week 20 and the Exit visit mapped as another Week 20, map the Exit visit to Week 24.

For safety reporting, unscheduled laboratory visits will also be remapped into the appropriate planned visit based on the original visit number (e.g. if unscheduled visit number =80.01, set analysis visit number= 80). The following hierarchical rules apply:

- If the scheduled visit exists, use the scheduled visit as is.
- If no scheduled visit exits, use the unscheduled visit closest to the target study day.
- If there are two visits equidistant from the target date, the earliest date will be used as the scheduled visit

For efficacy reporting, data will be used based on the visit it was collected, scheduled or

Exit/Withdrawal and Unscheduled Visits
unscheduled, and any visits with missing data will follow the imputation rules (e.g., last observation carried forward) as indicated in the endpoint derivation section.

Exit/withdrawal Visits

Phase	*Visit*	*Visit Number*
Double-Blind	Exit Double Blind	366

14.4. Appendix 4: Double Blind Data and Treatment Emergent Adverse Events

14.4.1. Double Blind Data Classification

Assessments and events will be classified according to the time of occurrence relative to the randomized treatment start date. For subjects not entering the open-label extension, all data will be reported in the double-blind reporting; otherwise data will be reported up to the first infusion in the open-label extension. The classifications below also define the data to be included in the ADaM datasets for the double-blind reporting.

Classification	Definition
Screening	Date < Treatment Start Date
Double Blind	Treatment Start Date ≤ Date ≤ Double blind end date where double blind end date is as follows: For subjects continuing in the open-label phase: • The date of the first infusion in the open-label period. For subjects not continuing in the open-label phase, all data in the double-blind/follow-up phase will be included in the ADaM datasets; therefore, depending on the subject's course in the study, the following hierarchy illustrates the last date for a subject in descending order: • 8-Week Follow-up visit date • Week 104 visit date • Exit visit date • Earliest of death date or early termination date • Last date of contact. NB: For labs, serum creatinine is collected at Week 104 + 3 days and used to derive cGFR; therefore, the date of the Week 104 + 3 days visit is used in the above hierarchy in place of the Week 104 visit. Exit visits for subjects that withdrew early in the double-blind phase will be slotted to a visit based on the calculated Study Day. Non-withdrawal visits will be assigned a visit based on the case report form Visit tab the data was entered under. The primary (Double-blind) reporting will include all records where the assessment date is less than or equal to the Open label period start date. For Pharmacokinetic Concentration and Laboratory datasets, all records where assessment date/time is less than or equal to Open label period start date/time are included. For Adverse Events include all records where AE start date is less than or equal to date of first infusion in the open-label period. For Concomitant Medications include all records where imputed start date is less than or equal to the date of first infusion in the open-label period. Note that Adverse Events and Concomitant Medications beginning on the first Open label treatment start date will be

Classification	Definition
	included for both the primary (Double-blind) and final (Open-label) reporting.

14.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• A treatment-emergent AE is an adverse event that emerges on or after the first treatment dose, having been absent pre-treatment, or that worsens relative to the pre-treatment state. AEs with missing start and/or stop dates will be assumed to be treatment-emergent. • Study Treatment Start Date ≤ AE Start Date

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
The currently supported versions of SAS software will be used.	
Reporting Area for end of Double Blind	
HARP Server	: us1salx00259
HARP Compound	: \arenv\arprod\gsk1550188\bel114054
HARP Area	: \arenv\arprod\gsk1550188\bel114054\primary_02
QC Spreadsheet	: \arenv\arprod\gsk1550188\bel114054\primary_02\documents
Analysis Datasets	
• Analysis datasets will be created per CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.0). If the Study Data Standardization Plan (SDSP) exists for a study, ensure the CDISC versions are consistent. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
RTF files will be generated for all reporting efforts.	

14.5.2. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics (Logged Transformed), Graphical Displays and Listings	Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. N, n, mean, standard deviation, 95% confidence interval, geometric mean, geometric standard deviation, geometric 95% confidence interval, coefficient of variation (CVb (%)*), median, 25th and 75th percentiles, minimum, and maximum will be reported. *CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
NONMEM/Pop PK File	An input data set (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created. Data set specifications guiding the generation of the input data set will be reported together with the PK results.
NONMEM/PK/PD File	Not applicable.

Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the POP-PK analysis: • Steady-state trough concentration: Cmin (μg/mL) • Steady-state maximal concentration: Cmax (μg/mL) • Steady-state area under the serum drug time-concentration curve and/or average concentration for the dosing interval: AUC0-τ (day*μg/mL) and/or Cavg (μg/mL) • Distribution half-life: t1/2α (day) • Terminal half-life: t1/2β (day) • Steady-state volume of distribution: Vss (mL)
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	In the POP-PK NQ values will be excluded, unless more than 10% of the total number of PK values are NQ in which case available methods to model NQ values will be considered.
Descriptive Summary Statistics, Graphical Displays and Listings	Geometric mean, geometric standard deviation, coefficient of variation (CVb (%)*), geometric 95% confidence interval, minimum, and maximum will be reported.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

14.6.1.1. Multiple Measurements at One Analysis Time Point

Multiple Measurements at One Analysis Time Point
• If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target, then use the value prior to the target visit date. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to the Laboratory Toxicity Grade tables.

14.6.1.2. Study Day

Study Day
Calculated as the number of days from treatment start date: • Ref Date = Missing → Study Day = Missing • Ref Date < Treatment Start Date → Study Day = Ref Date – Treatment Start Date • Ref Date ≥ Treatment Start Date → Study Day = Ref Date – (Treatment Start Date) + 1

14.6.1.3. IP Discontinuation Date

IP Discontinuation Date
Since the CRF data associated with the IP discontinuation form represents the date the form was completed and not the date the investigator made the decision to discontinue randomized treatment, IP discontinuation will be assigned the date of the first visit IP is not administered after the final infusion. For example, if a subject's last infusion is at Week 60, then the Week 64 visit will be the first Week the subject missed an infusion; therefore, the Week 64 visit date will be considered the IP discontinuation date. If the subject misses a visit after the last IP infusion without withdrawing from the study, the target date for the next planned visit will be used for the IP discontinuation date. For subjects who withdraw from IP without a follow-up, the date of last infusion + 28 days or the date of last contact, whichever is earlier, will be considered the IP discontinuation date.

14.6.1.4. Changes from Baseline

Change from Baseline
Change from baseline will be calculated as: *Visit value – baseline value.* If either value is missing the change from baseline will be missing

14.6.1.5. Percent Change from Baseline

Percent Change from Baseline
Percent change from baseline will be calculated as $$\frac{\textit{Visit Value - Baseline Value}}{\textit{Baseline Value}} \; X \; 100.$$ 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.

14.6.1.6. On Treatment for Safety Endpoints

Safety	Definition
Pre-Treatment	Date < Treatment Start Date
On-Treatment	Treatment Start Date ≤ Date ≤ Safety On-Treatment End Date Where Safety On-Treatment End date is defined as: For subjects who Complete DB phase through Week 104 without IP Discontinuation, End date for Safety On-Treatment End Date is • the Week 104 visit date, OR • the first infusion in open-label extension, whichever is later. For subjects who prematurely discontinue IP prior to Week 104, Safety On-Treatment End Date is • IP Discontinuation date (see Section 14.6.1.3), OR • last infusion + 28 days, whichever is later.
Post-Treatment	Date > Safety On-Treatment End Date

14.6.1.7. On Treatment for Efficacy Endpoints

Efficacy and Biomarker Treatment Phase	Definition
Pre-Treatment	Date < Treatment Start Date
On-Treatment	Treatment Start Date ≤ Date ≤ Efficacy On-treatment End Date Where Efficacy On-Treatment End date is defined as: For subjects who prematurely discontinue IP prior to Week 104, Efficacy On-Treatment End Date is • IP Discontinuation date (see Section 14.6.1.3). For subjects who Complete DB phase through Week 104 without IP Discontinuation, Efficacy On-Treatment End Date is

Efficacy and Biomarker Treatment Phase	Definition
	• the Week 104 visit date, • else if Week 104 is missing, then use the first infusion in open-label extension. Otherwise, use the last date of IP infusion.
Post-Treatment	Date > Efficacy On-Treatment End Date

14.6.2. Study Population

14.6.2.1. Analysis Age

Analysis Age

• Analysis age will be calculated from birth date to Day 1.
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.
• Age will be rounded down to the nearest year and stored as an integer.

14.6.2.2. Race and Race Stratification Factor

Race and Race Stratification Factor
• Subjects who check more than one race category are counted under an individual race category per the minority rule as well as the multiracial category. • The following minority rule will be applied to all analyses related to race (except for stratification): If a subject checks multiple race categories on the CRF, the subject will be assigned to a unique race group per the following priority order: • Native Hawaiian or Other Pacific Islander • Alaska Native or American Indian from North/Central/South America • Asian • Black • White/Caucasian • Race stratification is sometimes entered into the randomization system incorrectly. If the subject is randomized with an incorrect race stratum (black vs other); this cannot be corrected as it could impact the treatment assignment of the subject in question as well as that of subjects randomized subsequently. Therefore, another race variable will be derived as Black vs. Non-Black which is determined based on Black being ticked on the CRF or not. Note the minority rule does not apply. This race variable will be used as the race stratification variable for the

subgroup analyses and as a covariate in the efficacy analyses.

14.6.2.3. Body Mass Index (BMI)

Body Mass Index (BMI)
Baseline body mass index (BMI) will be calculated from baseline weight and height measurements as: $$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{[Height\ (m)]^2}$$ Since height is collected in centimetres (cm), it must 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.

14.6.2.4. Extent of Exposure

Extent of Exposure
• Extent of Exposure to study treatment through end of Double-Blind Week will be assessed by examining the total number of infusions a subject receives and the duration of exposure to study treatment in days. • The Treatment Stop Date for the Double-Blind period will be the date of the last infusion prior to Week 104 (Note: Week 104 infusions represent Day 1 of the Open Label period.) • Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 28 • Participants who were randomized but did not report a treatment start date will be categorised as having zero days 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.

14.6.2.5. Lupus Nephritis Medication Categories

Lupus Nephritis Medication Categories	
Medication Category	**Rule**
Anti-malarials	Set to "ANTIMALARIALS" if the preferred term begins with "QUINACRINE", "QUININE", "HYDROXYCHLOROQUINE", "MEPACRINE", or CHLOROQUINE"
Steroids	Set to 'STEROIDS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02'
Immunosuppressants	Set to 'IMMUNOSUPPRESSANTS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04A' and is NOT one of the anti-malarial preferred terms or the preferred term begins with "CYCLOPHOSPHAMIDE" or "MERCAPTOPURINE".
Angiotensin Pathway	Set to 'ACE' if at least one associated ATC code (ATCCD1 – ATCCD6)

Lupus Nephritis Medication Categories	
Antihypertensive	begins with 'C09A' or 'C09C'.
Prohibited	Set to "PROHIBITED" if any of the following conditions are met, if preferred term contains "INVESTIGATIONAL DRUG", "IMMUNOGLOBULIN", "ADALIMUMAB", "BELIMUMAB", "ETANERCEPT", "INFLIXIMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "GOLIMUMAB" or "CERTOLIZUMAB" **and/or** A review of the surgeries/procedures form indicates the subject had "PLASMAPHERESIS", "PLEX PLASMA EXCHANGE".

14.6.2.6. Systemic Medication Flag

Systemic Medication Flag	
Systemic Flag	**Rule**
Blank	If medication category =blank
Y	'Y' if medication category ne blank and the route of administration is "INTRADERMAL", "INTRAMUSCULAR", "INTRAVENOUS", "ORAL", or "SUBCUTANEOUS"
N	'N' otherwise and medication category ne blank

14.6.2.7. Prednisone Equivalent Conversion

Prednisone Equivalent Conversion
• A concomitant medication is identified as a steroid if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02.' Mineralocorticords are included in the group of ATC codes beginning with 'H02' but do not have sufficient anti-inflammatory properties to be considered as a prednisone equivalent. For this reason, the conversion factor for mineralocorticords is set to 0. • Only systemic routes of administration are used in the prednisone equivalent conversions; topical routes of administration are excluded (e.g., topical, conjunctival, intranasal). • At data base release, all preferred terms identified with an ATC code beginning with 'H02' will be reviewed to ensure a conversion factor exists for all terms with a systemic route of administration. • Similarly, all routes of administration for preferred terms with an ATC code beginning with 'H02'will be reviewed to ensure all systemic routes have been identified in the list above. • To be converted the frequency and dose of the steroid must be present with the unit dose in milligrams (mg) or grams (g). Doses recorded in grams will be converted to milligrams by multiplying the dose in grams by 1000 prior to applying the conversion factor.). Doses recorded in micrograms will be converted to milligrams by dividing the dose in micrograms by 1000 prior to applying the conversion factor. • Reported dose for systemic steroid is converted to prednisone equivalent dose using conversion factor for each medication (refer to online calculator

Prednisone Equivalent Conversion
http://www.globalrph.com/corticocalc.htm).

Prednisone Conversion Factors (mg)	
Single Ingredient Products: Prednisone Conversion Factors (mg)	
Preferred term	**Conversion factor for converting to a prednisone-equivalent dose**
BETAMETHASONE	8.3333
BETAMETHASONE DIPROPIONATE	8.3333
BETAMETHASONE SODIUM PHOSPHATE	8.3333
BETROSPAM	8.3333
BUDESONIDE	0.3333
CELESTONA BIFAS	8.3333
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.3333
DECADRON (NOS)	6.6667
DEFLAZACORT	0.8333
DEXAMETHASONE	6.6667
DEXAMETHASONE ACETATE	6.6667
DEXAMETHASONE SODIUM PHOSPHATE	6.6667
FLUDROCORTISONE	0
FLUOCORTOLONE	3
HYDROCORTISONE	0.25
HYDROCORTISONE ACETATE	0.25
HYDROCORTISONE SODIUM SUCCINATE	0.25
MEPREDNISONE	1.25
METHYLPREDNISOLONE	1.25
METHYLPREDNISOLONE ACETATE	1.25
METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
PARAMETHASONE	2.5
PREDNISOLONE	1
PREDNISOLONE ACETATE	1
PREDNISOLONE SODIUM PHOSPHATE	1
PREDNISOLONE SODIUM SUCCINATE	1
PREDNISONE	1
PREDNISONE ACETATE	1
TRIAMCINOLONE	1.25
TRIAMCINOLONE ACETATE	1.25
TRIAMCINOLONE ACETONIDE	1.25

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

Frequency Factors	
Frequency	**Factor**
BID	2
BIW	2/7
CONTINUOUS	1
HS	1
OAM	1/30
Once	1
PRN	null
Q2H	12
Q2W	1/14
Q3H	8
Q3M	1/84
Q3MO	1/84
Q3w	1/21
Q4H	6
Q4W	1/28
Q6H	4
Q8H	3
QAM	1
QD	1
QH	24
QHS	1
QID	4
QM	1/30
QOD	1/2
QPM	1
QW	1/7
QWK	1/7
TID	3
TIW	3/7
UNK	null

Frequency Factors	
Frequency	**Factor**
2 TIMES PER WEEK	2/7
3 TIMES PER WEEK	3/7
EVERY 2 WEEKS	1/14
EVERY 3 WEEKS	1/21
EVERY 4 Weeks	1/28
EVERY WEEK	1/7
Prednisone Equivalent Daily Dose (mg)	
Prednisone Equivalent Daily Dose (mg) = Collected Dose (mg) x Conversion Factor x Frequency Factor. The prednisone conversion factors and frequency conversion factors should be rounded to 4 decimal places and the resulting prednisone equivalent dose rounded to 3 decimal places.	

14.6.3. Efficacy

14.6.3.1. PERR

Primary Efficacy Renal Response (PERR)
When all 3 criteria are met at two consecutive assessments, a subject is a PERR responder at the confirmatory assessment. PERR criteria are: • eGFR ≥ 60 mL/min/1.73m2 or no decrease in eGFR from pre-flare of >20% [eGFR ≥ pre-flare eGFR x (0.80)] ; and • uPCR ≤ 0.7; and • Not a Treatment Failure (see Section 14.6.3.3)

14.6.3.2. PERR uPCR and eGFR components

uPCR Responder Criterion for PERR
If uPCR is missing, then responder variable is missing If uPCR is not missing, then If uPCR ≤ 0.7 then responder variable is 1 (Y) If uPCR > 0.7 then responder variable is 0 (N)
eGFR Responder Criterion for PERR
If eGFR is missing then responder variable is missing Else if eGFR is not missing then If eGFR ≥ 60 mL/min/1.73m2 OR eGFR no more than 20% below pre-flare eGFR [eGFR ≥ pre-flare eGFR x (0.80)] then the eGFR responder variable is 1 (Y) Else the eGFR responder variable is 0 (N)

14.6.3.3. Time to First Renal Response Maintained through Week x

Time to First Renal Response Maintained to Week x
The following endpoints are covered by this section: • Time to the first PERR that is maintained through Week 52 • Time to the first PERR that is maintained through Week 104 • Time to the first CRR that is maintained through Week 52. • Time to the first CRR that is maintained through Week 104 The definition is written generically to cover all four endpoints where 'renal response' can represent PERR or CRR, and Week x represents Week 104 or Week 52. The first renal response maintained to Week x refers the earliest response in a series of consecutive renal responses that extends to and includes Week x. If a subject does not have a

Time to First Renal Response Maintained to Week x
renal response at Week x then the Time to First Renal Response that is Maintained to Week x is 0 days. Intercurrent events are incorporated into the renal response endpoints using the IPD/TF/WD=NR strategy. Time to first renal response maintained through Week x is calculated as: *Time to first Renal Response maintained to Week x (days)* = *Date of first of a consecutive series of RR 'responder' outcomes through Week x – treatment start date + 1.*

14.6.3.4. Treatment Failures

Treatment Failures
General Conventions • Treatment failure (TF) rules are only applicable during the double-blind treatment phase from the treatment start date to the discontinuation of investigational product (see definition for IP Discontinuation Date in Section 14.6.1.3). • To accommodate a regulatory request, treatment failure rules post-IP discontinuation will be assessed and reported but will not be included in the intercurrent event strategy. • Treatment failure rules only apply to routes of administration that provide systemic exposure to the medication. • The treatment failure date is the earliest date a treatment failure criterion was met. • Prohibited medications/dosages started on the day the subject **completes** the double-blind treatment phase (Week 104) do not result in TF designation. • Prohibited medications/dosages started on the date of early IP discontinuation are considered a TF. If the prohibited medication/dose starts after the date of withdrawal it will not be part of the TF assessment. • Actual visit date, not target visit date, is used to assess treatment failures. For example, the Week 24 visit (target Day 169) can occur on study day 169 $\pm$ 7 days. If the subject's Week 24 visit occurs on Day 171, the date for Day 171 is used when applying the treatment failure rules. • If a critical visit (Week 24, 76 or 104) is missing then the date is imputed as the target date for the visit (target visit date = treatment start date + visit study day – 1). • Assessment of dose is based on analysis dose. Analysis dose is the sum of all doses given on a single day, accounting for the frequency. For steroids, all systemically administered steroids (SYSTEMIC='Y') given on a single day are converted to a daily prednisone equivalent dose (mg) adjusting for frequency and then summed for a total daily dose.

Treatment Failures

- Generally, only the first instance of each unique TF rule violation type is output programmatically. If this instance is adjudicated as not being a TF then the clinical adjudicators will review the entirety of the relevant concomitant medication records to assess if the subject subsequently became a TF for the same violation type (e.g., prednisone dose > 10mg/kg after Week 24).

Steroids

- Only steroids with systemic routes of administration are included in prednisone dose calculations (SYSTEMIC='Y').

- All systemically administered steroids given on a single day are converted to a daily prednisone equivalent dose (mg) adjusting for frequency and then summed for a total daily dose. There should be an analysis dose created for each CMTYPCD and for total steroid use combining steroid doses across all CMTYPCDs.

- 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.

- Rules pertaining to rescue doses of steroids are specific to the maintenance phase of the study and are identified by a steroid dose >10mg/day.

Systemic Steroids for Renal SLE-related Disease Activity

Identified by
CMTYPCD =158 [Lupus nephritis induction or maintenance therapy] or
CMTYPCD=164 [Corticosteroids for non-renal SLE with concurrent worsening of renal disease]

- Prednisone dose >10mg/day for treatment of a renal flare (with or without concurrent non-renal SLE activity) after the Week 24 visit date will deem the subject a **treatment failure**. [PARAMCD=PRGT1024; PARAM=Prednisone Renal-SLE > 10mg/d after Week 24]

Systemic Steroids for Rescue within 90 days for non-Renal Disease Activity

Identified by
CMTYPCD=165 [Corticosteroids for non-renal SLE without concurrent worsening of renal disease]
or
CMTYPCD=*blank* [Other],

Treatment Failures

or a combination of the two

- 2nd Rescue within 3 months (90 days) of the first rescue (a second occurrence of prednisone > 10mg/day) within 90 days of ending the previous one). [PARAMCD=P2RES90; PARAM=Prednisone 2nd rescue in 90 days]

Systemic Steroids for Non-Renal SLE-related Disease Activity

Identified by
CMTYPCD=165 [Corticosteroids for non-renal SLE without concurrent worsening of renal disease]

The following situations will deem the subject a **treatment failure**.

- Prednisone rescue (>10mg/day) from Week 76 to Week 104. [PARAMCD=PNGT1076; PARAM=Prednisone Non-Renal SLE > 10mg/d from Week 76]
- Rescue (prednisone dose >10mg/day) that cannot be tapered to ≤10mg/day by Day 14 of rescue therapy. [PARAMCD=PNTAP14; PARAM=Prednisone Non-Renal SLE not tapered by Day 14]
- 3 or more rescues (>10mg/day; max of 2 allowed). [PARAMCD=PN3RESC; PARAM=Prednisone Non-Renal >= 3 rescues]
- Rescue dose >20mg/day (on any given day during the 14-day rescue). [PARAMCD=PNRES20; PARAM=Prednisone Non-Renal SLE > 20mg/d]

Systemic Steroids for Non-SLE Disease Activity

Identified by
CMTYPCD=*blank* [Other]

The following situations will deem the subject a **treatment failure**.

- Prednisone rescue (>10mg/day) from Week 76 to Week 104. [PARAMCD=POGT1076; PARAM=Prednisone Non-SLE > 10mg/d from Week 76]
- 4 or more rescues (>10mg/day; max of 3 allowed). [PARAMCD=PO4RESC; PARAM=Prednisone Non-SLE >= 4 rescues]
- Rescue (>10mg/day) that cannot be tapered to ≤10mg/day by Day 14 of rescue therapy. [PARAMCD=POTAP14; PARAM=Prednisone Non-SLE not tapered by Day 14]
- Maximum dose (=60mg) >3 days in duration. [PARAMCD=POMAX3; PARAM=TF Prednisone Non-SLE =60mg for > 3 days consecutively]
- Rescue dose >60mg/day (the max on any given day during the 14-day period). [PARAMCD=PORESC60; PARAM=Prednisone Non-SLE >60mg/d during 14-day period]

Anti-Malarials

- Starting any new anti-malarial treatment after the Week 24 visit date will deem the subject a **treatment failure**. Select all records with CMCAT='ANTIMALARIALS' with a start date after the Week 24 visit date if there was no record of an agent in the same class (CMCAT) being taken from baseline through Week 24. Exclude any records with non-systemic routes of administration. [PARAMCD=NEWAM24; PARAM=New Anti-malarial after Week

Treatment Failures

24]

- An anti-malarial treatment will be considered new if the subject did not receive the anti-malarial at any time in the interval from baseline through the Week 24 visit date.
- Treatment failure date will be the anti-malarial start date occurring post the Week 24 visit date that resulted in treatment failure.
- An anti-malarial may be replaced by another anti-malarial at any time during the study.
- A dose change is allowed during the study if the anti-malarial treatment was initiated by Week 24 visit

Immunosuppressant/Immunomodulatory agents

IV Cyclophosphamide, mycophenolate, and azathioprine (AZA) are part of subject's induction/maintenance regimen. Immunosuppressant doses provided in grams (g) should be converted to milligrams (mg) by multiplying by 1000. The term MMF will be used to represent all forms of mycophenolate (i.e., mycophenolate mofetil, mycophenolate sodium, mycophenolic acid) collectively. Rules around their use are listed below:

- Azathioprine (AZA) taken for maintenance therapy is permitted. Doses > 200mg/day will result in **treatment failure**. [PARAMCD=AZADOSE; PARAM=AZA >200mg/day]
- Doses of mycophenolate mofetil or mycophenolic acid > 3g/day (i.e., 3000mg/day) or mycophenolate sodium > 2160 mg/day will result in **treatment failure**. [PARAMCD=MMFDOSE; PARAM=MMF >3g or Mycophenolate >2160mg]
- MMF administered intravenously (IV) will result in **treatment failure**. [PARAMCD=MMFIV; PARAM=Mycophenolate taken IV]
- Switching maintenance therapy from AZA to MMF or MMF to AZA due to toxicity is permitted. Replacing AZA with MMF or MMF with AZA due to insufficient disease control will constitute treatment failure. Instances of AZA to MMF/MMF to AZA switches should be **output for clinical adjudication** to identify cases of lack of efficacy. [PARAMCD=MNTSWTCH; PARAM=AZA to MMF/MMF to AZA switch for lack of efficacy]. Instances of using MMF for maintenance post CYC induction without first attempting AZA should be **output for clinical adjudication** to assess potential of using MMF as new induction. [PARAMCD=MMFNEWID; PARAM=MMF as new Induction post IV CYC]
- Restarting cyclophosphamide (CYC) therapy after attempting maintenance therapy (i.e., starting AZA or MMF) would constitute a **treatment failure**. Select first record of CYC that occurs after use of AZA or MMF. [PARAMCD=CYCNEWID; PARAM=New CYC induction after attempting maintenance]
- Replacement due to toxicity/lack of availability will be assessed during clinical adjudication for switches between AZA and mycophenolate (all forms).

The following rule applies to all other immunosuppressants (not CYC, AZA, or mycophenolate):

- Starting a new immunosuppressant after baseline will deem the subject a **treatment failure**. Note, immunosuppressants administered as topical, conjunctival, or other non-systemic routes are allowed at any time. Select all records with CMCAT='IMMUNOSUPPRESSANT' with a start date on or after the IP start date (TRTSDT). Exclude any records with non-systemic routes of administration. [PARAMCD=NEWIM; PARAM=New Immunosuppressant post-baseline]

Treatment Failures
Angiotensin Pathway Antihypertensives • Starting a new angiotensin pathway antihypertensive (ACE inhibitor, angiotensin receptor blocker) treatment after Week 24 absent any use from baseline through the Week 24 visit will deem the subject a **treatment failure**. • Replacing an angiotensin pathway antihypertensive or titrating a new agent to dose is allowed. • Select all records with CMCAT='ACE' with a start date after the Week 24 visit date if there was no record of an agent in this class (CMCAT) being taken from baseline through Week 24. [PARAMCD=NEWACE24; PARAM=New ACE/ARB after Week 24] **Prohibited medications/non-Drug Therapies** • Date of treatment failure is date subject started Prohibited medication/non-Drug Therapy. In addition to the rules defined for steroids, antimalarials, angiotensin pathway inhibitors, and immunosuppressants, the following medications and therapies are forbidden at any time during 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.] • Anti-TNF therapy (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, infliximab). • Other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist [anakinra], tocilizumab). • Intravenous immunoglobulin (IVIG). • Plasmapheresis • Select all records with CMCAT='PROHIBITED' and append all records from Medical Surgical Procedures form listed as 'Plasmapheresis'. Note the surgical procedures are in the SURGERY dataset, variable SPTERM (verbatim text, not coded so will need to check for misspellings also). [PARAMCD=PROHIB; PARAM=Prohibited Medication]

14.6.3.5. CRR

Complete Renal Response (CRR)
When all 3 criteria are met at two consecutive assessments, a subject is a CRR responder at the confirmatory assessment. CRR criteria are: • eGFR no more than 10% below pre-flare GFR [eGFR ≥ pre-flare eGFR x (0.90)] or within normal range (eGFR ≥ 90 mL/min/1.73m2); and • uPCR < 0.5; and • Not a Treatment Failure (see Section 14.6.3.3)

14.6.3.6. CRR uPCR and eGFR components

uPCR Responder Criterion for CRR
If uPCR is missing, then responder variable is missing If uPCR is not missing, then If uPCR < 0.5 then responder variable is 1 (Y) If uPCR ≥ 0.5 then responder variable is 0 (N)
eGFR Responder Criterion for CRR
If eGFR is missing, then responder variable is missing Else if eGFR is not missing then If eGFR is within the normal range (eGFR ≥ 90 mL/min/1.73m) OR eGFR ≥ pre-flare eGFR x (0.90) then the eGFR responder variable is 1 (Y) Else the eGFR responder variable is 0 (N)

14.6.3.7. Renal Worsening

Renal Worsening
Renal worsening is the development of increased proteinuria and/or impaired renal function defined as follows: <u>Increased Proteinuria (using spot urine)</u> A reproducible increase in 24-hour urine protein levels (as measured in uPCR) to: • >1g if the baseline value was <0.2g OR • >2g if the baseline value was between 0.2g and 1g OR • More than twice the value at baseline if the baseline value was >1g

Renal Worsening

Impaired Renal Function

A reproducible decrease in GFR of >20% accompanied by at least one of the following: proteinuria (>1), RBC casts, WBC casts.

The definition above expresses proteinuria in g/24-hour which is a 1:1 equivalent to proteinuria assessed using the urine protein:creatinine ratio (uPCR) in mg/mg (i.e., 1 g/24-hours = 1 mg/mg).

GFR is estimated from serum creatinine by the simplified MDRD formula [Levey , 2006] and will be used for the renal function assessments at all study visits,

eGFR = 175 x serum creatinine$^{-1.154}$x Age$^{-0.203}$ x [1.212 if Black] x [0.742 if Female]

where serum creatinine concentration is expressed in mg/dL.

"Reproducible" requires the criterion to be met at two consecutive visits, including unscheduled visits and the 8-week Follow-up.

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

Criterion	Parameter	SI Dataset LBTESTCD
Proteinuria	Urine Protein:Creatinine Ratio (mg/mg)	PRTCRT_URQ
GFR	estimated GFR by the MDRD equation (mL/min)	GFRMDR_PLR
RBC cellular casts	RBC cellular casts	RBCSTM_URQ
WBC cellular casts	WBC cellular casts	WBCSTM_URQ

14.6.3.8. End Stage Renal Disease (ESRD)

End Stage Renal Disease (ESRD)

ESRD is an adjudicated event and is defined as the need for chronic dialysis or renal transplantation. Chronicity of dialysis is defined as need for it for at least 90 days. Once ESRD is flagged, it should be flagged for all subsequent observed visits.

If the subject died or is lost to follow up shortly after initiation of dialysis, pre-existing renal function and intention of dialysis (chronic vs. acute renal insufficiency management) will be taken into consideration while adjudicating ESRD event.

14.6.3.9. Doubling of Serum Creatinine

Doubling of Serum Creatinine

Doubling of serum creatinine is defined as a value greater than or equal to double the baseline value that is confirmed with a second consecutive measurement at least 3 weeks later; there can

Doubling of Serum Creatinine
be no values between the first and confirmatory assessment that do not meet the doubling criteria. Since the final serum creatinine value in the double-blind period will not have a second measurement in the period to confirm the result, a rule will be applied such that if the Week 100/visit prior to the final value is greater than or equal to double the baseline value, then the Week 104/final double blind visit result will be considered a confirmed doubling.

14.6.3.10. ORR

Ordinal Renal Response (ORR)
Complete Renal Response (CRR) • uPCR < 0.5; and • eGFR no more than 10% below *pre-flare* GFR [eGFR ≥ pre-flare eGFR x (0.90)] or within normal range (eGFR ≥ 90 mL/min/1.73m2); and • Not a Treatment Failure [1]

Ordinal Renal Response (ORR)

Partial Renal Response (PRR)

- ≥ 50% decrease from baseline in uPCR and one of the following: value <1 if baseline ≤3, or value <3 if the baseline was >3; and
- eGFR no more than 10% below *baseline* GFR [eGFR ≥ baseline eGFR x (0.90)] or within normal range (eGFR ≥ 90 mL/min/1.73m2); and
- Not a Treatment Failure [1]

No Response

- Not meeting criteria for either complete or partial renal response

[1] Treatment failure is defined in Section 5.5 and Section 5.6 of the protocol and further described in Section 14.6.3.3 of this RAP.

The ORR at Week 104 is defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit. Table 13 provides the derived primary Week 104 renal response based on the combination of possible responses at Week 100 and 104.

Table 13 Ordinal Renal Response Derived from Week 100 and Week 104

Week 100	Week 104	ORR Endpoint at Week 104*
Complete	Complete	Complete
Complete	Partial	Partial
Partial	Complete	Partial
Partial	Partial	Partial
Complete	No Response	No Response
Partial	No Response	No Response
No Response	Complete	No Response
No Response	Partial	No Response
No Response	No Response	No Response

*Requires a response at Week 100 that is reproduced at Week 104.

Ordinal Renal Response (ORR)

Example of the Ordinal Renal Response Endpoint Derivation

The example in Table 14 illustrates the following:

- Imputation of a missing lab component at a visit (i.e., missing eGFR at Week 100 and uPCR at Week 104)
- Indicator variables for response criterion met within a visit (Y or N; shown in black)
- Imputed indicator variable for missing lab component (Y or N; shown in parentheses)
- Indicator variables for renal response category (complete, partial, or no response) met within a visit (Y or N; shown in ***bold italic***). Complete and partial response categories are assessed independently.
- Ordinal Renal Response at the visit (complete, partial, or no response; shown in ***bold italic*** in

Ordinal Renal Response (ORR)

last row within visit column); each visit is assessed independently.

- Confirmed Ordinal Renal Response at Week 104 (complete, partial, or no response; shown in **bold** last row/last column) based on Week 100 and Week 104 as detailed in Table 13.

Table 14 Example of Renal Response Endpoint Derivation including Imputation due to Missing uPCR at Week 104

	Week 96	Week 100 (Imputed)	Week 104 (Imputed)	ORR at Week 104
CRR				
eGFR no more than 10% below *pre-flare* or w/in NR	Y	Missing (Y)	Y	
uPCR < 0.5	Y	N	Missing (N)	
Not a Treatment Failure	Y	Y	Y	
Complete Response**		***N***	***N***	
PRR				
eGFR no more than 10% below *baseline* or w/in NR	Y	Missing (Y)	Y	
≥ 50% decrease from baseline in uPCR which is <1 if baseline ≤3, or <3 if the baseline was >3*	Y	Y	Missing (Y)	
Not a Treatment Failure	Y	Y	Y	
Partial Response**		***Y***	***Y***	
NRR				
Not meeting criteria for either complete or partial renal response	N	N	--	
No Response		***N***	***N***	
Ordinal Renal Response		***Partial***	***Partial***	**Partial**

*If baseline uPCR is missing such that the %decrease from baseline cannot be calculated, then the ordinal endpoint will be treated as missing and the subject will not contribute to the analysis.

**Requires a 'Y' indicating criterion met for each component within the response category (complete or partial) at the visit to be a responder for that category.

14.6.3.11. ORRUS

Ordinal Renal Response including Urinary Sediment (ORRUS)

Ordinal renal response including urinary sediment component (ORRUS): measured by complete, partial or no response at Week 104 defined as follows:

Complete Renal Response including urinary sediment (CRRUS):

- Complete renal response (as defined in Section 14.6.3.10

AND

-Inactive urinary sediment [< 5 RBCs/hpf and < 5 WBCs/hpf (or within the reference range of the laboratory)]; and no cellular casts (no RBC or WBC casts)

Partial Renal Response including urinary Sediment (PRRUS):

-Partial response (as defined in Section 14.6.3.10)

AND

-[RBCs/hpf ≥ 50% reduction from baseline or < 5 RBCs/hpf (or within the normal reference range for the central laboratory)]; and no RBC casts

No Renal Response:

-Not meeting criteria for either complete or partial renal response above.

14.6.3.12. ORRUS using cGFR at Week 104

Ordinal Renal Response including Urinary Sediment using calculated GFR (ORRUS using cGFR)

Ordinal renal response including urinary sediment component (ORRUS) and using calculated (vs. estimated) GFR: measured by complete, partial or no response at Week 104 defined as follows:

Complete Renal Response including urinary sediment (CRRUSC):

-Complete renal response (as defined in Section 14.6.3.9) using calculated GFR with the exception of the pre-flare assessment which uses the estimated GFR since cGFR was not measured pre-flare:

- cGFR no more than 10% below pre-flare eGFR [cGFR ≥ pre-flare eGFR x (0.90)] or within normal range (cGFR ≥ 90 mL/min/1.73m2); and

AND

-Inactive urinary sediment [< 5 RBCs/hpf and < 5 WBCs/hpf (or within the reference range of the laboratory)]; and no cellular casts (no RBC or WBC casts)

Partial Renal Response including urinary Sediment (PRRUSC):

-Partial response (as defined in Section 14.6.3.9) using calculated GFR

Ordinal Renal Response including Urinary Sediment using calculated GFR (ORRUS using cGFR)
AND -[RBCs/hpf ≥ 50% reduction from baseline or < 5 RBCs/hpf (or within the normal reference range for the central laboratory)]; and no RBC casts No Renal Response: -Not meeting criteria for either complete or partial renal response above. For a complete renal response to be declared at Week 104, a calculated GFR (as defined in RAP Section 14.6.3.12) should be available for both of the Week 100 and 104 assessments. However, if a calculated GFR is only available for one of the timepoints, a complete renal response can be based on estimated GFR for the missing calculated GFR assessment. If calculated GFR is missing for both assessments, then the best response possible will be partial renal response using estimated GFR.

14.6.3.13. Calculated GFR (cGFR)

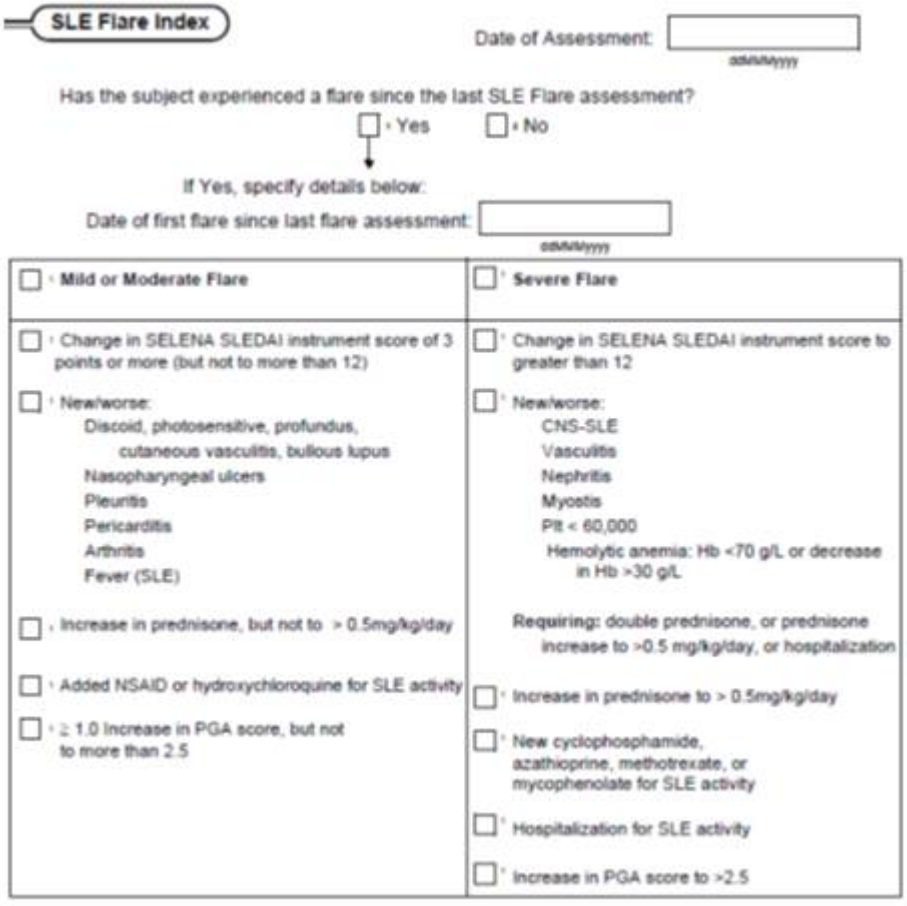
Calculated GFR (cGFR)
At baseline (Week 0), Week 24, 48, 52, 76, 100 and 104 the calculated GFR will be based on the mean of two creatinine clearance values derived from 24-hour urine collection and serum creatinine, one set of measurements taken at the visit and another taken 3 days later. Since the protocol allows the urine collection to be postponed for up to 14 days at the investigator's discretion if menstrual bleeding or a genitourinary tract infection is present at anytime during the 24-hour urine collection period, a 14-day window will be applied to the creatinine clearance values. cGFR = (Week x Value + Week x+3 days Value) / 2, where 'Value' is Creatinine Clearance adjusted for BSA (original units in mL/min/1.73m2).

14.6.3.14. SFI Flares

14.6.3.14.1. SLE Flare Index (SFI) Scoring

SLE Flare Index

CRF Information



Additional SLE Flare Index Log

[MSEV(8)] [MPRED(8)] [MPGA(8)] [SSLED(8)] [SMED(8)]

Date of Flare (ddMMMyyyy)	**Mild or moderate Flare**	Change in SELENA SLEDAI of 3 points or more	Mild new or worsening symptoms	Mild increase in Prednisone to 0.5 mg/kg/day	New added NSAID or Hydroxy-chloroquine	Increase in PGA of > 1	**Severe Flare**	Change in SELENA SLEDAI score to >12	Severe new or worsening symptoms	Hospital-ization	New Azathioprine, Cytoxan, Mycophenolate or Methotrexate	Increase in Prednisone to > 0.5 mg/kg/day	Increase in PGA to > 2.5
[DFLARE($9)]	☐1	☐1 [MSLED(8)]	☐1 [MNEW(8)]	☐1	☐1 [MMED(8)]	☐1	☐1 [SSEV(8)]	☐1	☐1 [SNEW(8)]	☐1 [SHOSP(8)]	☐1	☐1 [SPRED(8)]	☐1 [SPGA(8)]
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1
	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1	☐1

☐ Check here if you need an additional SLE Flare Index Log Page

Derivations

- SFI reports the first mild /moderate or severe flare occurrence since the last visit assessment.
- The SLEDAI criteria will be assessed programmatically to determine if the SELENA SLEDAI criteria for a flare has been met and used for the assessment of flare, irrespective of what was recorded on the SFI form.
- Although there are boxes on the form for the investigator to classify the most recent flare to mild/moderate or severe, the classification will be re-derived from the subcategory scores. Flares originally marked severe will be downgraded to “Not Severe” if the only reason marked is a change in SELENA SLEDAI score to > 12.
    - In this case, if any of the mild/moderate reasons are checked or if the modified SELENA SLEDAI score has a change from previous visit of at least 3, then the flare will be considered Mild/Moderate.
- Flares that are marked mild/moderate where the only reason checked is SELENA SLEDAI increase of at least 3 points but not more than 12 points will be re-derived using the modified SELENA SLEDAI score.
    - If it’s found that the change is not actually ≥ 3, and no other reasons are checked, then the flare will not be counted.

14.6.3.14.2. Time to First SFI Flare Censoring and Disposition Rules

Time to First SFI Flare Censoring and Disposition Rules

The rules described in this section apply to SLE Flares and Severe SLE Flares.

Only post-baseline flares are included in the analysis, therefore flares (not subjects) occurring on the treatment start date should be removed from the analysis set prior to determining the first flare. If a subject is a treatment failure during the period being analyzed, the subject will be considered as having a flare at the time of treatment failure. In the rare situation that a treatment failure occurs on the treatment start date, the treatment failure will be counted as a flare as the assessment of treatment failure is performed post-dose.

Time to first flare is calculated as:

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

After Week 24

For the time to first flare from Week 24 to Week 104, flares (not subjects) occurring on the Week 24 visit date should be removed from the analysis set prior to determining the first flare. If a subject is a treatment failure on the Week 24 visit date, the treatment failure will be counted as a flare at Week 24. Time to first flare from Week 24 to Week 104 is calculated as:

Time to first flare (days) = Date of first flare – Week 24 visit date + 1.

Table 15 Subject Disposition Rules for SLE Flares (Double-Blind Phase)

Subject Disposition	Event Met	Event Date
Subject has a flare or is a treatment failure, whichever occurs first		
Subject has an SLE flare [1]	Yes	Date of first SFI flare
Subject is a treatment failure [1]	Yes	Treatment failure date
Subject does not have a flare and is not a treatment failure		
Subject discontinues IP	No	Censored at last flare assessment prior to IP Discontinuation
Subject withdraws	No	Censored at last flare assessment date
Lost to Follow-up	No	Censored at last flare assessment date
Subject dies	No	Censored at date of death
Subject completes Week 104	No	Censored at the Week 104 study visit
[1] If a subject has a flare and is a treatment failure then the event date is the earliest of the first flare date and the date of treatment failure.		

14.6.3.15. Proteinuria

Proteinuria
For analysis, urine protein in g/24-hour will be approximated by the urine protein:creatinine ratio (uPCR) in mg/mg, also referred to as the PC Ratio which is stored in the variable for the original unit in the SI dataset, not the standard unit which is reported in mg/mmol. In SDTM this variable is mapped to lab test code 'PROTCRT' with units reported as g/g. Note, the value in mg/mg from the SI dataset is the same as the value in g/g in the SDTM dataset as the units cancel out so no data conversion is required. The data will be reported as g/g in the displays. Change from baseline and percent change from baseline values will be derived as described in Section 14.6.1.4 and Section 14.6.1.5.

14.6.3.16. SELENA SLEDAI and SLEDAI-S2K Scoring and Endpoints

SELENA SLEDAI Total and Organ System Domain Scores
SELENA SLEDAI assessments consist of 24 individual items in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed if present (marked 'Yes') at the time of the visit or in the preceding 10 days. The maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No'), but in practice few subjects have scores >45 [Buyon, 2005; Petri, 2005]. Organ system domain scores are the sum of the weights of items within the organ domain as defined in Table 16. If any items are missing, the domain score is the sum of non-missing items.

Table 16 SELENA SLEDAI Scoring

Organ System	Descriptor	Weight	Definition
CNS	Seizure	8	Recent onset (last 10 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
	Psychosis	8	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
	Organic Brain Syndrome	8	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
	Visual Disturbance	8	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate of hemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
	Cranial Nerve	8	New onset sensory or motor neuropathy involving cranial

Organ System	Descriptor	Weight	Definition
	Disorder		nerves. Include vertigo due to lupus.
	Lupus Headache	8	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
	CVA	8	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
Vascular	Vasculitis	8	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
Musculoskeletal	Arthritis	4	More than 2 joints with pain & signs of inflammation (i.e., tenderness, swelling or effusion).
	Myositis	4	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
Renal	Urinary Casts	4	Heme-granular or red blood cell casts.
	Hematuria	4	>5 red blood cells/high power field. Exclude stone, infection, or other causes.
	Proteinuria	4	New onset or recent increase of more than 0.5 g/24 hours.
	Pyuria	4	>5 white blood cells/high power field. Exclude infection.
Mucocutaneous	Rash	2	New or ongoing inflammatory lupus rash.
	Alopecia	2	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
	Mucosal Ulcers	2	New or ongoing oral or nasal ulcerations due to active lupus.
Cardiovascular & Respiratory	Pleurisy	2	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
	Pericarditis	2	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
Immunologic	Low Complement	2	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
	Increased DNA Binding	2	>25% binding by Farr assay or above normal range for testing laboratory.
Constitutional	Fever	1	>38° C. Exclude infectious cause.
Hematologic	Thrombocytopenia	1	<100,000 platelets/mm^3.
	Leukopenia	1	<3,000 white blood cells/mm^3. Exclude drug causes.

SS-S2K- differs from SS [Gladman, 2002] in that it also reflects persistent disease activity in certain descriptors whereas the SS only reflects new or recurrent disease activity (see Table 17).

Table 17 SELENA SLEDAI compared with S2K

Descriptors	Original SELENA SLEDAI	SELENA SLEDAI-2K
Alopecia, Mucous Membrane Lesions, Rash	Items are only scored if they are new or recurrent.	Items are scored if they are present, regardless of history.
Proteinuria	Scored if it is a new onset or a recent increase of more than 0.5g/24hr.*	Scored if it was new, recurrent or persistent (i.e., any result >0.5g/24hr*).

*Urine protein:creatinine ratio of 0.5 mg/mg is considered equivalent to 0.5 g/24 hours for urine protein.

Proteinuria is evaluated using spot-urine protein [represented as urine protein-creatinine ratio (uPCR) or PC Ratio in the laboratory dataset] in lieu of the 24-hour urine collection (see

Section 14.6.3.15). Only proteinuria is programmatically re-scored per the S2K rules as the other clinical descriptors would require subjective assessment by the investigator.

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. In such instances where an item is ticked unknown, LOCF will be used.

14.6.3.16.1. SLEDAI-S2K < 4

SLEDAI-S2K < 4		
The SLEDAI-S2K < 4 responder endpoints is defined as :		
Endpoint	**Criterion**	**Responder**
SLEDAI-S2K < 4	SLEDAI-S2K < 4 and not missing	Y
	SLEDAI-S2K ≥ 4	N
	SLEDAI-S2K post-baseline = missing	TF/IP Disc = NR
	S2K baseline = missing	Missing

14.6.3.16.2. SLEDAI-S2K Organ System Improvement and Worsening

SLEDAI-S2K Organ System Improvement and Worsening
For the SS, each organ system (as defined in Section 14.6.3.16.2) will be evaluated for improvement and worsening as follows:

Endpoint	**Criterion**	**Responder**
Improvement	Organ score post-baseline – baseline organ score<0	Y
	Organ score post-baseline – baseline organ score ≥0	N
	Organ score post-baseline = missing	TF/IP Disc = NR
	Organ score baseline = missing	Missing
Worsening	Organ score post-baseline – baseline Organ score <0	N
	Organ score post-baseline – baseline Organ score ≥ 0	Y
	Organ score post-baseline = missing	LOCF of worsening status
	Organ score baseline = missing	Missing

14.6.3.16.3. SLEDAI-S2K excluding renal items

SLEDAI-S2K excluding renal items
SLEDAI-S2K score excluding renal items will be computed by adding up the score of all items marked as present in the SLEDAI-S2K except for the Renal items (urinary casts, hematuria, pyuria, proteinuria). See Section 14.6.3.16.3 for further details.

14.6.3.17. Prednisone

14.6.3.17.1. Baseline Prednisone Dose

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

14.6.3.17.2. Prednisone Average Daily Dose Since Previous Visit

Prednisone Average Daily Dose Since Previous Visit
The prednisone average daily dose since previous visit will be calculated at every 4-week visit post-baseline (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104)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) and rounding the result to 3 decimal places. 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 one of the 4-week visit intervals, the average daily dose for that interval will be calculated as the sum of all prednisone doses since the previous visit up to and including the date of withdrawal, IP discontinuation date or date of treatment failure, whichever is earlier. See RAP Section 7.3.1 for imputation rules for this endpoint.

14.6.3.18. SLICC/ACR Damage Index Scoring

SLICC/ACR Damage Index Scoring
• The SLICC/ACR Damage Index (SDI) score is the sum of all points for items marked as present on the instrument. • The SDI increases over time. Once a subject meets the criteria for positive scoring of an item, that item should always be marked as present, even if the subject subsequently recovered. • In the event the SLICC/ACR Damage Index is scored inconsistently (a decrease relative to previous items has occurred) and the data are unable to be queried and/or corrected, a worst observation carried forward (WOCF) approach will be used at the item level for the SLICC/ACR damage Index questions. The WOCF approach will carry baseline forward if there is a decrease from baseline. Note: renal items are an exception such that if a subject had scored points for glomerular filtration rate (GFR) or proteinuria which are each 1-point items and progresses to end stage renal disease (ESRD), a 3-point item, then GFR and proteinuria should no longer be scored, and the renal total would be assigned a value of 3 for ESRD. The WOCF values will be used to calculate the total score. • **Worsening** is defined as an increase from baseline in SLICC/ACR Damage Index score

SLICC/ACR Damage Index Scoring

[(post-baseline visit score – baseline score)] >0.

•

SLICC/ACR Damage Index for Systemic Lupus Erythematosus

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 >1)	1(2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria >3.5 gm/24hours	1
Or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1(2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months, or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (eg loss of digit or limb) (score 2 if >1 site)	1(2)
Venous thrombosis with swelling, ulceration, or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if >1 site)	1(2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1

SLICC/ACR Damage Index Scoring	
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if >1)	1(2)
Osteomyelitis	1
Skin	
	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1(2)

([SLICC, 1996; and Gladman, 1996]

14.6.4. Safety

Adverse Events

AEs of Special Interest

- Adverse Events of Special Interest (AESIs) will be reported based on the current version of the Program Safety Analysis Plan (PSAP) at the time of reporting. See the PSAP (PSAP, 2018) for a list of preferred term definitions for each category of AESI. AESIs currently include malignant neoplasms, post-infusion systemic reactions, infections, depression/suicide/self-injury, and fatalities.

Laboratory Parameters

- If a laboratory value is expected to have a numeric value for summary purposes, but the numeric value is missing, and the character value starts with '<x' or '>x' (or indicated as less than x or greater than x in the comment field), the numeric version of the value must be derived. The derived value will be set to one unit less (if <x) or more (if >x) based on the number of significant digits in the observed values.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

14.6.5. Pharmacokinetic

Belimumab Concentration Units

Belimumab concentration data should be reported as ug/mL in the data displays. If the data is transferred in ng/mL it should be converted to ug/mL using the following formula:

Belimumab Concentration Units
ug/mL = ng/mL x 1000

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Completion of the Double-Blind treatment period is defined as completing through the Week 104 visit without permanent discontinuation of study treatment. Similarly, completion through the end of Open Label is defined as completing through the Open Label Week 28 visit. • Withdrawn subjects were not replaced in the study. • Data from participants who were withdrawn from the study will be listed and planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Section 14.3.1 or will be summarised as withdrawal visits.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated using a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
LOCF	• For the LOCF imputation, missing values will be carried forward from the previous, non-missing assessment per the intercurrent event strategy being employed for the endpoint.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	○ Partial stop dates will not be imputed. • Partial and completely missing start or end dates will remain partial/missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications /Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day

Element	Reporting Detail
	(dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings. • Completely missing start or end dates will remain missing.

14.8. Appendix 8: Laboratory Toxicity Grades

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

(continued)

*ULN = Upper Limit of Normal.

Modified from (DMID) Adult Toxicity Tables, 2001

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

(continued)

Modified from (DMID) Adult Toxicity Tables, 2001

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

(continued)

*[Goldfarb, 2001; Yamani, 2001; and Eibl, 1995).

Modified from (DMID) Adult Toxicity Tables, 2001

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria:				
Dipstick: Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 - < 10 RBC/hpf	Gross, No clots ≥ 10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required

(continued)

RBC = red blood cell; hpf = high power field.

Modified from (DMID) Adult Toxicity Tables, 2001

14.9. Appendix 9: 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 PopPK model that characterizes the PK disposition of belimumab following intravenous administration in adult subjects with active lupus nephritis
- Evaluate the potential effect of selected covariates including proteinuria on belimumab PK parameters
- Estimate and summarize individual subject PK parameters and document these for the purposes of any subsequent exposure-response (PK/PD) analysis

14.9.1. 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.

14.9.2. 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.

A previously generated NONMEM data set of PK data from adult systemic lupus erythematosus (SLE) patients (without active lupus nephritis) may be merged with the PK data from this study to allow for a pooled PopPK analysis, if deemed appropriate.

Data set specifications guiding the generation of the NONMEM input data set will be reported together with the PK results.

14.9.3. Model Development

A population pharmacokinetic model for IV belimumab in adult SLE patients without active nephritis (SLE PopPK model) was developed [Struemper, 2013; model version with continuous proteinuria covariate] and will be the starting point for this population PK analysis.

Initially, the appropriateness of the structure and parameters of the original SLE PopPK model for representing also the PK data form this study will be explored by applying (i) either the complete set of parameters (MAXEVAL=0 option) to the PK data from this study or (ii) by re-estimating only specific parameters (e.g. only for proteinuria effect) and leaving the other parameters fixed to the values of the SLE PopPK model.

If the parameter set of the SLE PopPK model applied to the PK data from this study results in substantial bias or if a further exploration of the covariate effect in the lupus nephritis population is deemed necessary, the parameters of the SLE PopPK model will be re-estimated for the PK data from this study alone and/or for a pooled SLE/lupus nephritis data set. Covariate not available for this study but present in the SLE PopPK model may be removed from the PopPK model. The set of remaining covariate-parameter relationships of the SLE PopPK model may then be reduced using the full model approach [Gastonguay, 2011]. Lastly, a model refinement step may be applied including a qualification and possible modification of the PopPK model's random effect structure.

14.9.4. 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)

14.9.5. Endpoints

Along with model PK parameters (e.g. central clearance etc.) the following parameters, if appropriate relative to the final model structure, will be derived, listed for each subject and summarized:

- Steady-state trough concentration: Cmin (µg/mL)
- Steady-state maximal concentration: Cmax (µg/mL)
- Steady-state area under the serum drug time-concentration curve and/or average concentration for the dosing interval: AUC0-τ (day*µg/mL) and/or Cavg (µg/mL)

- Distribution half-life: t1/2α (day)
- Terminal half-life: t1/2β (day)
- Steady-state volume of distribution: Vss (mL)

14.9.6. Simulations

If one or more covariate effect of clinical interest for lupus nephritis subjects is identified, simulations to characterize the impact of any such covariate effect on belimumab exposure may be performed.

14.10. Appendix 10: B Cells

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

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

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

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

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

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

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

Given:

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

Then:

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

14.10.2. B Cell Mappings

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
FLWTRANS	CD19	CD19	CD19E	CD19_Number of events	EVENTS
FLWPLSM	CD20	CD20	CD20CD19	CD20_Percentage	%
FLWPLSM	CD20	CD20	CD20	CD20_Number of events	EVENTS
FLWPLSM	CD20	CD20	CD20E	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

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)
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
FLWTRANS	CDX199	CD19+ CD24b+ CD38b+ CD27	CDX19919	CD19+ CD24b+ CD38b+ CD27/CD19+	%
FLWTRANS	CDX199	CD19+ CD24b+ CD38b+ CD27	CDX199	CD19+ CD24b+ CD38b+ CD27	CELLS/CUMM
FLWTRANS	CDX199	CD19+ CD24b+ CD38b+ CD27	CDX199E	CD19+ CD24b+ CD38b+ CD27 Number of Events	EVENTS

14.10.3. 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)
CDX13619	CD20+ CD27-/CD19+	%	Naive CD19+CD20+CD27- (%CD19)
CDX137	CD20+ CD27+	GI/L	Memory CD19+CD20+CD27+ (/uL)
CDX13719	CD20+ CD27+/CD19+	%	Memory CD19+CD20+CD27+ (%CD19)
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)
CDX199N	CD19+ CD24b+ CD38b+ CD27-	GI/L	Transitional CD19+CD24b+CD38b+CD27- Normalized (COUNT/mL)

[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.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
aCL	Anti-cardiolipin
ACR	American College of Rheumatology
ACE	Angiotensin Converting Enzyme
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
ANA	Anti-nuclear Antibody
ANCOVA	Analysis of Covariance
anti-C1q	Anti-C1q Antibody
anti-dsDNA	Anti-double-stranded DNA
anti-Sm	Anti-Smith Antibody
A&R	Analysis and Reporting
ARB	Angiotensin Receptor Antagonists/Blockers
ATC	Anatomical Therapeutic Chemical
AZA	Azathioprine
BLyS	B Lymphocyte Stimulator
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
cm	Centimeter
CMQ	Customized MedDRA Query
CPMS	Clinical Pharmacology Modelling & Simulation
CRR	Complete Renal Response
CS	Clinical Statistics
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
CYC	Cyclophosphamide
DBF	Database Freeze
DBR	Database Release
DC	Discontinue
dL	Deciliter
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESRD	End Stage Renal Disease

Abbreviation	Description
FACS	Florescence Activated Cell Sorting
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HDCS	High Dose Corticosteroids
HZ	Herpes Zoster
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMMS	International Modules Management System
IP	Investigational Product
IPD	Investigational Product Discontinuation
ISN	International Society for Nephrology
IU	International Unit
IV	Intravenous
GUI	Guidance
kg	Kilogram
KU	International Unit for enzymatic activity
L	Litre
LLN	Lower Limit of Normal
LN	Lupus Nephritis
LOC	Last Observation Carries Forward
LOQ	Limit of Quantification
LS	Least Squares
MAH	Marketing Authorization Holder
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MMF	Mycophenolate Mofetil
MMRM	Mixed Model Repeated Measures
M=NR	Missing = Non-Responder
MITT	Modified Intent-To-Treat
ng	nanogram
NMSC	Mon-melanoma Skin Cancer
NQ	Non-quantifiable
NR	Non-Responder
OI	Opportunistic Infections
OR	Odds Ratio

Abbreviation	Description
ORR	Ordinal Renal Response.
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PERR	Primary Efficacy Renal Response
PGA	Physician's Global Assessment
PISR	Post-Infusion Systemic Reactions
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
PSAP	Program Safety Analysis Plan
PT	Preferred Term
PSRQ	Possible Suicidality Related Questionnaire
QC	Quality Control
Q_L	Likelihood Ratio chi-square
Q_P	Pearson chi-square
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RPS	Renal Pathology Society
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SBC	Schwarz Bayesian criterion
SAE	Serious Adverse Event
SFI	SLE Flare Index
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SDI	SLICC Damage Index
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
SOP	Standard Operation Procedure
SRT	Safety Review Team
TA	Therapeutic Area
TB	Tuberculosis
TF	Treatment Failure
TFL	Tables, Figures & Listings
ULN	Upper Limit of Normal
uPCR	Urine Protein-Creatinine Ratio
WD	Withdraw

14.11.2. Trademarks

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14.12. Appendix 12: List of Data Displays

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.52	1.01 to 1.02
Efficacy	2.01 to 2.70	2.01 to 2.39
Safety	3.01 to 3.83	3.01 to 3.06
Biomarker	4.01 to 4.15	4.01 to 4.12
Pharmacokinetic	5.01 to 5.05	5.01 to 5.05
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

14.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced based on the display number and example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

14.12.3. Deliverables

Delivery [Priority] [1]	Description
DB [1]	Double Blind Statistical Analysis Complete – Primary SAC

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01.	Randomized	NS1	Randomization by Country and Site ID	EudraCT, IDSL	DB [1]
1.02.	Screened	SP1	Populations	IDSL	DB [1]
1.03.	Screened		Reasons for Failing Screening		DB [1]
Population Analysed					
1.04.	MITT		Subject Status by Week 104		DB [1]
1.05.	MITT	ES1	Subject Status and Reason for Study Withdrawal	IDSL	DB [1]
1.06.	MITT		Study Withdrawal by Visit		DB [1]
1.07.	MITT	SD1	Investigational Product Status and Reasons for Discontinuation	ICH E310.1, IDSL	DB [1]
1.08.	MITT		Investigational Product Discontinuation by Visit		DB [1]
Protocol Deviation					
1.09.	MITT	IE3	Inclusion/Exclusion Criteria Deviations		
1.10.	MITT	DV1	Important Protocol Deviations	ICH E310.2, IDSL	DB [1]
1.11.	MITT	SP2	Exclusions from the Per Protocol Population	IDSL	DB [1]
Demographic and Baseline Characteristics					
1.12.	MITT		Shift Table of Differences between Stratification Factors at Screening and as Randomized		
1.13.	MITT	DM1	Demographic and Baseline Characteristics	ICH E3 12.5, FDAAA, EudraCT, IDSL	DB [1]
1.14.	Randomized	DM11	Summary of Age Ranges	EudraCT, IDSL	DB [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.15.	MITT	DM6	Race and Racial Combination Details	IDSL	DB [1]
1.16.	MITT		Vital Signs at Baseline		DB [1]
1.17.	MITT	MH4	Current Medical Conditions	ICH E3 12.5	DB [1]
1.18.	MITT	MH4	Past Medical Conditions	ICH E3 12.5	DB [1]
1.19.	MITT		Stratification Factors at Baseline		DB [1]
1.20.	MITT		Baseline Disease Activity		DB [1]
1.21.	MITT		Pre-Flare Serum Creatinine and eGFR Values		DB [1]
1.22.	MITT		Lupus Nephritis Therapy History		DB [1]
1.23.	MITT		ACR Classification Criteria at Baseline		DB [1]
1.24.	MITT		SLEDAI-S2K Organ and Item Involvement at Baseline		DB [1]
1.25.	MITT		Immunoglobulin Levels at Baseline		DB [1]
1.26.	MITT		Autoantibody Levels at Baseline		DB [1]
1.27.	MITT		Complement Levels and Other Biomarkers at Baseline		DB [1]
1.28.	MITT		B Cells at Baseline		DB [1]
1.29.	MITT		C-SSRS Responses by Behaviour and Ideation Components - Pre-treatment		DB [1]
Prior and Concomitant Medications					
1.30.	MITT		Allowable SLE and LN Medication Usage at Baseline		
1.31.	MITT		Concomitant Medications by ATC Level 1 and ATC Level 4 Term		DB [1]
1.32.	MITT		Concomitant Medications by ATC Level 4 and Preferred Term		DB [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.33.	MITT		First Medication Usage Resulting in Treatment Failure Designation through Week 104		DB [1]
1.34.	MITT	EX3	Exposure to Study Treatment through Week 104	ICH E3 16.2.5Dose and/or time on treatment, as applicable. IDSL	DB [1]
Subgroup Displays					
1.35.	MITT		Demographic and Baseline Characteristics by Gender		DB [1]
1.36.	MITT		Baseline Disease Activity by Gender		DB [1]
1.37.	MITT		Allowable SLE Medication Usage at Baseline by Gender		DB [1]
1.38.	MITT		Demographic and Baseline Characteristics by Race Stratification Factor		DB [1]
1.39.	MITT		Baseline Disease Activity by Race Stratification Factor		DB [1]
1.40.	MITT		Allowable SLE and LN Medication Usage at Baseline by Race Stratification Factor		DB [1]
1.41.	MITT		Demographic and Baseline Characteristics by Region		DB [1]
1.42.	MITT		Baseline Disease Activity by Region		DB [1]
1.43.	MITT		Allowable SLE and LN Medication Usage at Baseline by Region		DB [1]
1.44.	MITT		Demographic and Baseline Characteristics by Baseline Anti-dsDNA		DB [1]
1.45.	MITT		Baseline Disease Activity by Baseline Anti-dsDNA		DB [1]
1.46.	MITT		Allowable SLE and LN Medication Usage at Baseline by Baseline Anti-dsDNA		DB [1]
1.47.	MITT		Demographic and Baseline Characteristics by Baseline C3/C4 Levels		DB [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.48.	MITT		Baseline Disease Activity by Baseline C3/C4 Levels		DB [1]
1.49.	MITT		Allowable SLE Medication Usage at Baseline by Baseline C3/C4 Levels		DB [1]
1.50.	MITT		Demographic and Baseline Characteristics by Baseline C3/C4 Levels and Anti-dsDNA	EMA Labeled population	DB [1]
1.51.	MITT		Baseline Disease Activity by Baseline C3/C4 Levels and Anti-dsDNA	EMA Labeled population	DB [1]
1.52.	MITT		Allowable SLE Medication Usage at Baseline by Baseline C3/C4 Levels and Anti-dsDNA	EMA Labeled population	DB [1]
1.53.	MITT		Demographic and Baseline Characteristics by Baseline Body Weight Quartiles		DB [1]
1.54.	MITT		Baseline Disease Activity by Body Weight Quartiles		DB [1]
1.55.	MITT		Allowable SLE Medication Usage at Baseline by Baseline Body Weight Quartiles		DB [1]
1.56.	MITT		Demographic and Baseline Characteristics by Renal Biopsy Subgroup		DB [1]
1.57.	MITT		Baseline Disease Activity by Renal Biopsy Subgroup		DB [1]
1.58.	MITT		Allowable SLE Medication Usage at Baseline by Renal Biopsy Subgroup		DB [1]

14.12.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.01.	MITT		Study Withdrawal by Visit		DB [1]
1.02.	MITT		Investigational Product Discontinuation by Visit		DB [1]

14.12.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Renal Response					
2.01.	MITT		Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.02.	MITT		Logistic Regression Analysis of Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.03.	MITT		Primary Efficacy Renal Response and the 3 Components at Week 104 (IPD/TF/WD=NR)		DB [1]
2.04.	MITT		Disposition of Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.05.	MITT		Primary Efficacy Renal Response and the 3 Components at Week 104 (Hybrid Treatment Policy for Non-TF Intercurrent Events Sensitivity Analysis) (TF/WD=NR)		DB [1]
2.06.	MITT		Primary Efficacy Renal Response and the 3 Components at Week 104 (Treatment Policy for All Intercurrent Events Sensitivity Analysis) (WD=NR)		DB [1]
2.07.	MITT		Primary Efficacy Renal Response at Week 104 (Unadjusted Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]
2.08.	Completer		Primary Efficacy Renal Response at Week 104 (Completer Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]
2.09.	PP		Primary Efficacy Renal Response at Week 104 (Per Protocol Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT		PERR Responder Rate Grid Values with 95% CI for the Difference in Proportions (Tipping Point Analysis of Hybrid Treatment Policy for Non-TF Intercurrent Events)		DB [1]
2.11.	MITT		PERR Responder Rate Grid Values with 95% CI for the Difference in Proportions (Tipping Point Analysis of Treatment Policy for All Intercurrent Events)		DB [1]
2.12.	MITT		Primary Efficacy Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
2.13.	MITT		PERR uPCR Component (uPCR <=0.7) by Visit (IPD/TF/WD=NR)		DB [1]
2.14.	MITT		PERR eGFR Component (eGFR no more than 20% below Pre-flare Value or >= 60 mL/min/1.73m2) by Visit (IPD/TF/WD=NR)		DB [1]
2.15.	MITT		Not a Treatment Failure by Visit (IPD/TF/WD=NR)		DB [1]
2.16.	MITT		Treatment Failure Reason by First Criterion Met While on Treatment		DB [1]
2.17.	MITT		Time to First PERR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.18.	MITT		Kaplan Meier Estimates of Time to First PERR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.19.	MITT		Time to First PERR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]
2.20.	MITT		Kaplan Meier Estimates of Time to First PERR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]
2.21.	MITT		Primary Efficacy Renal Response at Week 104 by Induction Regimen (IPD/TF/WD=NR)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22.	MITT		Primary Efficacy Renal Response at Week 104 by Race Stratification Factor (IPD/TF/WD=NR)		DB [1]
2.23.	MITT		Primary Efficacy Renal Response at Week 104 by Region (IPD/TF/WD=NR)		DB [1]
2.24.	MITT		Primary Efficacy Renal Response at Week 104 by Baseline Anti-dsDNA (IPD/TF/WD=NR)		DB [1]
2.25.	MITT		Primary Efficacy Renal Response at Week 104 by Baseline C3/C4 Levels (IPD/TF/WD=NR)		DB [1]
2.26.	MITT		Primary Efficacy Renal Response at Week 104 by Baseline C3/C4 Levels and Anti-dsDNA (IPD/TF/WD=NR)		DB [1]
2.27.	MITT		Primary Efficacy Renal Response at Week 104 by Baseline Renal Biopsy Subgroup (IPD/TF/WD=NR)		DB [1]
Complete Renal Response					
2.28.	MITT		Complete Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.29.	MITT		Logistic Regression Analysis of Complete Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.30.	MITT		Complete Renal Response and the 3 Components at Week 104 (IPD/TF/WD=NR)		DB [1]
2.31.	MITT		Disposition of Complete Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.32.	MITT		Complete Renal Response and the 3 Components at Week 104 (Hybrid Treatment Policy for Non-TF Intercurrent Events Sensitivity Analysis) (TF/WD=NR)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.33.	MITT		Complete Renal Response and the 3 Components at Week 104 (Treatment Policy for All Intercurrent Events Sensitivity Analysis) (WD=NR)		DB [1]
2.34.	MITT		Complete Renal Response at Week 104 (Unadjusted Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]
2.35.	Completer		Complete Renal Response at Week 104 (Completer Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]
2.36.	PP		Complete Renal Response at Week 104 (Per Protocol Sensitivity Analysis) (IPD/TF/WD=NR)		DB [1]
2.37.	MITT		CRR Responder Rate Grid Values with 95% CI for the Difference in Proportions (Tipping Point Analysis of Hybrid Treatment Policy for non-TF Intercurrent Events)		DB [1]
2.38.	MITT		CRR Responder Rate Grid Values with 95% CI for the Difference in Proportions (Tipping Point Analysis of Treatment Policy for All Intercurrent Events)		DB [1]
2.39.	MITT		Complete Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
2.40.	MITT		CRR uPCR Component (uPCR <0.5) by Visit (IPD/TF/WD=NR)		DB [1]
2.41.	MITT		CRR eGFR Component (eGFR no more than 10% below Pre-flare Value or within Normal Range) by Visit (IPD/TF/WD=NR)		DB [1]
2.42.	MITT		Time to First CRR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.43.	MITT		Kaplan Meier Estimates of Time to First CRR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.44.	MITT		Time to First CRR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.45.	MITT		Kaplan Meier Estimates of Time to First CRR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]
2.46.	MITT		Complete Renal Response at Week 104 by Induction Regimen (IPD/TF/WD=NR)		DB [1]
2.47.	MITT		Complete Renal Response at Week 104 by Race (IPD/TF/WD=NR)		DB [1]
2.48.	MITT		Complete Renal Response at Week 104 by Region (IPD/TF/WD=NR)		DB [1]
2.49.	MITT		Complete Renal Response at Week 104 by Baseline Anti-dsDNA (IPD/TF/WD=NR)		DB [1]
2.50.	MITT		Complete Renal Response at Week 104 by Baseline C3/C4 Levels (IPD/TF/WD=NR)		DB [1]
2.51.	MITT		Complete Renal Response at Week 104 by Baseline C3/C4 Levels and Anti-dsDNA (IPD/TF/WD=NR)		DB [1]
2.52.	MITT		Complete Renal Response at Week 104 by Baseline Renal Biopsy Subgroup (IPD/TF/WD=NR)		DB [1]
PERR at Week 52					
2.53.	MITT		Primary Efficacy Renal Response and the 3 Components at Week 52 (IPD/TF/WD=NR)		DB [1]
2.54.	MITT		Disposition of Primary Efficacy Renal Response at Week 52 (IPD/TF/WD=NR)		DB [1]
2.55.	MITT		Primary Efficacy Renal Response at Week 52 by Induction Regimen (IPD/TF/WD=NR)		DB [1]
2.56.	MITT		Primary Efficacy Renal Response at Week 52 by Baseline C3/C4 levels and Anti-dsDNA (IPD/TF/WD=NR)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Death or Renal-related Event					
2.57.	MITT		Time to Death or Renal-related Event Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.58.	MITT		Event Summary for Time to Death or Renal-related Event (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.59.	MITT		Kaplan-Meier Estimates of Time to Death or Renal-related Event (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.60.	MITT		Time to Death or Renal-related Event by Baseline C3/C4 Levels and Anti-dsDNA (IPD/TF not related to renal disease/WD=Censor)		DB [1]
Ordinal Renal Response					
2.61.	MITT		Ordinal Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.62.	MITT		Ordinal Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
2.63.	MITT		Ordinal Renal Response including Urinary Sediment at Week 104 (IPD/TF/WD=NR)		DB [1]
2.64.	MITT		Ordinal Renal Response at Week 104 by Baseline C3/C4 Levels and Anti-dsDNA (IPD/TF/WD=NR)		DB [1]
SFI Flare					
2.65.	MITT		Time to First Severe SFI Flare (TF=Flare, IPD/WD=Censor)		DB [1]
2.66.	MITT		Kaplan Meier Estimates of Time to First Severe SFI Flare (TF=Flare, IPD/WD=Censor)		DB [1]
2.67.	MITT		Time to First Severe SFI Flare from Week 24 (TF=Flare, IPD/WD=Censor)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.68.	MITT		Kaplan Meier Estimates of Time to First Severe SFI Flare from Week 24 (TF=Flare, IPD/WD=Censor)		DB [1]
uPCR					
2.69.	MITT		uPCR Percent Change from Baseline by Visit While On Treatment (Observed)		DB [1]
2.70.	MITT		uPCR Change from Baseline by Visit While On Treatment (Observed)		DB [1]
Serum Creatinine from Baseline and/or End Stage Renal Disease					
2.71.	MITT		Doubling of Serum Creatinine from Baseline and/or Progression to End Stage Renal Disease (ESRD) by Visit (LO on or prior to IPD/TF CF)		DB [1]
SLEDAI-S2K					
2.72.	MITT		SLEDAI-S2K Change from Baseline by Visit While On Treatment (Observed)		DB [1]
2.73.	MITT		SLEDAI-S2K Change from Baseline Excluding Renal Items by Visit While On Treatment (Observed)		DB [1]
2.74.	MITT		SLEDAI-S2K Score < 4 by Visit (IPD/TF/WD=NR)		DB [1]
2.75.	MITT		SLEDAI-S2K Organ System Improvement by Organ System and Visit among Subjects with Organ System Involvement at Baseline (IPD/TF/WD=No Improvement)		DB [1]
2.76.	MITT		SLEDAI-S2K Organ System Worsening by Organ System and Visit among Subjects with No Organ System Involvement at Baseline (LO on or prior to IPD/TF CF)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prednisone					
2.77.	MITT		Prednisone ≤ 5 mg Average Daily Dose Since Previous Visit (IPD/TF/WD=NR)		DB [1]
2.78.	MITT		Prednisone ≤ 7.5 mg Average Daily Dose Since Previous Visit (IPD/TF/WD=NR)		DB [1]
SLICC					
2.79.	MITT		SLICC/ACR Damage Index Change from Baseline by Visit While on Treatment (Observed with WOCF)		DB [1]
2.80.	MITT		SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit While on Treatment (WOCF)		DB [1]
2.81.	MITT		SLICC/ACR Damage Index Change from Baseline by Visit While on Study (WOCF)		DB [1]
2.82.	MITT		SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit While on Study (WOCF)		DB [1]
Supplementary Analyses					
2.83.	MITT		Renal-related Treatment Failure Reason by First Criterion Met While on Treatment		DB [1]
2.84.	MITT		Treatment Failure Reason for Each Unique Criterion Met While on Study		DB [1]
2.85.	MITT		Ordinal Renal Response including Urinary Sediment and using Calculated GFR at Week 104 (IPD/TF/WD=NR)		DB [1]
2.86.	MITT		Primary Efficacy Renal Response and the 3 Components at Week 104 (Treatment Policy, WD=NR)		DB [1]
2.87.	MITT		Time to Death Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.88.	MITT		Time to End Stage Renal Disease (ESRD) Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.89.	MITT		Time to Doubling of Serum Creatinine Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.90.	MITT		Time to Renal Worsening Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.91.	MITT		Time to Renal Event-related Treatment Failure Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)		DB [1]
2.92.	MITT		Time to Death or Renal-related Event Overall and by Induction Regimen (Treatment Policy)		DB [1]
2.93.	MITT		Time to Death Overall and by Induction Regimen (Treatment Policy)		DB [1]
2.94.	MITT		Time to End Stage Renal Disease (ESRD) Overall and by Induction Regimen (Treatment Policy)		DB [1]
2.95.	MITT		Time to Doubling of Serum Creatinine Overall and by Induction Regimen (Treatment Policy)		DB [1]
2.96.	MITT		Time to Renal Worsening Overall and by Induction Regimen (Treatment Policy)		DB [1]
2.97.	MITT		uPCR Percent Change from Baseline by Visit While On Study (Observed)		DB [1]
2.98.	MITT		uPCR Change from Baseline by Visit While On Study (Observed)		DB [1]
2.99.	MITT		Doubling of Serum Creatinine from Baseline and/or Progression to End Stage Renal Disease by Visit (Observed)		DB [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.100.	MITT		SLEDAI-S2K Change from Baseline by Visit While On Study (Observed)		DB [1]
2.101.	MITT		SLEDAI-S2K Change from Baseline Excluding Renal Items by Visit While On Study (Observed)		DB [1]
2.102.	MITT		SLEDAI-S2K Score < 4 by Visit (Observed)		DB [1]
2.103.	MITT		SLEDAI-S2K Organ System Improvement by Organ System and Visit among Subjects with Organ System Involvement at Baseline [1] (Observed)		DB [1]
2.104.	MITT		SLEDAI-S2K Organ System Worsening by Organ System and Visit among Subjects with No Organ System Involvement at Baseline [1] (Observed)		DB [1]
2.105.	MITT		Prednisone ≤ 5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)		DB [1]
2.106.	MITT		Prednisone ≤ 7.5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)		DB [1]
2.107.	MITT		Prednisone ≤ 5 mg/day Average Daily Dose Since Previous Visit (Observed)		DB [1]
2.108.	MITT		Prednisone ≤ 7.5 mg/day Average Daily Dose Since Previous Visit (Observed)		DB [1]
2.109.	MITT		SLICC/ACR Damage Index Change from Baseline by Visit While On Study (Observed with WOCF)		DB [1]
2.110.	MITT		SLICC/ACR Damage Index Worsening (Change > 0) Compared with Baseline by Visit (Observed)		DB [1]

14.12.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Renal Response					
2.01.	MITT		Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.02.	MITT		Disposition of Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.03.	MITT		Primary Efficacy Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
2.04.	MITT		PERR uPCR Component (uPCR <=0.7) by Visit (IPD/TF/WD=NR)		DB [1]
2.05.	MITT		PERR eGFR Component (eGFR no more than 20% below Pre-flare Value or >= 60 mL/min/1.73m2) by Visit (IPD/TF/WD=NR)		DB [1]
2.06.	MITT		Not a Treatment Failure by Visit (IPD/TF/WD=NR)		DB [1]
2.07.	MITT		Time to First PERR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.08.	MITT		Time to First PERR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]
2.09.	MITT		Odds Ratio of Primary Efficacy Renal Response at Week 104 by Subgroup (IPD/TF/WD=NR)		DB [1]
2.10.	MITT		Odds Ratio of Primary Efficacy Renal Response at Week 104 Sensitivity Analyses (IPD/TF/WD=NR)		DB [1]
Complete Renal Response					
2.11.	MITT		Complete Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	MITT		Disposition of Complete Renal Response at Week 104 (IPD/TF/WD=NR)		DB [1]
2.13.	MITT		Complete Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
2.14.	MITT		CRR uPCR Component (uPCR <0.5) by Visit (IPD/TF/WD=NR)		DB [1]
2.15.	MITT		CRR eGFR Component (eGFR no more than 10% below Pre-flare Value or within Normal Range) by Visit (IPD/TF/WD=NR)		DB [1]
2.16.	MITT		Time to First CRR that is maintained through Week 52 (IPD/TF/WD=NR)		DB [1]
2.17.	MITT		Time to First CRR that is maintained through Week 104 (IPD/TF/WD=NR)		DB [1]
2.18.	MITT		Odds Ratio of Complete Renal Response at Week 104 by Subgroup (IPD/TF/WD=NR)		DB [1]
2.19.	MITT		Odds Ratio of Complete Renal Response at Week 104 by Sensitivity Analyses (IPD/TF/WD=NR)		DB [1]
PERR at Week 52					
2.20.	MITT		Disposition of PERR at Week 52 (IPD/TF/WD=NR)		DB [1]
Death or Renal-related Event					
2.21.	MITT		Time to Death or Renal-related Event (IPD/TF not related to renal disease/WD=Censor)		DB [1]
Ordinal Renal Response					
2.22.	MITT		Ordinal Renal Response by Visit (IPD/TF/WD=NR)		DB [1]
SFI Flare					
2.23.	MITT		Time to First Severe SFI Flare (TF=Flare, IPD/WD=Censor)		DB [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.24.	MITT		Time to First Severe SFI Flare from Week 24 (TF=Flare, IPD/WD=Censor)		DB [1]
Proteinuria					
2.25.	MITT		uPCR Percent Change from Baseline by Visit While on Treatment (Observed)		DB [1]
2.26.	MITT		uPCR Change from Baseline by Visit While on Treatment (Observed)		DB [1]
Serum Creatinine from Baseline and/or End Stage Renal Disease					
2.27.	MITT		Doubling of Serum Creatinine from Baseline and/or Progression to End Stage Renal Disease (ESRD) by Visit (LO on or prior to IPD/TF CF)		DB [1]
SLEDAI-S2K					
2.28.	MITT		SLEDAI-S2K Change from Baseline by Visit While on Treatment (Observed)		DB [1]
2.29.	MITT		SLEDAI-S2K < 4 by Visit (IPD/TF/WD=NR)		DB [1]
Prednisone					
2.30.	MITT		Prednisone ≤ 5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)		DB [1]
2.31.	MITT		Prednisone ≤ 7.5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)		DB [1]
Tipping Point (if applicable)					
2.32.	MITT		Tipping Point for PERR at Week 104 – Hybrid Treatment Policy for Non-TF Intercurrent Events		DB [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.33.	MITT		Tipping Point for PERR at Week 104 – Treatment Policy for All Intercurrent Events		DB [1]
2.34.	MITT		Tipping Point for CRR at Week 104 – Hybrid Treatment Policy for Non-TF Intercurrent Events		DB [1]
2.35.	MITT		Tipping Point for CRR at Week 104 – Treatment Policy for All Intercurrent Events		DB [1]
2.36.	MITT		Tipping Point for Time to Death or Renal-related Event – Treatment Policy using Censored-at-Random Assumption for Placebo		DB [1]
SLEDAI-S2K Excluding Renal Items					
2.37.	MITT		SLEDAI-S2K Change from Baseline Excluding Renal Items by Visit While on Treatment (Observed)		DB [1]

14.12.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.01.	Safety		Pre-treatment Adverse Events by SOC and PT		DB [1]
3.02.	Safety		Adverse Events Summary		DB [1]
3.03.	Safety		Adverse Events by SOC		DB [1]
3.04.	Safety	IDSL1.1.1 AE1	Adverse Events by SOC and PT	IDSL	DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.05.	Safety	IDSL 1.1.4 AE3	Adverse Events by PT	IDSL	DB [1]
3.06.	Safety		Study Agent Related Adverse Events by SOC		DB [1]
3.07.	Safety	IDSL 1.1.2 AE1	Study Agent Related Adverse Events by SOC and PT	IDSL	DB [1]
3.08.	Safety		Study Agent Related Adverse Events by PT		DB [1]
3.09.	Safety	IDSL 1.1.7 AE5A	Adverse Events by SOC, PT, and Maximum Intensity	FDAAA, IDSL	DB [1]
3.10.	Safety	IDSL 1.1.8	Study Agent Related Adverse Events by SOC, PT, and Maximum Intensity	IDSL	DB [1]
3.11.	Safety		Severe Adverse Events by SOC		DB [1]
3.12.	Safety		Severe Adverse Events by SOC and PT		DB [1]
3.13.	Safety		Severe Adverse Events by PT		DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events by Subgroup					
3.15.	Safety		Adverse Events by SOC and PT and Gender		DB [1]
3.16.	Safety		Adverse Events by SOC and PT and Race Stratification Factor		DB [1]
3.17.	Safety		Adverse Events by SOC and PT and Region		DB [1]
3.18.	Safety		Adverse Events by SOC and PT and Baseline C3/C4 Levels and Anti-dsDNA		DB [1]
3.19.	Safety		Adverse Events by SOC and PT and Baseline Body Weight Quartiles		DB [1]
Serious and Other Significant Adverse Events					
3.20.	Safety		Death by Category and PT		DB [1]
3.21.	Safety		Serious Adverse Events by SOC		DB [1]
3.22.	Safety	IDSL 1.1.6 AE16	Serious Adverse Events by SOC and PT	IDSL	DB [1]
3.23.	Safety		Serious Adverse Events by PT		DB [1]
3.24.	Safety		Study Agent Related Serious Adverse Events by SOC and PT		DB [1]
3.25.	Safety		Adverse Events Resulting in Study Agent Discontinuation by SOC		DB [1]
3.26.	Safety		Adverse Events Resulting in Study Agent Discontinuation by SOC and PT		DB [1]
3.27.	Safety		Adverse Events Resulting in Study Agent Discontinuation by PT		DB [1]
3.28.	Safety	IDSL 1.1.5 AE15	Common (>=5%) Non-Serious Adverse Events by SOC and PT	FDAAA, EUDraCT, IDSL	DB [1]
3.29.	Safety	IDSL AE16	Serious Adverse Events by SOC and PT (Number of Subjects and Occurrences)	FDAAA, EUDraCT, IDSL	DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events of Special Interest					
3.30.	Safety		Adverse Events of Special Interest by Category		DB [1]
3.31.	Safety		Malignant Neoplasm Adverse Events of Special Interest by Category and PT		DB [1]
3.32.	Safety		Post-Infusion Systemic Reactions Adverse Events of Special Interest by Category and PT		DB [1]
3.33.	Safety		Serious Post-Infusion Systemic Reactions Adverse Events of Special Interest by Category and PT		DB [1]
3.34.	Safety		Post-Infusion Systemic Reactions per Anaphylactic Reactions CMQ Broad Search by PT in First Six Infusions		DB [1]
3.35.	Safety		Serious Post-Infusion Systemic Reactions per Anaphylactic Reactions CMQ Broad Search by PT in First Six Infusions		DB [1]
3.36.	Safety		Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK Adjudication by PT in First Six Infusions		DB [1]
3.37.	Safety		Serious Delayed Acute Hypersensitivity Reactions per GSK Adjudication by PT in First Six Infusions		DB [1]
3.38.	Safety		Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Adjudication by PT in First Six Infusions		DB [1]
3.39.	Safety		Infection Adverse Events of Special Interest by Category and PT		DB [1]
3.40.	Safety		Infection Adverse Events of Special Interest Leading to Study Agent Discontinuation by Category and PT		DB [1]
3.41.	Safety		Depression/Suicide/Self-injury Adverse Events of Special Interest by Category and PT		DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
C-SSRS					
3.42.	Safety	IDSL CSSRS1	C-SSRS Suicidal Ideation or Behaviour Post-Baseline	IDSL	DB [1]
3.43.	Safety	IDSL CSSRS2	Treatment-Emergent C-SSRS Suicidal Ideation or Behaviour Relative to Pre-treatment	IDSL	DB [1]
3.44.	Safety	IDSL CSSRS3	Shift Table of Changes in C-SSRS Categories from Pre-treatment to Post-Baseline	IDSL	DB [1]
Laboratory: Hematology					
3.45.	Safety		Laboratory Results by Visit: Hematology		DB [1]
3.46.	Safety		Worst Laboratory Toxicity Grade: Hematology		DB [1]
3.47.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Hematology		DB [1]
3.48.	Safety		Laboratory Reference Range Shifts from Baseline by Visit: Hematology		DB [1]
Laboratory: Liver Function					
3.49.	Safety		Laboratory Results by Visit: Liver Function	ICH E3 12.4.2.1	DB [1]
3.50.	Safety		Worst Laboratory Toxicity Grade: Liver Function		DB [1]
3.51.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Liver Function	ICH E3 12.4.2.2	DB [1]
3.52.	Safety		Laboratory Reference Range Shifts from Baseline by Visit: Liver Function	ICH E3 12.4.2.2.	DB [1]
Laboratory: Electrolytes					
3.53.	Safety		Laboratory Results by Visit: Electrolytes	ICH E3 12.4.2.1	DB [1]
3.54.	Safety		Worst Laboratory Toxicity Grade: Electrolytes		DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.55.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Electrolytes	ICH E3 12.4.2.2	DB [1]
3.56.	Safety		Laboratory Reference Range Shifts from Baseline by Visit: Electrolytes	ICH E3 12.4.2.2	DB [1]
Laboratory: Other Chemistries					
3.57.	Safety		Laboratory Results by Visit: Other Chemistries	ICH E3 12.4.2.1	DB [1]
3.58.	Safety		Worst Laboratory Toxicity Grade: Other Chemistries		DB [1]
3.59.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Other Chemistries	ICH E3 12.4.2.2	DB [1]
3.60.	Safety		Laboratory Reference Range Shifts from Baseline by Visit: Other Chemistries	ICH E3 12.4.2.2	DB [1]
Laboratory: Urinalysis					
3.61.	Safety		Laboratory Results by Visit: Urinalysis		DB [1]
3.62.	Safety		Worst Laboratory Toxicity Grade: Urinalysis		DB [1]
3.63.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Urinalysis	ICH E3 12.4.2.2	DB [1]
Laboratory: Immunoglobulins					
3.64.	Safety		Laboratory Results by Visit: Immunoglobulins	ICH E3 12.4.2.1	DB [1]
3.65.	Safety		Worst Laboratory Toxicity Grade: Immunoglobulins		DB [1]
3.66.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Immunoglobulins	ICH E3 12.4.2.2	DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.67.	Safety		Laboratory Reference Range Shifts from Baseline by Visit: Immunoglobulins	ICH E3 12.4.2.2	DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunoglobulin					
3.68.	Safety		Immunoglobulin Levels below the Lower Limit of Normal (LLN) by Visit		DB [1]
3.69.	Safety		Immunoglobulin Levels below the Lower Limit of Normal (LLN) at each Visit among Subjects with Immunoglobulins >= LLN at Baseline		DB [1]
3.70.	Safety		Immunoglobulin Levels >= the Lower Limit of Normal (LLN) by Visit		DB [1]
3.71.	Safety		Immunoglobulin Levels >= the Lower Limit of Normal (LLN) at each Visit among Subjects with Immunoglobulins < LLN at Baseline		DB [1]
3.72.	Safety		Immunogenic Response by Visit		DB [1]
Vital Signs					
3.73.	Safety		Vital Signs by Visit (Observed)		DB [1]
3.74.	Safety	IDSL VS1	Vital Signs Change from Baseline by Visit (Observed)	ICH E3 12.5	DB [1]
Survival Status					
3.75.	Safety		Survival Status at Week 104		DB [1]
Adverse Events (Through/Post Week 24)					
3.76.	Safety		Adverse Events by SOC and PT from Baseline through Week 24		DB [1]
3.77.	Safety		Adverse Events by SOC and PT Post Week 24		DB [1]
3.78.	Safety		Serious Adverse Events by SOC and PT from Baseline through Week 24		DB [1]
3.79.	Safety		Serious Adverse Events by SOC and PT Post Week 24		DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.80.	Safety		Adverse Events of Special Interest by Category from Baseline through Week 24		DB [1]
3.81.	Safety		Adverse Events of Special Interest by Category Post Week 24		DB [1]
Adverse Events (Post-Treatment)					
3.82.	Safety		Post-Treatment Serious Adverse Events by SOC and PT		DB [1]
3.83.	Safety		Post-Treatment Adverse Events of Special Interest by Category		DB [1]
Serious and Non-Serious Drug-Related Events by Overall Frequency					
3.84.	Safety		Non-Serious Drug-Related Adverse Events by Overall Frequency		DB [1]
3.85.	Safety		Serious Drug-Related Adverse Events by Overall Frequency		DB [1]
Worst Laboratory Toxicity Grade While on Study					
3.86.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Hematology		DB [1]
3.87.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Liver Function		DB [1]
3.88.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Electrolytes		DB [1]
3.89.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Other Chemistries		DB [1]
3.90.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Urinalysis		DB [1]
3.91.	Safety		Worst Laboratory Toxicity Grade Post-Treatment: Immunoglobulins		DB [1]
Laboratory Toxicity Grade Worsening Post-Treatment					
3.92.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Hematology		DB [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.93.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Liver Function		DB [1]
3.94.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Electrolytes		DB [1]
3.95.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Other Chemistries		DB [1]
3.96.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Urinalysis		DB [1]
3.97.	Safety		Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline Post-Treatment: Immunoglobulins		DB [1]

14.12.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.01.	Safety		Laboratory Results by Visit: Hematology		DB [1]
3.02.	Safety		Laboratory Results by Visit: Liver Function		DB [1]
3.03.	Safety		Laboratory Results by Visit: Electrolytes		DB [1]
3.04.	Safety		Laboratory Results by Visit: Other Chemistries		DB [1]
3.05.	Safety		Laboratory Results by Visit: Urinalysis		DB [1]
3.06.	Safety		Laboratory Results by Visit: Immunoglobulins		DB [1]

14.12.10. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunoglobulin					
4.01.	MITT		Immunoglobulin Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.02.	MITT		Immunoglobulin Levels Change from Baseline by Visit (Observed)		DB [1]
4.03.	MITT		Immunoglobulin Levels Shifts from Baseline by Visit (Observed)		DB [1]
Autoantibodies					
4.04.	MITT		Autoantibody Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.05.	MITT		Autoantibody Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (Observed)		DB [1]
4.06.	MITT		Autoantibody Levels Change from Baseline by Visit (Observed)		DB [1]
4.07.	MITT		Autoantibody Levels Change from Baseline by Visit among Subjects Positive at Baseline (Observed)		DB [1]
4.08.	MITT		Autoantibody Levels Shifts from Baseline by Visit (Observed)		DB [1]
Complement (C3/C4)					
4.09.	MITT		Complement Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.10.	MITT		Complement Levels Percent Change from Baseline by Visit among Subjects with Low Complement at Baseline (Observed)		DB [1]
4.11.	MITT		Complement Levels Change from Baseline by Visit (Observed)		DB [1]

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.12.	MITT		Complement Levels Change from Baseline by Visit among Subjects with Low Complement at Baseline (Observed)		DB [1]
4.13.	MITT		Complement Levels Shifts from Baseline by Visit (Observed)		DB [1]
B Cells					
4.14.	MITT		B cells Percent Change from Baseline by Visit (Observed)		DB [1]
4.15.	MITT		B cells Change from Baseline by Visit (Observed)		DB [1]
Autoantibodies Adjusted for IgG					
4.16.	MITT		Autoantibody Levels Change from Baseline by Visit Adjusted for IgG using Joint Modeling (Observed)		DB [1]

14.12.11. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunoglobulin					
4.01.	MITT		Immunoglobulin Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.02.	MITT		Immunoglobulin Levels Change from Baseline by Visit (Observed)		DB [1]
Autoantibodies					
4.03.	MITT		Autoantibody Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.04.	MITT		Autoantibody Levels Percent Change from Baseline by Visit among Subjects Positive at Baseline (Observed)		DB [1]
4.05.	MITT		Autoantibody Levels Change from Baseline by Visit (Observed)		DB [1]
4.06.	MITT		Autoantibody Levels Change from Baseline by Visit among Subjects Positive at Baseline (Observed)		DB [1]
Complement (C3/C4)					
4.07.	MITT		Complement Levels Percent Change from Baseline by Visit (Observed)		DB [1]
4.08.	MITT		Complement Levels Percent Change from Baseline by Visit among Subjects with Low Complement at Baseline (Observed)		DB [1]
4.09.	MITT		Complement Levels Change from Baseline by Visit (Observed)		DB [1]
4.10.	MITT		Complement Levels Change from Baseline by Visit among Subjects with Low Complement at Baseline (Observed)		DB [1]

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
B Cells					
4.11.	MITT		B cells Percent Change from Baseline by Visit (Observed)		DB [1]
4.12.	MITT		B cells Change from Baseline by Visit (Observed)		DB [1]
Autoantibodies Adjusted for IgG					
4.13.	MITT		Autoantibody Levels Mean Difference in Change from Baseline by Visit Adjusted for IgG using Joint Modeling (Observed)		DB [1]
4.14.	MITT		Autoantibody Levels Ratio of Means for Change from Baseline by Visit Adjusted for IgG using Joint Modeling (Observed)		DB [1]

14.12.12. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Belimumab Concentrations					
5.01.	PK		Belimumab Concentrations (ug/mL) (Observed)		DB [1]
5.02.	PK		Belimumab Concentrations (ug/mL) (Observed) by Baseline Body Weight Quartiles		DB [1]
5.03.	PK		Belimumab Concentrations (ug/mL) (Observed) by Baseline BMI Categories		DB [1]
5.04.	PK		Belimumab Concentrations (ug/mL) (Observed) by Baseline Proteinuria Categories		DB [1]
5.05.	PK		Belimumab Concentrations (ug/mL) (Observed) by Immunogenicity Status		DB [1]

14.12.13. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Belimumab Concentrations					
5.01.	PK		Median Belimumab Concentrations (Observed)		DB [1]
5.02.	PK		Median Belimumab Concentrations (Observed) by Baseline Body Weight Quartile		DB [1]
5.03.	PK		Median Belimumab Concentrations (Observed) by Baseline BMI Category		DB [1]
5.04.	PK		Median Belimumab Concentrations (Observed) by Baseline Proteinuria Category		DB [1]
5.05.	PK		Median Belimumab Concentrations (Observed) by Immunogenicity Status		DB [1]

14.12.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.01.	Screened	ES7	Reasons for Screen Failure	Journal Guidelines	DB [1]
1.02.	MITT	ES1	Subject Disposition and Populations		DB [1]
1.03.	MITT	ES2 / ES3	Reasons for Study Withdrawal	ICH E3	DB [1]
1.04.	MITT	SD2/SD3	Reasons for Treatment Discontinuation	ICH E3	DB [1]
1.06	MITT	IE3 / IE4	Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	DB [1]
1.07	MITT	DV2	Important Protocol Deviations	ICH E3	DB [1]
1.08	MITT	DM2 / DM4	Demographic and Baseline Characteristics	ICH E3	DB [1]
1.09	MITT	DM9 / DM10	Listing of Race	ICH E3	DB [1]
1.10	MITT		Randomized and Actual Strata	IDSL Treatment Assignment standard	DB [1]
1.11	MITT		Current and Past Medical Conditions	IDSL Medical Conditions Displays	DB [1]
1.12	MITT	CP_CM3 / CP_CM4	Concomitant Medications	IDSL	DB [1]
1.15	MITT		Investigational Product Administration	ICH E3 11.3	DB [1]
1.16	MITT	TA1 / CP_RD1x	Randomized and Actual Treatments	IDSL	DB [1]
1.17	MITT	BL1 / BL2	Subjects for Whom the Treatment Blind was Broken During the Study	ICH E3	DB [1]
1.18	MITT	EG3 / EG4	ECG Findings at Baseline	IDSL	DB [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.01	Safety	AE8 / AE8CP / AE9 / AE9CP	All Adverse Events	ICH E3 12.2.4 (16.2.7)	DB [1]
3.02	Safety	AE7	Subject Numbers for Individual Adverse Events	ICH E3, IDSL 1.3.1 required AE7	DB [1]
Serious and Other Significant Adverse Events					
3.05	Safety	AE8 / AE8CPa/ AE9 / AE9CPa	Deaths	ICH E3	DB [1]
3.06	Safety	AE8 / AECP8 / AE9 / AE9CP	Adverse Events Resulting in Study Agent Discontinuation	ICH E3 12.3.1.2 / IDSL 1.3.5 required	DB [1]
All Laboratory					
3.15	Safety	LB5 / LB6	Laboratory Results: Hematology	ICH E3	DB [1]
3.16	Safety	LB5 / LB6	Laboratory Results: Liver Function	ICH E3	DB [1]
3.17	Safety	LB5 / LB6	Laboratory Results: Electrolytes	ICH E3	DB [1]
3.18	Safety	LB5 / LB6	Laboratory Results: Other Chemistries	ICH E3	DB [1]
3.19	Safety	LB5 / LB6	Laboratory Results: Urinalysis	ICH E3	DB [1]
3.20	Safety	LB5 / LB6	Laboratory Results: Immunoglobulins	ICH E3	DB [1]
3.21	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Hematology	ICH E3	DB [1]
3.22	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Liver Function	ICH E3	DB [1]
3.23	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Electrolytes	ICH E3	DB [1]
3.24	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Other Chemistries	ICH E3	DB [1]
3.25	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Urinalysis	ICH E3	DB [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.26	Safety	LB5 / LB6	Grade 3 or Grade 4 Laboratory Toxicity Results: Immunoglobulins	ICH E3	DB [1]

14.12.15. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.05.	MITT	SP3A	Subjects Excluded from Per Protocol Population	IDSL	DB [1]
1.13.	MITT		Relationship Between ATC Level 1, Ingredient and Verbatim Text		DB [1]
1.14.	MITT		Treatment Failures		DB [1]
1.19.	MITT		Pre-Flare Serum Creatinine and eGFR Values		DB [1]
1.20.	MITT		Lupus Nephritis Therapy History		DB [1]
1.21.	MITT		Renal Biopsy at Screening		DB [1]
Efficacy					
2.01	MITT		PERR, CRR, and ORR Results by Visit (IPD/TF/WD=NR)		DB [1]
2.02	MITT		Death or Renal-related Event		DB [1]
2.03	MITT		Severe SFI Flares		DB [1]
2.04	MITT		Doubling of Serum Creatinine from Baseline and/or Progression to End Stage Renal Disease (ESRD) by Visit		DB [1]
2.05	MITT		SLEDAI-S2K Results		DB [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.06	MITT		Prednisone Average Daily Dose Since Previous Visit While on Treatment		DB [1]
2.07	MITT		SLICC/ACR Damage Index Results		DB [1]
Safety					
3.03	Safety		Survival Status		DB [1]
3.04	Safety		Serious Adverse Events While on Treatment		DB [1]
3.07	Safety	AE2	Relationship Between System Organ Class and Verbatim Text	IDSL 1.3.7 required AE2	DB [1]
3.08	Safety	AE14	Reasons for Considering as a Serious Adverse Event	IDSL 1.3.8 required AE14	DB [1]
3.09	Safety		Adverse Events of Special Interest While on Treatment		DB [1]
3.10	Safety		C-SSRS Suicidal Ideation and Behaviour Data		DB [1]
3.11	Safety		C-SSRS Suicidal Behavior Details		DB [1]
3.12	Safety		Details of Most Severe C-SSRS Suicidal Ideation at Each C-SSRS Assessment		DB [1]
3.13	Safety		Possible Suicidality-Related Questionnaire		DB [1]
3.14	Safety		Medical/Surgical Procedures		DB [1]
3.27	Safety		IgG Protocol Specified Events		DB [1]
3.28	Safety		Immunogenicity Results		DB [1]
3.29	Safety	AE8 / AE8CP / AE9 / AE9CP	All Adverse Events for Subjects in Mexico		DB [1]
3.30	Safety		Serious Adverse Events for Subjects in Countries Other than Mexico		DB [1]
3.31	Safety		Post-Treatment Serious Adverse Events		DB [1]
3.32	Safety		Post-Treatment Non-Serious Adverse Events		DB [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.33	Safety		Post-Treatment Adverse Events of Special Interest		DB [1]
Liver Events					
3.34	Safety	LIVER5	Liver Monitoring/Stopping Event Reporting		DB [1]
3.35	Safety	SU2	Substance Use Reported with Liver Event		DB [1]
3.36	Safety	LIVER6	Liver Stopping Event Information for RUCAM Score		DB [1]
Biomarker Results					
4.01	MITT		Biomarker Results		DB [1]
4.02	MITT		B Cell Results		DB [1]
PK Concentration					
5.01	PK		Serum Belimumab PK Concentration-Time Data		DB [1]

14.13. Appendix 13: Example Mock Shells for Data Displays

Data display specifications are available on request.

14.14. Appendix 14: Headline Results

The following tables will be produced as headline results:

Display	Display Title
Table 1.02	Populations
Table 1.04	Subject Status by Week 104
Table 1.07	Investigational Product Status and Reasons for Discontinuation
Table 1.13	Demographic and Baseline Characteristics
Table 1.20	Baseline Disease Activity
Table 2.01	Primary Efficacy Renal Response at Week 104 (IPD/TF/WD=NR)
Table 2.03	Primary Efficacy Renal Response and the 3 Components at Week 104 (IPD/TF/WD=NR)
Table 2.12	Primary Efficacy Renal Response by Visit (IPD/TF/WD=NR)
Table 2.21	Primary Efficacy Renal Response at Week 104 by Induction Regimen (IPD/TF/WD=NR)
Table 2.28	Complete Renal Response at Week 104 (IPD/TF/WD=NR)
Table 2.30	Complete Renal Response and the 3 Components at Week 104 (IPD/TF/WD=NR)
Table 2.39	Complete Renal Response by Visit
Table 2.46	Complete Renal Response at Week 104 by Induction Regimen (IPD/TF/WD=NR)
Table 2.53	Primary Efficacy Renal Response and the 3 Components at Week 52 (IPD/TF/WD=NR)
Table 2.56	Time to Death or Renal-related Event Overall and by Induction Regimen (IPD/TF not related to renal disease/WD=Censor)
Table 2.60	Ordinal Renal Response at Week 104 (IPD/TF/WD=NR)
Table 2.77	Prednisone ≤ 5 mg/day Average Daily Dose Since Previous Visit (IPD/TF/WD=NR)
Table 2.78	Prednisone ≤ 7.5 mg/day Average Daily Dose Since Previous Visit (IPD/TF/WD=NR)
Table 2.105	Prednisone <= 5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)
Table 2.106	Prednisone <= 7.5 mg Average Daily Dose Since Previous Visit by Week 104 PERR Response (IPD/TF/WD=NR)
Table 3.02	Adverse Events Summary
Table 3.04	Adverse Events by SOC and PT (Double-Blind Phase)
Table 3.20	Death by Category and PT (Double-Blind Phase)
Listing 3.05	Deaths
Table 3.22	Serious Adverse Events by SOC and PT
Table 3.30	Adverse Events of Special Interest by Category