Statistical Analysis Plan

Study ID: 205646

Official Title of Study: Reporting and Analysis Plan Addendum 2 for 205646, a Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 104-Week Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE)

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Description:

- This second RAP addendum is supplemental to the RAP (Dated: 05/AUG/2020), and the first RAP addendum (Dated: 08/OCT/2020).
- It is based on protocol amendment 04 (Dated: 30/APR/2020) of study 205646.
- The main purpose of this addendum is to list an abridged set of outputs that will be produced for the final study report. These changes are being made following the first database lock and primary analyses at the end of Year 1 of the study.

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ABBREVIATIONS

Abbreviation	Description
ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
anti-dsDNA	Anti-double-stranded DNA
ATC	Anatomical, Therapeutic, Clinical
BLyS	B-Lymphocyte Stimulator
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue Scale
GSK	GlaxoSmithKline
IBA	Independent Blinded Assessor
IP	Investigational Product
ITT	Intent-To-Treat
IV	Intravenous
LLDAS	Lupus Low Disease Activity State
LSLV	Last Subject Last Visit
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat
PGA	Physician Global Assessment
PI	Principal Investigator
PISR	Post-Injection Systemic Reactions
PK	Pharmacokinetic
PT	Preferred Term
PtGA	Patient Global Assessment
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
TF	Treatment Failure
WPAI	Work Productivity and Activity Impairment Questionnaire

1. INTRODUCTION

This RAP addendum is supplemental to the RAP (Dated: 05/AUG/2020), and the first RAP addendum (Dated: 08/OCT/2020). It is based on protocol amendment 04 (Dated: 30/APR/2020) of study 205646.

The main purpose of this addendum is to list an abridged set of outputs that will be produced for the final study report. These changes are being made following the first database lock and primary analyses at the end of Year 1 of the study.

2. CHANGES/CLARIFICATIONS TO THE RAP

2.1. Modifications to the planned list of outputs for the end of study analyses

As specified in the original RAP (Section 3.2), there are two database locks for this study, corresponding to the primary analyses and the end of study analyses.

- The primary analyses would include data up to the 52 week visit for the primary endpoint.

- The final analyses would be conducted following the last subject completion of year 2 (including all 8 week-follow-up visits).

The original RAP (Section 3.2) had the following text: “This RAP details the planned analysis for both database locks, with the expectation of an observed treatment benefit at Week 52. If the Week 52 reporting does not identify a treatment benefit, an abridged set of analysis may be conducted at the end of the study, which will be detailed in a RAP amendment or RAP addendum.”.

Following the results of the primary analyses, an abridged set of outputs will be produced and these are detailed below.

2.1.1. Study Population Tables

Study Population Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Subject Disposition				
21.01.	21.01	Screened	Study Populations (Year 1&2)	
21.02.	21.02	ITT	Subject Status (Year 1&2)	
21.03.	21.04	ITT	Subject Status and Reason for Study Withdrawal (Year 1&2)	
21.04.	21.05	ITT	Time to Withdrawal from the Study (Year 1&2)	
21.05.	21.06	ITT	Treatment Status and Reasons for Discontinuing Belimumab SC Study Treatment (Year 1&2)	
21.06.	21.07	ITT	Time to Belimumab SC Study Treatment Discontinuation [1] (Year 1&2)	
Protocol Deviations				
21.07.	21.09	ITT Year 2	Important Protocol Deviations after Week 52 (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
Concomitant Medications				
21.08.	21.11	ITT Year 2	Concomitant Medications by ATC Level 1 and ATC Level 4 Term (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
21.09.	21.13	ITT	First Medication Usage Resulting in Treatment Failure Designation (Year 1&2)	
Extent of Exposure				
21.10.	21.14	ITT	Exposure to Belimumab SC (Study Treatment and Re-start [1]) (Year 1&2)	

Study Population Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
21.11.	21.15	ITT Year 2	Exposure to Belimumab SC [1] (Arms A&B: Re-start; Arm C: Study Treatment) (Year 2)	• Belimumab doses that occur up to and including the Week 52 visit date are included as Year 1 doses. Belimumab doses that occur after the Week 52 visit date are included as Year 2 doses. This was incorrect in the original RAP Section 6.5. • Use new 'ITT Year 2' Population defined in Section 2.2.
Coronavirus Disease 2019 (COVID-19) Pandemic				
21.12.	NEW	ITT	COVID-19 Pandemic Visit Impacts (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)
21.13.	NEW	ITT	Reason for Study Withdrawal by Relationship to COVID-19 Pandemic (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)
21.14.	NEW	ITT	Reasons for Discontinuing Belimumab SC Study Treatment by Relationship to COVID-19 Pandemic (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)
21.15.	NEW	ITT	Important Protocol Deviations by Relationship to COVID-19 Pandemic (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)

2.1.2. Study Population Figures

Study Population Figures				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Subject Disposition				
21.01.	21.01	ITT	Time to Withdrawal from Study (Year 1&2)	
21.02.	21.02	ITT	Time to Belimumab SC Study Treatment Discontinuation (Year 1&2)	
COVID-19 Pandemic				
21.03.	NEW	ITT	Visits Impacted by COVID-19 Pandemic (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)

2.1.3. Study Population Listings

Study Population Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Subject Disposition				
21.01.	21.01	Randomized	Subject Disposition (Year 1&2)	
21.02.	21.02	Randomized	Reasons for Study Withdrawal (Year 1&2)	
21.03.	21.03	Randomized	Reasons for Belimumab SC Study Treatment Discontinuation (Year 1&2)	
Protocol Deviations				
21.04.	21.04	Randomized	Important or COVID-19 Protocol Deviations (Year 1&2)	
Concomitant Medications				
21.05.	21.06	Randomized	Concomitant Medications (Year 2)	

Study Population Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
21.06.	21.07	Randomized	Medications that Result in Treatment Failure Designation (Year 2)	
Extent of Exposure				
21.07.	21.08	Randomized	Study Treatment Administration (Year 1&2)	
COVID-19 Pandemic				
21.08.	21.09	Randomized	Country Level Listing of Dates of Waves of COVID-19 Pandemic Measures	
21.09.	NEW	Randomized	All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic (Year 1&2)	• New output (recommended in GSK COVID-19 guidance document)

2.1.4. Efficacy Tables

Efficacy Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Clinical Remission				
22.01.	22.01	MITT	Clinical Remission (IBA) at Week 64 (Hybrid)	
22.02.	22.02	MITT	Logistic Regression Analysis of Clinical Remission (IBA) at Week 64 (Hybrid)	
22.03.	22.03	MITT	Disposition of Clinical Remission (IBA) at Week 64 (Hybrid)	
22.04.	NEW	MITT	Disposition of Clinical Remission (IBA) by First Reason for Non-Response at Week 64 (Hybrid)	• New output (omission in original RAP)

Efficacy Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
22.05.	22.04	MITT	Clinical Remission (IBA) and its Components at Week 64 (Hybrid)	• The planned component for 'Corticosteroid >0 to <=5mg/day' has been modified to match the actual component of the endpoint, i.e. "Corticosteroids at a prednisone equivalent dose of 0 mg/day"
22.06.	NEW	MITT	Clinical Remission (IBA) and its Components by Baseline C3/C4 Level & Anti-dsDNA at Week 64 (Hybrid)	• New output (key subgroup of interest) • The planned component for 'Corticosteroid >0 to <=5mg/day' has been modified to match the actual component of the endpoint, i.e. "Corticosteroids at a prednisone equivalent dose of 0 mg/day"
22.07.	22.08	MITT	Clinical Remission (IBA) by Visit (Hybrid) (Year 2)	
22.08.	22.09	MITT	Clinical Remission (PI) by Visit (Hybrid) (Year 2)	
22.09.	22.25	MITT	Duration of Clinical Remission (PI) (Hybrid) (Year 1&2)	
22.10.	22.20	MITT	Clinical Remission (PI) Sustained for at least 24 Weeks by Visit (Hybrid) (Year 2)	
22.11.	22.33	MITT	Time to Clinical Remission (PI) Sustained for at least 24 weeks and maintained through to Week 104 [1] (Hybrid)	
Disease Control				
22.12.	22.10	MITT	Disease Control (IBA) at Week 104 (Hybrid)	
22.13.	22.11	MITT	Logistic Regression Analysis of Disease Control (IBA) at Week 104 (Hybrid)	
22.14.	22.12	MITT	Disposition of Disease Control (IBA) at Week 104 (Hybrid)	
22.15.	NEW	MITT	Disposition of Disease Control (IBA) by First Reason for Non-Response at Week 104 (Hybrid)	• New output (omission in original RAP)

Efficacy Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
22.16.	22.13	MITT	Disease Control (IBA) and its Components at Week 104 (Hybrid)	
22.17.	NEW	MITT	Disease Control (IBA) and its Components by Baseline C3/C4 Level & Anti-dsDNA at Week 104 (Hybrid)	• New output (key subgroup of interest)
22.18.	22.17	MITT	Disease Control (IBA) by Visit (Hybrid) (Year 1&2)	
22.19.	22.18	MITT	Disease Control (PI) by Visit (Hybrid) (Year 1&2)	
22.20.	NEW	MITT	Duration of Disease Control (PI) (Hybrid) (Year 1&2)	• New output (omission in orginal RAP)
22.21.	22.24	MITT	Time to Disease Control (PI) Sustained for at least 24 weeks and maintained through to Week 104 [1] (Hybrid)	
Complete Remission				
22.22.	22.21	MITT	Complete Remission (PI) by Visit (Hybrid) (Year 2)	
22.23.	22.19	MITT	Complete Remission (PI) Sustained for at Least 24 Weeks by Visit (Hybrid) (Year 2)	
Flares				
22.24.	22.22	MITT	Time to First Severe Flare (Treatment Policy, TF=Severe Flare) (Year 1&2) (Modified SLE Flare Index)	
22.25.	NEW	MITT	Time to First Severe Flare (Treatment Policy) (Year 1&2) (Modified SLE Flare Index)	• New output (of interest following post SAC request for Year 1) • Treatment Failures are not included as severe flares
22.26.	22.23	MITT	Time to First Flare (Treatment Policy, TF=Flare) (Year 1&2) (Modified SLE Flare Index)	
Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)				
22.27.	22.26	MITT	SLEDAI-2K (PI) - Change from Baseline by Visit (Hypothetical) (Year 1&2)	

Efficacy Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
22.28.	22.27	MITT	SLEDAI-2K (PI) - Organ System Improvement by Organ System and Visit Among Subjects with Organ System Involvement at Baseline [1] (Treatment Policy) (Year 1&2)	
22.29.	22.28	MITT	SLEDAI-2K (PI) - Organ System Worsening by Organ System and Visit Among Subjects with No Organ System Involvement at Baseline [1] (Observed) (Year 1&2)	
Physician Global Assessment (PGA)				
22.30.	22.29	MITT	Physician Global Assessment (PGA) - Change from Baseline by Visit (Hypothetical) (Year 1&2)	
Systemic Lupus International Collaborating Clinics (SLICC)				
22.31.	22.30	MITT	SLICC/ACR Damage Index Worsening (Change>0) Compared with Baseline at Week 104 (Treatment Policy, WOCF)	
Lupus Low Disease Activity State (LLDAS)				
22.32.	22.31	MITT	Lupus Low Disease Activity State (LLDAS) (PI) by Visit (Treatment Policy) (Year 1&2)	
22.33.	22.32	MITT	Lupus Low Disease Activity State (LLDAS) (PI) and its Components at Weeks 52, 64 and 104 (Treatment Policy) (Year 1&2)	
Modified Disease Control				
22.34.	22.39	MITT	SLEDAI-2K Score <=2 (IBA), Without Current Immunosuppressants, Without Current Belimumab dosing (Arms A & B) and Corticosteroids dose <=5mg/day at Week 104 (COVID-19 Modified, Treatment Policy)	
Proteinuria				
22.35.	NEW	ITT	Proteinuria Shifts from Baseline by Visit (Observed) (Year 1&2)	• New output (of interest following post SAC request for Year 1)

2.1.5. Efficacy Figures

Efficacy Figures				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Efficacy Figures				
22.01.	22.01	MITT	Clinical Remission (IBA) at Week 64 (Hybrid)	
22.02.	22.03	MITT	Clinical Remission (PI) by Visit (Hybrid) (Year 2)	
22.03.	22.04	MITT	Disease Control (IBA) at Week 104 (Hybrid)	
22.04.	22.06	MITT	Time to First Severe Flare (Treatment Policy, TF=Severe Flare) (Year 1&2) (Modified SLE Flare Index)	
22.05.	22.07	MITT	Time to First Flare (Treatment Policy, TF=Flare) (Year 1&2) (Modified SLE Flare Index)	
22.06.	22.10	MITT	SLEDAI-2K (PI) - Change from Baseline by Visit (Observed) (Year 1&2)	
22.07.	22.11	MITT	Physician Global Assessment (PGA) - Change from Baseline by Visit (Observed) (Year 1&2)	
22.08.	NEW	ITT	Proteinuria Shifts from High at Baseline to Normal by Visit (Observed) (Year 1&2)	• New output (of interest following post SAC request for Year 1)

2.1.6. Efficacy Listings

Efficacy Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Efficacy Listings				
22.01.	22.01	ITT	Disease Control, Clinical Remission, and Complete Remission by Visit (Year 1&2)	

2.1.7. Safety Tables

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Adverse Events				
23.01.	23.01	ITT Year 2	Adverse Events Summary - On Study (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
23.02.	23.02	ITT	Adverse Events Summary - On Study (Year 1&2)	
23.03.	23.03	ITT Year 2	Adverse Events by SOC and PT - On Study (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
23.04.	23.04	ITT	Adverse Events by SOC and PT - On Study (Year 1&2)	
23.05.	23.05	ITT	Adverse Events by PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.06.	23.06	ITT	Study Treatment Related Adverse Events by SOC and PT – Belimumab Only [1] – On Study (Year 1&2)	• Now presents data for Year 1&2
23.07.	23.07	ITT	Study Treatment Related Adverse Events by SOC and PT – Rituximab Only [1] – On Study (Year 1&2)	• Now presents data for Year 1&2

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
23.08.	23.08	ITT	Study Treatment Related Adverse Events by SOC and PT – Both Belimumab & Rituximab [1] – On Study (Year 1&2)	• Now presents data for Year 1&2
23.09.	NEW	ITT	Study Treatment Related Non-Serious Adverse Events by PT – Belimumab Only [1] – On Study (Year 1&2)	• New output (required for Plain Language Summary)
23.10.	NEW	ITT	Study Treatment Related Non-Serious Adverse Events by PT – Rituximab Only [1] – On Study (Year 1&2)	• New output (required for Plain Language Summary)
23.11.	NEW	ITT	Study Treatment Related Non-Serious Adverse Events by PT – Both Belimumab & Rituximab [1] – On Study (Year 1&2)	• New output (required for Plain Language Summary)
23.12.	23.09	ITT	Adverse Events by SOC, PT and Maximum Severity – On Study (Year 1&2)	• Now presents data for Year 1&2
23.13.	23.11	ITT	Adverse Events by SOC and PT and Race - On Study (Year 1&2)	• Now presents data for Year 1&2
23.14.	23.13	ITT	Adverse Events by SOC and PT and Baseline C3/C4 Levels and Anti-dsDNA – On Study (Year 1&2)	• Now presents data for Year 1&2
23.15.	23.22	ITT	Adverse Events Leading to Permanent Discontinuation of Study Treatment by SOC and PT – Belimumab – On Study (Year 1&2)	• Now presents data for Year 1&2
23.16.	23.23	ITT	Common [1] Non-Serious Adverse Events by SOC and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
Deaths and Serious Adverse Events				
23.17.	23.18	ITT	Death by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.18.	23.19	ITT Year 2	Serious Adverse Events by SOC and PT - On Study (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
23.19.	23.20	ITT	Serious Adverse Events by SOC and PT - On Study (Year 1&2)	
23.20.	23.24	ITT	Study Treatment Related Serious Adverse Events by SOC and PT - Belimumab Only [1] - On Study (Year 1&2)	• Now presents data for Year 1&2

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
23.21.	23.25	ITT	Study Treatment Related Serious Adverse Events by SOC and PT - Rituximab Only [1] - On Study (Year 1&2)	• Now presents data for Year 1&2
23.22.	23.26	ITT	Study Treatment Related Serious Adverse Events by SOC and PT – Both Belimumab and Rituximab [1] - On Study (Year 1&2)	• Now presents data for Year 1&2
23.23.	NEW	ITT	Study Treatment Related Serious Fatal and Non-Fatal Adverse Events by PT – Belimumab Only [1] - On Study (Year 1&2)	• New output (required for Plain Language Summary)
23.24.	NEW	ITT	Study Treatment Related Serious Fatal and Non-Fatal Adverse Events by PT - Rituximab Only [1] - On Study (Year 1&2)	• New output (required for Plain Language Summary)
23.25.	NEW	ITT	Study Treatment Related Serious Fatal and Non-Fatal Adverse Events by PT – Both Belimumab and Rituximab [1] - On Study (Year 1&2)	• New output (required for Plain Language Summary)
Survival Staus				
23.26.	23.29	ITT	Survival Status at Week 104	
Adverse Events of Special Interest (AESI)				
23.27.	23.30	ITT Year 2	Adverse Events of Special Interest by Category - On Study (Year 2)	• Use new 'ITT Year 2' Population defined in Section 2.2.
23.28.	NEW	ITT	Adverse Events of Special Interest by Category - On Study (Year 1&2)	• New output (omission in original RAP)
23.29.	23.31	ITT	Malignant Neoplasm Adverse Events of Special Interest by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.30.	23.32	ITT	Post Belimumab SC Injection Systemic Reactions Adverse Events of Special Interest by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.31.	23.33	ITT	Serious Post Belimumab SC Injection Systemic Reactions Adverse Events of Special Interest by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
23.32.	23.34	ITT	Infection Adverse Events of Special Interest by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.33.	23.35	ITT	Infection Adverse Events of Special Interest Leading to Belimumab SC Study Treatment Discontinuation by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.34.	23.36	ITT	Depression/Suicide/Self-injury Adverse Events of Special Interest by Category and PT - On Study (Year 1&2)	• Now presents data for Year 1&2
23.35.	23.41	ITT	Adverse Events of Special Interest including Exposure-Adjusted Incidence Rates by Category – On Study (Year 1&2)	• Now presents data for Year 1&2
COVID-19 Pandemic Adverse Events				
23.36.	23.42	ITT	Exposure Adjusted Incidence Rates of Adverse Events Over Time in Relation to COVID-19 Pandemic – On Study (Year 1&2)	• Now presents data for Year 1&2
Columbia-Suicide Severity Rating Scale (C-SSRS)				
23.37.	23.45	ITT	C-SSRS Suicidal Ideation or Behavior during On Study Period (Year 1&2)	• Now presents data for Year 1&2
23.38.	23.46	ITT	Treatment-Emergent C-SSRS Suicidal Ideation or Behavior On Study Relative to Pre-treatment (Year 1&2)	• Now presents data for Year 1&2
Laboratory Results				
23.39.	23.50	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Hematology (Year 1&2)	• Now presents data for Year 1&2
23.40.	23.51	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Hematology (Year 1&2)	• Now presents data for Year 1&2
23.41.	23.54	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Liver Function (Year 1&2)	• Now presents data for Year 1&2

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
23.42.	23.55	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Liver Function (Year 1&2)	• Now presents data for Year 1&2
23.43.	23.58	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Electrolytes (Year 1&2)	• Now presents data for Year 1&2
23.44.	23.59	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Electrolytes (Year 1&2)	• Now presents data for Year 1&2
23.45.	23.62	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Other Chemistries (Year 1&2)	• Now presents data for Year 1&2
23.46.	23.63	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Other Chemistries (Year 1&2)	• Now presents data for Year 1&2
23.47.	23.65	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Urinalysis (Year 1&2)	• Now presents data for Year 1&2
23.48.	23.66	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Urinalysis (Year 1&2)	• Now presents data for Year 1&2
23.49.	23.69	ITT	Worst Post-Baseline Laboratory Toxicity Grade: Immunoglobulins (Year 1&2)	• Now presents data for Year 1&2
23.50.	23.70	ITT	Laboratory Toxicity Grade Worsening of at Least 2 Grades from Baseline: Immunoglobulins (Year 1&2)	• Now presents data for Year 1&2
23.51.	23.71	ITT	Laboratory Reference Range Shifts from Baseline by Visit: Immunoglobulins (Year 1&2)	• Now presents data for Year 1&2
Immunogenicity				
23.52.	23.76	ITT	Immunogenic Response to Belimumab SC by Visit (Year 1&2)	• Now presents data for Year 1&2
Vital Signs				
23.53.	23.78	ITT	Vital Signs Change from Baseline by Visit (Observed) (Year 1&2)	• Now presents data for Year 1&2

Safety Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Serious Adverse Events (additional outputs)				
23.54.	NEW	ITT Year 2	Serious Adverse Events by SOC and PT - On Study (Year 2)	• New output (formatting appropriate for CSR) • Use new 'ITT Year 2' Population defined in Section 2.2.
23.55.	NEW	ITT	Serious Adverse Events by SOC and PT - On Study (Year 1&2)	• New output (formatting appropriate for CSR)

2.1.8. Safety Figures

There are no Safety Figures to produce.

2.1.9. Safety Listings

Safety Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Adverse Events				
23.01.	23.02	ITT	Adverse Events (Year 2)	
23.02.	23.03	ITT	Adverse Events Related to Belimumab SC (Year 2)	
23.03.	23.05	ITT	Adverse Events Resulting in Belimumab SC Study Treatment Discontinuation (Year 2)	
23.04.	23.07	ITT	Year 1 Adverse Events reported after LSLV (Year 1)	
23.05.	23.08	ITT	Serious Adverse Events (Year 2)	

Safety Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
23.06.	23.11	ITT	Reasons for Considering as a Serious Adverse Event (Year 2)	
23.07.	23.13	ITT	MedDRA coding changes (Year 2)	
Laboratory Results				
23.08.	23.14	ITT	Laboratory Results: Hematology (Year 2)	
23.09.	23.15	ITT	Laboratory Results: Liver Function (Year 2)	
23.10.	23.16	ITT	Laboratory Results: Electrolytes (Year 2)	
23.11.	23.17	ITT	Laboratory Results: Other Chemistries (Year 2)	
23.12.	23.18	ITT	Laboratory Results: Urinalysis (Year 2)	
23.13.	23.19	ITT	Laboratory Results: Immunoglobulins (Year 2)	
Immunogenicity				
23.14.	23.26	ITT	Immunogenicity Results for Belimumab SC (Year 2)	
COVID-19 Pandemic				
23.15.	23.27	ITT	COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events (Year 1&2)	

2.1.10. Health Outcomes Tables

Health Outcomes Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Health Outcome Tables				
24.01.	24.01	MITT	Patient Global Assessment of Disease Activity Change from Baseline by Visit (Hypothetical) (Year 1&2)	
24.02.	24.02	MITT	Lupus Quality of Life Domain Scores Change from Baseline by Visit (Hypothetical) (Year 1&2)	
24.03.	24.03	MITT	FACIT-Fatigue Scale Score Change from Baseline by Visit (Hypothetical) (Year 1&2)	
24.04.	24.04	MITT	Improvement in FACIT-Fatigue Scale Score exceeding the MCID (>=4 point increase) by Visit (Hypothetical) (Year 1&2)	
24.05.	24.05	MITT	WPAI: Overall Work Productivity Impairment Change from Baseline by Visit (Hypothetical) (Year 1&2)	
24.06.	24.06	MITT	WPAI: Percent Activity Impairment Score Change from Baseline by Visit (Hypothetical) (Year 1&2)	

2.1.11. Health Outcomes Figures

Health Outcomes Figures				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Health Outcome Figures				
24.01.	24.02	MITT	Lupus Quality of Life Domain Scores Change from Baseline by Visit (Observed) (Year 1&2)	

Health Outcomes Figures				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
24.02.	24.03	MITT	FACIT-Fatigue Scale Score Change from Baseline by Visit (Observed) (Year 1&2)	
24.03.	24.04	MITT	Improvement in FACIT-Fatigue Scale Score Exceeding the MCID (>=4 points increase) by Visit (Observed) (Year 1&2)	

2.1.12. Health Outcomes Listings

Health Outcomes Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Health Outcomes Listings				
24.01.	24.04	ITT	Health Care Resource Utilization (Year 1&2)	

2.1.13. Biomarkers Tables

Biomarkers Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Immunoglobulins				
25.01.	25.02	ITT	Immunoglobulin Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	

Biomarkers Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
25.02.	25.03	ITT	Immunoglobulin Levels Shifts from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	
Autoantibodies				
25.03.	25.06	ITT	Autoantibody Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	
25.04.	25.07	ITT	Autoantibody Levels Change from Baseline by Visit among Subjects Positive at Baseline who Completed Week 52 On Treatment (Observed) (Year 1&2)	
25.05.	25.08	ITT	Autoantibody Levels Shifts from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	
Complement				
25.06.	25.11	ITT	Complement Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	
25.07.	25.12	ITT	Complement Levels Change from Baseline by Visit among Subjects with Low Complement at Baseline who Completed Week 52 On Treatment (Observed) (Year 1&2)	
25.08.	25.13	ITT	Complement Levels Shifts from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	
B Cells, T Cells and B-Lymphocyte Stimulator				
25.09.	25.15	ITT	B Cells, T Cells and B-Lymphocyte Stimulator Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	

2.1.14. Biomarkers Figures

Biomarkers Figures				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Biomarker Figures				
25.01.	NEW	ITT	Immunoglobulin Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	• New output (omission in original RAP)
25.02.	NEW	ITT	Autoantibody Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	• New output (omission in original RAP)
25.03.	NEW	ITT	Complement Levels Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	• New output (omission in original RAP)
25.04.	NEW	ITT	B Cells, T Cells and B-Lymphocyte Stimulator Change from Baseline by Visit among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	• New output (omission in original RAP)

2.1.15. Biomarkers Listings

Biomarkers Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
Biomarker Listings				
25.01.	25.01	ITT	Biomarker Results (Year 1&2)	
25.02.	25.02	ITT	B Cells, T Cells and B-Lymphocyte Stimulator Results (Year 1&2)	

2.1.16. Pharmacokinetic Tables

PK Tables				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
26.01.	26.01	PK	Belimumab Concentrations (ug/mL) among Subjects who Completed Week 52 On Treatment (Observed) (Year 1&2)	

2.1.17. Pharmacokinetic Figures

There are no PK Figures to produce.

2.1.18. Pharmacokinetic Listings

PK Listings				
New output number	**Old output number**	**Population**	**Title**	**Major modifications since original RAP**
26.01.	26.01	PK	Serum Belimumab PK Concentrations (Observed) (Year 1&2)	

2.2. New 'Intent-to-Treat Year 2' Population

An additional population has been defined for use in any Study Population and Adverse Event table that presents data only for Year 2.

The 'Intent-to-Treat Year 2' population is defined as "All ITT population participants who are ongoing in Year 2. This includes subjects who confirm that they are continuing in the study for Year 2 and/or have an exposure date or early withdrawal visit after the Week 52 visit date.".

2.3. Biomarker and Pharmacokinetic (PK)

2.3.1. Specifications in the original RAP

The original RAP gave minimal information about the data that should be used in the Biomarker and PK analyses for the Year 2 reporting.

For Biomarkers, the original RAP Section 10.1 stated that "The Year 1&2 analyses will be performed on the observed data for subjects who completed Week 52 on treatment (Ongoing and on treatment at Week 52 analysis as defined in Section 7.1.5). No imputation will be performed for missing data (data post re-start Belimumab will not be considered)."

For PK, the original RAP Section 11 gave no details.

Section 2.3.2 clarifies the approach that will be used for Year 2 reporting of both Biomarker and PK data. The intended approach for Biomarkers (described above) is utilised, explained further and broadened so that the method is also consistent for PK analyses.

2.3.2. Clarifications for the Year 2 reporting

The original definition of subjects who completed Week 52 on treatment (referenced in the original RAP Section 7.1.5) was based on the MITT population as it was intended to be used for Efficacy data. However, for Biomarker and PK analyses, this needs to be modified to be based on all subjects from the ITT population. Therefore, it has been copied directly but with the ITT population as the original population as follows:

All ITT population Arm A and Arm B participants who are ongoing after 52 weeks of the planned double-blind treatment period who received all of both IV doses of rituximab or rituximab-placebo, and did not have more than 28 consecutive days from baseline to Week 51 without a belimumab dose; includes ITT population Arm C subjects who remained on open-label belimumab through Week 52 and did not have more than 28 consecutive days baseline to Week 51 without a belimumab dose.

For Arms A&B, the Year 1&2 analyses will be performed on the observed data collected in Year 1 and prior to any re-start Belimumab in Year 2, for subjects who completed Week 52 on treatment.

For Arm C, the Year 1&2 analyses will be performed on the observed data up to IP discontinuation, for subjects who completed Week 52 on treatment.

No imputation will be carried out for missing data.

Note that the PK outputs will be presented for the PK population.

Signature Page for 205646 TMF-13873132 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 22-Jul-2021 12:38:41 GMT+0000

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan Addendum
Title	:	Reporting and Analysis Plan Addendum for 205646, a Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 104-Week Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE)
Compound Number	:	GSK1550188
Effective Date	:	08-OCT-2020

Description:

- This RAP addendum is supplemental to the RAP (Dated: 05/AUG/2020), and based on protocol amendment 04 (Dated: 30/APR/2020) of study 205646.
- The purpose of this RAP addendum is to document minor additions/clarifications made after RAP approval but before Database Release.

Author(s)

Author	Date	Approval Method
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RAP Team Confirmations:

Reviewer	Date	Approval Method
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Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
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ABBREVIATIONS

Abbreviation	Description
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
FDA	Food and Drug Administration
IBA	Independent Blinded Assessor
LLDAS	Lupus Low Disease Activity State
MedDRA	Medical Dictionary for Regulatory Activities
NR	Non-Responder
PI	Principal Investigator
R	Responder
RAP	Reporting and Analysis Plan
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000

Trademarks

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None

Trademarks not owned by GlaxoSmithKline group of companies
None

1. INTRODUCTION

This RAP addendum is supplemental to the RAP (Dated: 05/AUG/2020), and based on protocol amendment 04 (Dated: 30/APR/2020) of study 205646.

The purpose of this RAP addendum is to document minor additions/clarifications made after RAP approval but prior to Database Release.

2. CHANGES/CLARIFICATIONS TO THE RAP

2.1. Additional Cochran-Mantel-Haenszel (CMH) analysis (RAP Section 7)

The RAP specifies that CMH analysis will be conducted for

- Disease Control at Week 52: RAP Section 7.1.5.1
- Clinical Remission at Week 64: RAP Section 7.2.5.1
- Disease Control at Week 104: RAP Section 7.3.5.1

Following re-review of the FDA Request 29 June 2020 – comment 5:

> *To facilitate an evaluation of benefit-risk, report point estimates and 95% CI for the difference in proportions for these endpoints*

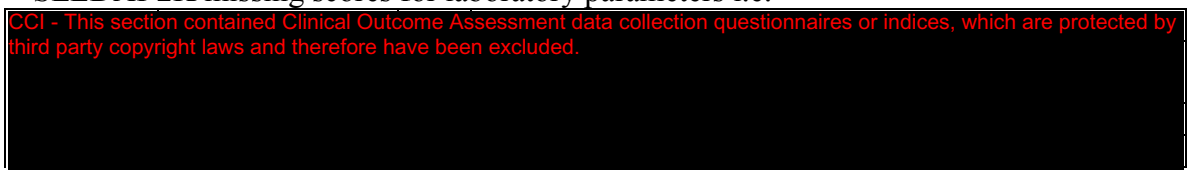
It was decided that most other binary endpoints would also conduct the CMH analysis. The exceptions are the following outputs:

- Disease control at Week 52 by subgroup
- Sensitivity analyses that were unadjusted for covariates (disease control and clinical remission)
- COVID-19 additional analyses using multiple imputation methods (disease control and clinical remission)

2.2. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K Missing Item Scores (RAP Section 15.6.3, Section 15.6.4, Section 15.6.5, Section 15.6.6 and Section 15.6.9)

The RAP Section 15.6.3 states the following:

"SLEDAI-2K missing scores for laboratory parameters i.e.



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

Will be imputed from the previous assessment if the previous assessment is no more than 35 days prior."

For clarification, the following rules apply for SLEDAI-2K missing item scores:

- It is only the 8 lab items that can be imputed. If any of the other 16 items are missing, they will be left missing.
- An imputed assessment cannot be used to impute another assessment.
- The imputation of these missing lab items is carried out independently for the Principal Investigator (PI) and Independent Blinded Assessor (IBA), i.e. the PI assessment of the lab items will never be carried forward to a missing IBA assessment and vice versa.

The following sections of the RAP should not re-define what happens with missing SLEDAI-2K item scores, they should all use the principles stated above:

- RAP Section 15.6.4: Disease Control
- RAP Section 15.6.5: Clinical Remission
- RAP Section 15.6.6: Complete Remission
- RAP Section 15.6.9: Lupus Low Disease Activity State (LLDAS)

2.3. Tipping Point Analysis (RAP Section 7.1.6)

The RAP Section 7.1.6 describes the tipping point analyses only in terms of "missing data caused by study withdrawal". This description is clarified here to also include any missing/partial non-informative SLEDAI-2K data, regardless of study withdrawal.

To explicitly clarify this in terms of the two strategies, the bold text has been added to the following existing RAP text:

"The first tipping point analysis will use the Hybrid strategy (as described in RAP Section 7.1.4 as per the primary estimand). If a subject's study withdrawal **(or missing data)** is subsequent to treatment failure the subject will still be considered as a non-responder, i.e. the non-responder assumption will only be varied for withdrawn subjects **(or subjects with missing/partial non-informative SLEDAI-2K data)** that were not treatment failures.

The second tipping point analysis will use the treatment policy strategy (RAP Section 7.1.4). In this approach, treatment failure data is ignored, i.e. the non-responder

assumption is varied for all withdrawn subjects **(or subjects with missing/partial non-informative SLEDAI-2K data)** regardless of treatment failures."

2.4. Analysis method to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the Primary Endpoint (RAP Section 7.1.7.1)

The RAP Section 7.1.7.1 states the following text as the first step in the method for the imputation of missing data due to COVID-19:

- A bayesian repeated measures logistic regression model will be fitted to the observed data, using a Markov Chain Monte Carlo (MCMC) approach, adjusting for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). Non-informative priors will be used.

However, the planned approach is not a repeated measures approach, it is an imputation approach that will proceed sequentially through affected visits, so the text 'repeated measures' should be removed.

2.5. Clarification on Missing Data for SLEDAI-2K in additional COVID-19 Analyses (RAP Section 7.1.7.4)

Table 3 in the RAP (Section 7.1.7.4) displays a graphical representation of specific scenarios for individual subjects, in terms of their completion status or any Intercurrent Events, and the timing of them in relation to the COVID-19 environment onset date.

In the existing table, there was one row for subjects who complete at Week 52 after the COVID environment onset date. To cover the scenario of missing (or partial non-informative) SLEDAI-2K data, that row has been split into two rows, as shown in Table 1 below:

Table 1 Graphical Representation of the Additional Analyses

COVID-19 environment Onset date	Description	Primary Analysis Hybrid	COVID Attributed	COVID Environment	Pre-COVID
X ——— 0 Comp.	Subject Completes Week 52 on or after COVID-19 environment onset date and has a completed (or partial but informative) S2K Score	R/NR	R/NR	Imputed	Excluded
X ——— 0 Comp.	Subject Completes Week 52 on or after COVID-19 environment onset date and has a missing or partial non-informative S2K Score that cannot be determined to definitely be either R or NR	NR	Imputed	Imputed	Excluded

Comp. = Completed; R/NR = Responder/Non-Responder based on SLEDAI-2K criteria; NR = Non-Responder

2.6. Duration of Disease Control (RAP Section 15.6.4)

The formula for the duration of disease control specified in RAP Section 15.6.4 should be as follows:

Duration of disease control = longest period where
Last visit of disease control – **First** visit of disease control + 1

Also, it is not appropriate to derive disease control at Baseline, therefore the first visit of disease control considered in this calculation will always be the first post-baseline visit where the subject meets the disease control criteria.

2.7. Lupus Low Disease Activity State (LLDAS) Missing Data (RAP Section 7.4 and Section 15.6.9)

The RAP does not explicitly state what happens when the subject has missing data for a component of their LLDAS assessment. Adding these clarifying sentences would be clearer:

"Within each criteria, a subject with an incomplete assessment (due to missing data) will be considered as missing, i.e. observed data will be presented for the individual criteria.

A subject is only considered an overall responder for LLDAS if they are a responder for all 6 criteria, i.e. missing data within one or more criteria would make them an overall non-responder."

2.8. LLDAS – clarification of endpoint definition (RAP Section 15.6.9)

Clarifications have been made to the LLDAS endpoint definition table in RAP Section 15.6.9. for the criteria of "well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs".

Firstly, the RAP Section 15.6.9 and protocol Section 7.7.14 refer to "Cyclosporine", however the MedDRA dictionary name is "Ciclosporin".

Secondly the existing text in RAP Section 15.6.9 (shown below) has been clarified to include the additional text shown in bold. This additional text makes it clearer that the Anti-TNF therapy and other biologics listed are just examples and it also provides additional examples of other biologics based on the Year 1 blinded data:

"Not to be taken within 28 days prior to the assessment:

- Intravenous Cyclophosphamide
- Other investigation agent

- Anti-TNF therapy (**e.g.** adalimumab, etanercept, infliximab)
- Other biologics (**e.g.** abatacept, anakinra**, commercial rituximab, tocilizumab**)
- IVIG
- Plasmapheresis"

The following sentence has also been added to clarify the use of commercial Belimumab: "Subjects can take commercial Belimumab IV or SC and this doesn't prevent them from being a responder on this criteria for the LLDAS.".

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Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 205646, a Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 104-Week Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE)
Compound Number	:	GSK1550188
Effective Date	:	5-AUG-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205646.
- This RAP is intended to describe the planned efficacy, safety, pharmacokinetics and biomarker analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author:

Author	Approval Method
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RAP Team Confirmationss:

Reviewer	Approval Method
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol versions:

Protocol Revision Chronology:		
Amendment 4 (Global)	30 APR 2020	COVID-19 amendments
Amendment 3 (Global)	15-AUG-2019	Treatment for subjects with neutropenia corrected
Amendment 2 (Global)	17-NOV-2018	Sample size increased following potential unblinding issue identified.
Amendment1 / ARG	02-JUL-2018	Argentina Specific amendment
Amendment1 / DEU-2	27-NOV-2017	Germany Specific amendment
Amendment1 / DEU -1	23-OCT-2017	Germany Specific amendment
Amendment1 / KOR- 1	22-JUN 2017	Korea Specific amendment
Amendment 1 (Global)	17-APR-2017	Comments and feedback from EMA and FDA
Original	16-JAN-2017	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

This the 2nd version of the Reporting and Analysis Plan, and is in keeping with additional detail to that provided in the Protocol (30 APR 2020), and the critical components document of 27FEB2018. Additional clarification has been added to text copied from the protocol when referring to the SLEDAI-2K, to clarify when referring to the independent blinded assessor assessment (IBA) and when referring to the principal investigator assessment (PI). The derivation of the endpoints (including the primary) has been clarified to be in accordance with ICH E9 R1 terminology. Additional analysis to assess the impact of the COVID-19 pandemic has been added.

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

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE	• Proportion of participants with a state of disease control defined as a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)- 2K (IBA) score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day at Week 52

Objectives	Endpoints
Secondary Objectives: Efficacy (Major)	**Secondary Endpoints: Efficacy (Major)**
• Secondary: Efficacy (Major)	• Proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score (IBA) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64. • Proportion of participants with a state of disease control defined as a SLEDAI-2K score (IBA) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day at Week 104
Secondary Objectives: Efficacy (Other)	**Secondary Endpoints: Efficacy (Other)**
• Secondary: Efficacy (Other)	• Proportion of participants with a state of disease control, defined as a SLEDAI-2K score (IBA) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day, by visit • Proportion of participants with a state of clinical remission, defined as a Clinical SLEDAI-2K score (IBA) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit. • Proportion of participants with a state of complete remission, defined as SLEDAI-2K score (PI) =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks. • Proportion of participants with a state of clinical remission, defined as Clinical SLEDAI-2K score (PI) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks. • Proportion of participants with a state of complete remission, defined as a SLEDAI-2K score (PI) =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit • Time to first severe flare (as measured by the modified SLE Flare Index) • Time to first flare (as measured by the modified SLE Flare Index) • Time to disease control sustained to Week 104, defined as SLEDAI-2K score (PI) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day.

Objectives	Endpoints
	• Time to clinical remission sustained to Week 104 , defined as Clinical SLEDAI-2K score (PI) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. • Duration of disease control, defined as SLEDAI-2K score (PI) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day • Duration of clinical remission, defined as Clinical SLEDAI-2K score (PI) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. • Change from baseline in SLEDAI-2K score (PI) by visit • Proportion of participants with SLEDAI-2K (PI) organ improvement by visit • Proportion of participants with SLEDAI-2K (PI) organ worsening by visit • Change from baseline in Physician Global Assessment (PGA) by visit • Proportion of participants with any SLICC Damage Index worsening (change >0) compared with baseline at Week 52 and Week 104 • Proportion of participants that meet the Lupus Low Disease Activity State (LLDAS) response criteria by visit. The LLDAS incorporates multiple measures of disease activity, specifically: (1) SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anaemia or gastrointestinal activity; (2) no new features of lupus disease activity compared with the previous assessment; (3) PGA (scale 0-3) ≤1; (4) current prednisolone (or equivalent) dose ≤7.5 mg daily; and (5) well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs. • Proportion of participants with a state of disease control, defined as a SLEDAI-2K score (PI) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day, by visit; using the principal investigators assessment of SLEDAI-2K • Proportion of participants with a state of clinical remission, defined as a Clinical SLEDAI-2K score (PI) =0 (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose

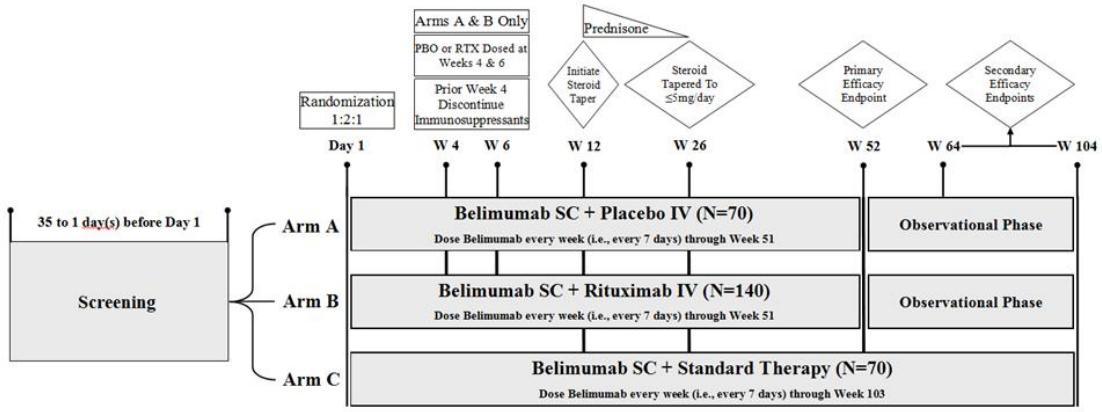
Objectives	Endpoints
	of 0 mg/day, by visit; using the principal investigators assessment of SLEDAI-2K.
Secondary (Safety) Objectives	**Secondary (Safety) Endpoints**
Secondary: Safety • To assess the safety and tolerability of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE	• Incidence of adverse events (AEs) including serious AEs (SAEs) and AEs of special interest (AESIs)
Secondary: Patient Reported Outcomes (PROs) Objectives	**Secondary: Patient Reported Outcomes (PROs) Endpoints**
Secondary: Patient Reported Outcomes (PROs) • To assess the impact of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE on PROs	• Change from baseline in Patient Global Assessment (PtGA) by visit • Change from baseline in LupusQoL domain summary scores (8 domains) by visit • Change from baseline in FACIT-Fatigue score by visit • Proportion of participants with improvement in FACIT-Fatigue score exceeding the Minimal Clinically Important Difference (MCID, ≥4) by visit
Exploratory: Pharmacokinetics and Biomarkers Objectives	**Exploratory: Pharmacokinetics and Biomarkers Endpoints**
Exploratory: Pharmacokinetics and Biomarkers • To assess pharmacokinetics of and biomarker response to belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE	• Belimumab and rituximab concentrations by visit • Change from baseline in autoantibodies by visit • Change from baseline in peripheral blood leukocytes including B cell subsets by visit • Change in BLyS levels from baseline by visit
Exploratory: Patient Reported Work Productivity Objectives	**Exploratory: Patient Reported Work Productivity Endpoints**
Exploratory: Patient Reported Work Productivity • To explore the impact of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE on patient experience and productivity	• Change from baseline in Work Productivity and Activity Impairment (WPAI): Lupus percent overall work productivity impairment by visit • Change from baseline in WPAI: Lupus percent activity impairment score by visit

These are the protocol defined endpoints (Protocol Section 4), protocol Section 10.4.1 Efficacy analysis then clarifies further that:

> For participants who withdraw prematurely from study treatment and for whom subsequent collection of data is not possible, it will be assumed for the primary analysis that they are treatment failures. A dropout/treatment failure = non-responder (DO/TF=NR) analysis will be used .

Hence when adopting the ICH Estimands and Sensitivity Analysis in Clinical Trials E9 R1 addendum terminology, an endpoint has been defined which combines this information.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-center, 3-arm, randomized, double-blind, placebo-controlled, 104 week superiority study to evaluate the efficacy and safety of belimumab administered in combination with a single cycle of rituximab to adult participants with active SLE, i.e. SLEDAI-2K score ≥6. The primary efficacy endpoint will be measured at Week 52. • At least 280 participants will be randomized in a 1:2:1 ratio to 1 of 3 arms: belimumab plus rituximab-placebo (Arm A, control, target N=70), belimumab plus rituximab (Arm B, combination, target N=140), or belimumab plus standard therapy (Arm C, reference, target N=70). Arms A and B are double-blind; participants will receive belimumab 200 mg/week for 52 weeks. Arm C (reference) is an open-label arm with belimumab subcutaneous (SC) 200 mg/week and standard therapy for 104 weeks. • Randomization and the first dose of belimumab should be completed within 35 days of initiation of screening procedures. • Participants will be stratified by their screening SLEDAI-2K score (≤9 vs. ≥ 10), by immunosuppressant use at screening (immunosuppressant use vs. no use), and by screening corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). • Participants randomized to Arms A and B, who enter the study on immunosuppressants, will discontinue immunosuppressants at or prior to the Week 4 infusion visit • After the initial 12 weeks of study treatment, a protocol-specified corticosteroid taper will be initiated and conducted under the direction of the investigator for participants in all 3 arms. The taper will proceed with a target of reaching a prednisone equivalent dose of ≤5 mg/day by Week 26.
Dosing	• Arms A and B are double-blind; participants will receive belimumab 200 mg/week SC for 52 weeks. Rituximab-placebo or rituximab (1000 mg IV) will be administered

Overview of Study Design and Key Features	
	by intravenous (IV) infusions in a double-blind manner at Weeks 4 and 6 for Arms A and B. • In Arms A and B, a pre-medication regimen will be given before each rituximab or rituximab-placebo infusion, including methylprednisolone 100 mg IV or equivalent, an oral antihistamine, and an acetaminophen or equivalent. • Arm C (reference) is an open-label arm with belimumab subcutaneous (SC) 200 mg/week and standard therapy for 104 weeks.
Schedule of Activities	• See Section 15.2 Appendix 2: Schedule of Activities

Treatment Assignment	• At least 280 participants will be randomized in a 1:2:1 ratio to 1 of 3 arms: belimumab plus rituximab-placebo (Arm A, control, target N=70), belimumab plus rituximab (Arm B, combination, target N=140), or belimumab plus standard therapy (Arm C, reference, target N=70).
	  • Arms A and B are double-blind; participants will receive belimumab 200 mg/week for 52 weeks.
	  • Arm C (reference) is an open-label arm with belimumab subcutaneous (SC) 200 mg/week and standard therapy for 104 weeks. Currently available standard therapy includes continuation of immunosuppressant agents throughout the course of the study (See Protocol Section 7.7.1.4 for detailed information regarding immunosuppressant medications dosing).
	• At randomization, participants will be stratified by their screening SLEDAI-2K score (≤9 vs. ≥ 10), by immunosuppressant use at screening (immunosuppressant use vs. no use), and by screening corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day)

Interim Analysis	• No formal interim analyses planned for this study

2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of the study is to demonstrate superiority (improvement in response rate) of co-administration of belimumab plus rituximab (Arm B: Combination) over belimumab monotherapy (Arm A: Control), when comparing the primary efficacy endpoint at Week 52 in subjects with SLE.

Analysis of the primary objective will use data from the whole population and therefore includes subjects from treatment Arms A, B, and C, even though the primary objective is only comparing treatment Arms A and B. Hence an exploratory assessment of the relative performance of Arm A (Control) and Arm B (Combination) vs. standard SLE therapy (Arm C: Reference) will also be conducted using the same analysis.

The primary efficacy endpoint is defined as: the proportion of participants with a state of disease control defined as a SLEDAI-2K score (IBA) ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 52.

Null Hypothesis (H_0):	There is no difference between Arm B (combination) and Arm A (control) in terms of the primary endpoint at Week 52.
Alternative Hypothesis (H_1):	There is a difference between Arm B (combination) and Arm A (control) in terms of the primary endpoint at Week 52.

A step-down sequential testing procedure will be used to control the overall type 1 error rate for comparing Arm B (combination) vs Arm A (control). With this procedure, the primary endpoint and the two major secondary endpoints will be evaluated for statistical significance based on a pre-specified sequence for interpretation (i.e., disease control at Week 52, followed by clinical remission at Week 64 and then disease control at Week 104, see Figure 1). Specifically, endpoints will be tested in the sequence above (2-sided alpha=0.05) provided that 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. Analyses of other efficacy endpoints will not be subject to any multiple comparison procedure.

3. PLANNED ANALYSES

3.1. Interim Analyses

There are no formal planned interim analyses.

An independent data monitoring committee (IDMC) will review unblinded safety data on an ongoing basis until all participants have completed the 104 week study (after which monitoring may be assumed by an internal GSK committee). The IDMC will include physicians with relevant clinical expertise and a statistician, none of whom is affiliated with the sponsor. The 1st IDMC data review meeting occurred in Sept 2018 (6months after the 1st subject was randomised) and continued in approximately 6 monthly intervals. Ad hoc meetings of the IDMC can also be requested as needed to review urgent safety information or AEs. Events to be monitored during the safety review will include at a minimum all SAEs (including deaths, serious psychiatric events, and serious infections), Grade 3 and Grade 4 laboratory abnormalities, opportunistic infections (serious and non-serious), malignancies, and hypersensitivity/anaphylactic reactions during the double-blind treatment phase (Year 1) and double-blind observational phase (Year 2) for Arms A & B and open-label treatment phase (Years 1 and 2) for Arm C. In addition, the IDMC will receive information within 72 hours of all SAEs that are life threatening or result in death. Other SAEs, all opportunistic infections, irrespective of relationship to study treatment, and protocol specified events (i.e., IgG <250 mg/dL) will be provided to the IDMC bi-weekly for review.

3.2. Final Analyses

There will be two database locks for this study, corresponding to the primary analyses and the end of study analyses. The primary analyses will include data up to the 52 week visits for the primary endpoint.

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

1. All subjects have completed the Week 52 visit (or Early Withdrawal visit for those subjects who withdraw from the study during Year 1).
2. All required database cleaning activities have been completed and final database release (DBR) has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met, including:
    - Review of Protocol Deviations through Week 52
    - Adjudication of AESI through Week 52
    - Review of treatment failures through Week 52
4. Randomisation codes have been distributed according to RandAll NG procedures.
5. Database freeze (DBF) has been declared by Data Management.

A final analysis will be conducted following the last subject completion of year 2 (including all 8 week-follow-up visits) when all required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management as described in Steps 2, 3 and 5 above

This RAP details the planned analysis for both database locks, with the expectation of an observed treatment benefit at Week 52. If the Week 52 reporting does not identify a treatment benefit, an abridged set of analysis may be conducted at the end of the study, which will be detailed in a RAP amendment or RAP addendum.

4. ANALYSIS POPULATIONS

During the early conduct of the study some participants in ARM C (n=29) were inappropriately identified on a laboratory report which could have unblinded the independent blinded assessors. Blinding of Arms A and B was not compromised. For this reason the sample size was increased, and a Modified Intent To Treat (MITT) population has been created to exclude the potentially unblinded (to the independent blinded assessor) Arm C subjects.

Population	Definition / Criteria	Analyses Evaluated
Screened (Enrolled)	• All screened candidates who sign the ICF	• Screen failures and Study Population
Randomized	• All participants who were randomly assigned to treatment in the study. • Any participant who receives a treatment randomization number will be considered to have been randomized. • This population will be based on the treatment the participant was randomized to.	• Study Population
Intent-To-Treat (ITT)	• All randomized participants who received at least one dose of study treatment (Belimumab or Rituximab/placebo) . • This population will be based on the treatment the subject was randomized to.	• Study Population • Safety • Pharmacodynamic and Biomarker
Modified Intent-To-Treat (MITT)	• All randomized participants who received at least one dose of study treatment (Belimumab or Rituximab/placebo) . • Arm C subjects randomized prior to 07 September 2018, whose independent blinded assessor had potential to be unblinded, are excluded from this population. • This population will be based on the treatment the subject was randomized to.	• Efficacy • Health Outcomes
Per Protocol (PP)	• All participants in the MITT population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in Section 4.2 (Per Protocol Population) and Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population. • The PP set will not be analysed if this population comprises more than 85% of the MITT population.	• Efficacy

These additional populations will also be considered in order to consider missing data

Population	Definition / Criteria	Analyses Evaluated
Ongoing on study treatment at Week 52	• All MITT population Arm A and Arm B participants who are ongoing after 52 weeks of the planned double-blind treatment period who received all of both IV doses of rituximab or rituximab-placebo, and did not have more than 28 consecutive days from baseline to Week 51 without a belimumab dose; includes MITT population Arm C subjects who remained on open-label belimumab through Week 52 and did not have more than 28 consecutive days baseline to Week 51 without a belimumab dose.	• Sensitivity analysis of the primary efficacy endpoint
Ongoing on study treatment at Week 64	• All MITT population Arm A and Arm B participants who are ongoing after 64 weeks who received all of both IV doses of rituximab or rituximab-placebo, and did not have more than 28 consecutive days from baseline to Week 51 without a belimumab dose; includes MITT population Arm C subjects who remained on open-label belimumab through Week 64 and did not have more than 28 consecutive days from baseline to Week 63 without a belimumab dose.	• Sensitivity analysis of the 1st Major secondary efficacy endpoint
Completers on study treatment	• All MITT population Arm A and Arm B participants who complete Week 104 who received all of both IV doses of rituximab or rituximab-placebo, and did not have more than 28 consecutive days from baseline to Week 51 without a belimumab dose; includes MITT population Arm C subjects who remained on open-label belimumab through Week 104 and did not have more than 28 consecutive days from baseline to Week 103 without a belimumab dose.	• Sensitivity analysis of the 2nd Major secondary efficacy endpoint
As Treated	• All randomized participants who received at least one dose of study treatment (Belimumab or Rituximab/placebo) . • Subjects in Arms A or B who receive one or more infusions of rituximab will be included in Arm B for the As Treated analysis. Subject in Arm B who receive two doses of rituximab-placebo (and no rituximab) will be included in Arm A.	• If more than 5% of subjects received the incorrect RTX treatment, then the Primary efficacy endpoint will be repeated for this population • Safety endpoints if more than 5% received the wrong RTX

		treatment, then this population will replace the ITT for safety
Pharmacokinetic (PK)	• All participants in the ITT population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ]. values will be considered as non-missing values).	• PK

The following additional populations will be defined as pre-COVID-19 populations. The COVID-19 environment onset date is defined in Section 15.6.16.

Population	Definition / Criteria	Analyses Evaluated
MITT Week 52 prior to COVID-19	• All randomized participants who received at least one dose of study treatment and had their first dose of study medication early enough that they should have completed their Week 52 visit prior to the COVID-19 environment onset date, i.e. their first dose of study treatment was prior to the onset date minus 52 weeks • Arm C subjects randomized prior to 07 September 2018, whose independent blinded assessor had potential to be unblinded, are excluded from this population • This population will be based on the treatment the subject was randomized to.	• Efficacy
MITT Week 64 prior to COVID-19	• All randomized participants who received at least one dose of study treatment and had their first dose of study medication early enough that they should have completed their Week 64 visit prior to the COVID-19 environment onset date, i.e. their first dose of study treatment was prior to the onset date minus 64 weeks • Arm C subjects randomized prior to 07 September 2018, whose independent blinded assessor had potential to be unblinded, are excluded from this population • This population will be based on the treatment the subject was randomized to.	• Efficacy

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and listed for both the double-blind phase (Year 1) and observational phase (Year 2) separately [T11.13, T21.09, L11.07, L21.04]. The tables will display the number and percentage of subjects who experience any important protocol deviation and for each deviation type.

All protocol deviations that relate to COVID-19 will be summarized and listed for both the double-blind phase (Year 1) and observational phase (Year 2) separately [T11.14, T21.10, L11.07, L21.04]. The tables will display the number and percentage of subjects who experience any protocol deviation related to COVID-19.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP). [Version 6].

- Year 1 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.
- Year 2 data will be reviewed by the blinded study team prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.

All deviations will be discussed and adjudicated as important or not important according to the PDMP.

This preliminary assessment of the deviation resulting in the subject being excluded from the per protocol population, but will be subject to a final review as detailed in Section 4.2.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF [T11.12, L11.06].

4.2. Per Protocol Population

Periodic review of the per protocol population will be conducted during the course of the study, with a final assessment made prior to unblinding the data for the Year 1 reporting.

The per protocol population will be primarily based on an assessment of the important protocol deviations. However non-important deviations or other study conduct issues may be identified during the study that warrant a subject's exclusion from the per protocol population. This will be documented in the protocol deviation adjudication

meeting minutes prior to database freeze. Only protocol deviations or study conduct issues that have the potential to impact the efficacy evaluation will lead to exclusion from the per protocol population.

The per protocol population will be derived based on the Year 1 data. If Year 2 reporting (or combined Year 1&2) per protocol analysis is required it will be based on the per protocol population defined for Year 1.

Subjects excluded from the Per Protocol (PP) population will be summarized [T11.15].

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Belimumab plus Placebo	BEL SC plus PBO IV	1
B	Belimumab plus Rituximab	BEL SC plus RTX IV	2
C	Belimumab Open-Label	BEL SC plus STD Therapy	3

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

1. BEL SC plus RTX IV vs BEL SC plus PBO IV
2. BEL SC plus RTX IV vs BEL SC plus STD Therapy
3. BEL SC plus PBO IV vs BEL SC plus STD Therapy

Table 1 Treatment Descriptors, Colors, Line Style and Symbols for Reporting in Double-Blind Phase

Treatment Descriptor	Color	SAS Color	Line Style	Symbol
BEL SC plus PBO IV	Blue	CX0000FF	Dashed	Triangle (filled)
BEL SC plus RTX IV	Green	CX2A8307	Long dashes	Circle (filled)
BEL SC plus Standard Therapy	Brown	CXA05000	Solid	Square (open)

5.2. Study Day

Study day is the number of days from Belimumab study treatment start date to the study day of interest and is calculated as:

Criteria:	Study day is:
Study date < treatment start date	Study date - treatment start date
Study date >= treatment start date	Study date - treatment start date + 1

Note: Study day cannot be zero. If either date is missing the study day is missing. Further detail is provided in Section 15.6.1

5.3. Baseline Definitions

For all the endpoints for both the Week 52 and Week 104 analysis (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy			
SLEDAI-2K Principal Investigator (PI)	X	X	Day 1
SLEDAI-2K Independent Blinded Assessor (IBA)		X	Day 1
SLICC Damage Index		X	Day 1
Physician Global Assessment (PGA)		X	Day 1
Safety and Biomarker			
Laboratory assessments (including liver chemistry, serum immunoglobulin, Anti-dsDNA/ANA, and complement C3/C4)	X	X	Day 1
Biomarkers (including Antiphospholipid antibodies, PBMC, B-Cells, BLys Protein, RNA for interferon, and immunogenicity)		X	Day 1
C-SSRS	X	X	Day 1
PROs			
Patient Global Assessment (PtGA)		X	Day 1
FACIT-Fatigue score		X	Day 1
LupusQoL		X	Day 1
WPAI: Lupus		X	Day 1

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

Concomitant medications are considered to be 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 (Section 15.4.1).

Adverse events (AEs) are considered pre-treatment if the start date is prior to Day 1. AEs with a start date on or after Day 1 are considered as being treatment-emergent.

Baseline flares are flares that occur on or prior to the treatment start date. Therefore, flares that occur on Day 1 are not counted as post-baseline flares.

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

5.4. Multicentre Studies

In this multicentre global study, enrolment will be presented by country and investigative site. Countries will be grouped into geographic regions for summary presentation [T11.01] as shown in Section 5.5.2.

5.5. Examination of Covariates, Strata and Subgroups

5.5.1. Covariates and Strata

The list of strata is based on the randomization stratification and will 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 have not been identified for planned analyses, but may be considered for post-hoc analyses.

Category	Details
Strata (As Randomized)	SLEDAI-2K: ≤9 vs. ≥10 Immunosuppressant: Use vs. Non-use Corticosteroid dose: ≤10 mg/day vs. >10 mg/day

The following covariates will be included in the analysis as detailed in Section 7 Efficacy Analyses

Covariate	Details
SLEDAI-2K: ≤9 vs. ≥10	Derived from the principal investigators' assessment at baseline (reference level: ≥10)
Immunosuppressant: Use vs. Non-use	Derived from reported concomitant medications at baseline (reference level: Non-use)
Corticosteroid dose: ≤10 mg/day vs. >10 mg/day	Derived from reported concomitant medications at baseline (reference level: >10mg/day)
Covariates	No additional covariates

5.5.2. 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 for post-hoc analyses.

- If the percentage of subjects responding is small within a subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the subgroup.

Subgroup	Categories
Age Group	<65 vs. >=65 If there are less than 10 subjects >=65, this sub group will be summarised but not analysed
Race	Black vs. Non-Black
Gender	Female vs Male
Country Region	USA/Canada: USA and Canada, Europe: France, Germany, Netherlands, Spain Rest of World: All other countries
Baseline SLEDAI	≤9 vs. ≥10
Baseline Immunosuppressant Use	Use vs. Non-use
Baseline corticosteroid dose	≤10 mg/day vs. >10 mg/day (Prednisone equivalent)
Baseline complement level	At least one low C3/C4 vs. No low C3/C4
Baseline anti-dsDNA	≥30 IU/mL vs. <30 IU/mL
Baseline C3/C4 levels & anti-dsDNA	At least one low C3/C4 & anti-dsDNA ≥30 IU/mL vs. Not (At least one low C3/C4 & anti-dsDNA ≥ 30 IU/mL)
Baseline BLyS (free) Protein	>= 75th Percentile vs. < 75th Percentile
Baseline RNA Interferon Signature	Low vs. High

5.6. Multiple Comparisons and Multiplicity

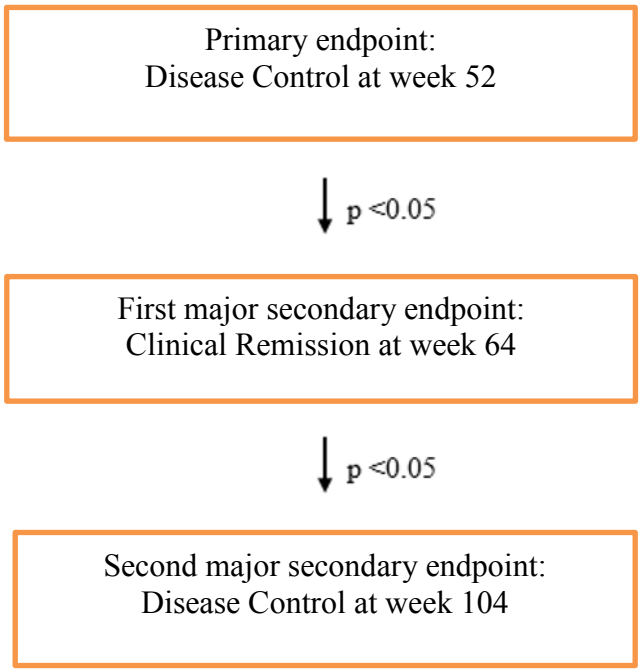
The primary comparison of interest is the comparison between Arm B (combination) vs Arm A (control) for the primary endpoint (SLEDAI-2K≤2 (IBA)) in the MITT population. This analysis will be adjusted for baseline SLEDAI-2K (≤9 vs. ≥10), baseline immunosuppressant (Use vs. Non-use) and baseline corticosteroid dose (≤10 mg/day vs. >10 mg/day). .

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 rate for comparing Arm B (combination) vs Arm A (control). With this procedure, the primary endpoint aand the two major secondary endpoints will be evaluated for statistical significance based on a pre-specified sequence for interpretation (i.e. the endpoints based on SLEDAI-2K score (IBA) ≤ 2 at Week 52, followed by Clinical SLEDAI-2K score (IBA) =0 at Week 64 and then SLEDAI-2K score (IBA) ≤ 2 at Week 104, see Figure 1). Specifically, endpoints will be tested in the sequence above (2-sided alpha=0.05)

provided that 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. The primary endpoint will be tested at the primary analysis using the first locked database; the first and second major secondary endpoints will be tested using the end of study locked database.

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

Figure 1 Overview of Multiplicity Control



Analyses of other efficacy endpoints will not be subject to any multiplicity adjustment.

5.7. Cut-off Date for Primary Analyses (Year 1)

For study participants continuing in the study past the Week 52 visit, the cut-off date in the Year 1 analysis dataset will be the date of the Week 52 visit.

For participants who discontinue from the study prior to the Week 52 visit, the exit/withdrawal visit will be assigned to an assessment window as defined in Section 15.3. Exit/withdrawal visit assigned to week 52 or earlier will be included in the week 52 report; exit/withdrawal visits assigned to an assessment window from Week 60 or later, will be reported in the Week 104 analysis.

Participants who withdraw at or prior to the Week 52 visit will have their follow-up visit included in the Year 1 reporting if the follow-up visit is prior to or on the day of the last subject's Week 52 visit. Follow-up visits that occur after the last subjects' Week 52

assessment will be reported in the Year 2 reporting. Hence subjects who withdraw at or prior to Week 52 will have a cut-off date that is the earliest of their week follow-up date and the last subject's Week 52 date.

Displays for the primary analysis reporting effort will include all data collected up to and including the Year 1 cut-off date for each participant. This includes adverse events and concomitant medications with a start date less than or equal to the cut-off date.

5.8. Database for End of Study Analyses (Year 2 and Years 1&2 Combined)

The final database will be an accumulation of all data from both Year 1 and Year 2 including the 8-week Follow-up visit.

5.9. Study Withdrawal

Study withdrawal (referred to in the protocol as dropout), is the combination of subjects who withdraw, are lost to follow-up (LTFU), or die during the study

Study withdrawal is defined as any subject who withdraws from the study prior to the analysis visit of interest (e.g. Week 52, Week 64, Week 104) and does not have a visit within ± 28 days of the target analysis visit date (excluding follow up visits).

This rule is applied consistently across all efficacy endpoints. The assessment of whether or not a subject had a visit within the ± 28 day of an analysis visit (e.g. Week 52) is performed at the domain level [e.g., a subject who had visit within 28 days for SLEDAI-2K but not a SLICC ACR assessment would be assessed on their observed data for SLEDAI-2K but would be considered withdrawn (non-responder) in SLICC ACR assessment].

5.10. Treatment Failures

Treatment failures are subjects meeting any of the criteria defined below, from the time they 1st met the criteria:

- Received a protocol prohibited medication
- Arm A&B: Received immunosuppressants after Week 4 rituximab infusion visit; Arm C: Increased immunosuppressants (at a dose higher than at baseline and Week 12) after Week 12
- Arms A&B only: Received PI prescribed re-start belimumab medication after Week 52 visit and prior to Week 104 visit
- Started any new immunosuppressant after Day 1
- Received a prednisone equivalent corticosteroid 7-day average dose of >5 mg/day after Week 26 visit
- Received a dose above the allowable level or after a protocol specified timepoint (Section 7.7.1 of the protocol) prior to Week 52 visit

Further detail is provided in Section 15.6.15 Treatment Failure Rules During Study Conduct

5.11. On Study

For Year 1, on study is defined as from 1st dose of belimumab to the earliest of:

- Week 52 visit assessment
- Study withdrawal (including LTFU and Death)

However, for subjects that withdraw during Year 1, the on treatment period could end later than the on study period. In this situation the on study period will be reset such that it ends at the same time as the on treatment period.

NOTE: Some subjects who are enrolled toward the end of the enrolment period and withdraw at or near their Week 52 assessment may have some of their Year 1 on study period reported at the end of the study (Section 5.7).

For Year 2, on study is defined as from the Week 52 visit assessment* until the date of study completion or study withdrawal (including LTFU and death).

*Subjects who did not complete week 52 but had not withdrawn prior to Week 52, and have post Week 52 assessments will use scheduled visit date.

For Year 1&2 on study is defined as from the 1st dose of belimumab until the date of study completion or study withdrawal (including LTFU and death).

5.12. On Treatment

For Year 1 on treatment is defined as from 1st dose of belimumab to the latter of: last dose of belimumab + 28 days or last dose of rituximab + 28 days

For Year 1&2 arm C, on treatment is defined as from 1st dose to last dose of belimumab + 28 days.

For Year 2 Arms A&B on treatment is not defined as there is no on treatment reporting (as all subjects are off treatment)

5.13. Race Hierarchy (minority rule)

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

1. Native Hawaiian or Other Pacific Islander
2. American Indian or Alaska Native
3. Asian
4. African American/African Heritage
5. White

For example, if African American/African Heritage and Asian are both checked, then the subject will be assigned as Asian since it appears highest in the list. Race assigned based on this minority rule will be applied to all analyses related to race (as per PSAP). In the race and racial combination details table, subjects with multiple race categories checked will be reported in the race per the minority rule as well as in the multiracial category.

5.14. 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
15.3	Appendix 3: Assessment Windows
15.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7: Reporting Standards for Missing Data
15.8	Appendix 8: Laboratory Parameters and Toxicity Grades
15.9	Appendix 9: Biomarkers

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Intent-to-Treat population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. See Study Population shells for mock displays.

6.2. Disposition of Subjects

The number and percentage of subjects randomized by country and site will be summarized overall and by treatment group using the Randomized population [T11.01].

The number of subjects in each population for the primary analyses (Screened, Randomized, ITT, MITT, MITT Week 52 prior to COVID-19, MITT Week 64 prior to COVID-19, Per Protocol, Ongoing at Week 52, Ongoing on study treatment at Week 52, As Treated and PK) and for the end-of-study analysis (Ongoing at Week 64, Ongoing on study treatment at Week 64, and Completed) will be summarized overall and by treatment group [T11.02, T21.01]. A summary of the reasons for the screen failures will be provided along with a listing of the subjects who were screen failures [T11.03, L11.01]. If there are any subjects who are randomized but do not receive any study treatment, they will be included on the subject disposition listing in the Randomized population, but not the ITT population.

Subject status through Week 52 (Year 1), and over the entire study (Years 1&2 Combined) will be summarized for the ITT [T11.04, T21.02] and MITT [T11.05, T21.03] populations.

For the ITT population, a summary of treatment status and reasons for discontinuation of study treatment will be produced at Week 52 and at end of study. The number and percentage of subjects who completed the study treatment as planned as well as subjects who stopped study treatment prematurely, including reasons for treatment discontinuation, will be displayed by treatment group [T11.08, T11.09, T21.04].

The cumulative number and percentage of subjects withdrawing from the study by visit will be summarized for the ITT (T11.07) population at Week 52, and at Week 104 (T21.05) and listed (L11.03, L21.02).

A Kaplan-Meier (KM) plot of time to study withdrawal will be generated to evaluate the pattern of study withdrawals/LTFU/death over time up to Week 52 [F11.01].

> Subjects who withdraw (including LTFU and death) will be considered to have experienced an event (cens=0) at:
> Time to study withdrawal = withdrawal date – 1st Belimumab injection date + 1

Subjects ongoing at Week 52 will be considered censored (cens=1) at:
Time to study withdrawal = Week 52 date – 1st Belimumab injection date + 1

The figure will be repeated for the Week 104 reporting with all data from Year 1 and 2 [F21.01].

Subjects completing at Week 104 will be considered censored (cens=1) at:
Time to study withdrawal = Week 104 date – 1st Belimumab injection date + 1

For the ITT population, the subject's study completion status will be assessed to evaluate percentages of study withdrawals by treatment group as well as the reasons for study withdrawal. The number and percentage of subjects who completed through Week 52 (Week 64 and 104) and who withdrew from the study, including reasons for withdrawal, will be displayed by treatment group and overall for Year 1 and Year 1&2 separately [T11.06, T21.06]. A listing of subjects who withdrew from the study, including reason for and time to study withdrawal will also be provided. [L11.03, L21.02].

Additionally, the cumulative number and percentage of subjects who prematurely discontinued from the planned study treatment by visit will be displayed by treatment group and overall for Year 1 and 2 separately for the ITT and MITT populations [T11.10, T11.11, T21.07, T21.08].

A listing of subject disposition will be provided showing their completion status and whether they are included in each population [L11.02, L21.01].

A shift table that summarizes the differences between the levels of each stratification factor at screening compared to values used in randomization will be provided [T11.16].

The COVID-19 environment onset and end dates will be listed (L11.15, L21.09). Current COVID-19 environment onset dates are shown in Section 15.6.16

6.3. 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, as well as stratification factors, will be listed for all patients [L11.08, L11.09].

The following Demographic and baseline disease activity indicators will be summarized:

PARAMETER	SUMMARY TYPE
Medical History	
Past Medical Conditions [T11.22]. and Current Medical Conditions [T11.23].	Categorical: presented if past [current]. medical history is present
Family History of Cardiovascular Risk Factors [T11.24].	Categorical: Yes, No
Stratification Factors at Randomization [T11.25]	
SLEDAI-2K (PI)	Categorical: <=9, >=10
Baseline immunosuppressant use	Categorical: - Use - Non-use
Corticosteroid dose (prednisone equivalent)	Categorical: - ≤10 mg/day - >10 mg/day
Demographic [T11.17, T11.18 (MITT population), T11.19]	
Age (years)	Continuous Categorical: - <=45 years, - >45 – <65 years - >=65 years o >=65 – <75 years o >=75 years
Country Region	USA/Canada, Europe, Rest Of World (Section 5.5.2)
Country	As observed
Corticosteroid dose (prednisone equivalent)	Categorical: - ≤5 mg/day >5 mg/day
Corticosteroid dose (prednisone equivalent)	Categorical: - 0 mg/day >0 mg/day
Height (cm)	Continuous
Weight (kg)	Continuous
Body Mass Index (BMI) (kg/m^2)	Continuous
Blood Pressure [T11.21].	Continuous
Heart Rate (beats/min) [T11.21].	Continuous
Sex	Categorical: Female, Male
Ethnicity: Hispanic or Latino origin	Categorical: Hispanic or Latino origin, Not Hispanic or Latino origin
Race and Racial Combination Details [T11.20].	Categorical: White/Caucasian, Asian, African American/African Heritage, Alaskan Native or American Indian, Native Hawaiian or Other Pacific Islander, and Multiracial

PARAMETER	SUMMARY TYPE
Baseline Disease Activity	
SLEDAI-2K score (IBA) [T11.26, T11.27 (MITT)].	Continuous Categorical: <=9, 10-11, >=12
SLEDAI-2K score (PI) [T11.26, T11.27 (MITT)].	Continuous Categorical: <=9, 10-11, >=12
PGA score [T11.26, T11.27 (MITT)].	Continuous Categorical: 0-1, >1 – 2.5, >2.5
SLICC/ACR Damage Index score [T11.26, T11.27 (MITT)].	Continuous Categorical: 0, 1, >1
SLE disease duration (years) [T11.26, T11.27 (MITT)].	Continuous
SLEDAI-2K (PI) by organ domain and item at baseline [T11.29].	Categorical: presented if Yes
Baseline immunoglobulin levels (g/L): IgA, IgG, and IgM [T11.30].	Continuous value Categorical: - IgA: <LLN (0.81 g/L), >ULN (4.63 g/L) - IgG: <LLN (6.94 g/L), >ULN (16.18 g/L) - IgM: <LLN (0.48 g/L), >ULN (2.71 g/L)
Baseline levels of complement: C3 [mg/dL] [T11.26, T11.27 (MITT)].	Continuous Categorical: high (>180 mg/dL), normal (90 - 180 mg/dL), low (<90 mg/dL)
Baseline levels of complement: C4 [mg/dL] [T11.26, T11.27 (MITT)].	Continuous Categorical: high (>40 mg/dL), normal (10 - 40 mg/dL), low (<10 mg/dL)
Complement Level [T11.26, T11.27 (MITT)]	Categorical: At least one low C3/C4, No low C3/C4
Anti-dsDNA [IU/mL] [T11.26, T11.27 (MITT)].	Continuous Categorical: -positive (≥ 30 IU/mL) -negative (< 30 IU/mL)
Complement Level and anti-dsDNA Level [T11.26, T11.27 (MITT)].	Categorical: At least one low C3/C4 and anti-dsDNA ≥30 IU/mL; Not (At least one low C3/C4 and anti-dsDNA ≥30 IU/mL)
Proteinuria (g/24h) [T11.26, T11.27 (MITT)]	Continuous value Categorical: <=0.5 >0.5-<1 1-<2 >=2

PARAMETER	SUMMARY TYPE
Baseline autoantibody levels [T11.31].	
ANA [Titer].	Continuous Categorical: -positive (≥ 80 Titer) -negative (< 80 Titer)
anti-cardiolipin (aCL)	Continuous for each of aCL-IgA, aCL-IgG, aCL-IgM Categorical (Positive is >=15) : -positive (if any of the three isotypes aCL-IgG, aCL-IgA or aCL-IgM are above the upper limit of normal) -negative (if at least one is non-missing and none of the isotypes above the limit of quantification) -missing (all three isotypes are missing)
anti-dsDNA and/or ANA positive	Categorical: Yes, No
Beta-2-glycoprotein [U/mL]. for each of the isotypes IgG, IgA, and IgM	Continuous Categorical: Positive (>=21 U/mL), Negative
Lupus anticoagulant	Continuous
RNA Interferon Signature [T21.16]	Continuous Categorical: Low, High
B cells and T-cells at Baseline [T11.32]	
CD19+ Total B cells (cells/mL) B cells CD20+ (cells/mL) B cells CD20+ (%) Naive B cells IgD+ (cells/mL) Naive B cells IgD+ (%) Naive CD20+ CD27- (cells/mL) Naive CD20+ CD27- (%) Activated Total B cells CD95+ (cells/mL) Activated Total B cells CD95+ (%) Memory CD20+ CD27+ (cells/mL) Memory CD20+ CD27+ (%) Non-switched memory CD27+ IgD+ (cells/mL) Non-switched memory CD27+ IgD+ (%) Switched memory CD27+ IgD- (cells/mL) Switched memory CD27+ IgD- (%) Plasmablasts CD27b CD38b (cells/mL) Plasmablasts CD27b CD38b (%) Plasmablasts CD20+ CD27b CD38b (cells/mL) Plasmablasts CD20+ CD27b CD38b (%) Plasmablasts CD20- CD27b CD38b (cells/mL) Plasmablasts CD20- CD27b CD38b (%)	Continuous

PARAMETER	SUMMARY TYPE
Transitional CD10+ CD24b CD27- CD38b (cells/mL) Transitional CD10+ CD24b CD27- CD38b (%) Transitional CD24b CD27- CD38b (cells/mL) Transitional CD24b CD27- CD38b (%) CD3+ Total T cells (/uL) CD8+ T cells (/uL) CD4+ T cells (/uL)	
BLyS (free) [ng/mL] .	Continuous Categorical: below limit of quantification [LOQ]. (<0.05 ng/mL), above LOQ; <75th percentile, >=75th percentile
Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline [T11.33].	
C-SSRS responses by behavior and ideation components for lifetime and over the last six months	Categorical: -Ideation: categories 1-5 with corresponding text -Behavior: categories 6-10 with corresponding text -Self-injurious behavior, no suicidal attempt
Patient Reported Outcomes (PROs) [T11.28]	
Patient Global Assessment (PtGA)	Continuous
Baseline FACIT-Fatigue scale score	Continuous Categorical: (<20; 20-<35; ≥35)
LupusQoL	Continuous
WPAI: Lupus	Continuous
Allowable SLE Medication Usage at Baseline [T11.34]	
Allowable SLE medications by class and drug	Categorical: Steroids, Anti-malarials, Immunosuppressants, Aspirin, NSAIDs
Average daily prednisone dose (mg/day) at baseline	Continuous Categorical: (0, >0 - ≤5, >5)
Steroid, Anti-malarial and Immunosuppressant Use at Baseline	Categorical: -Steroid Only -Immunosuppressant Only -Anti-malarial Only -Steroid and Immunosuppressant Only -Steroid and Anti-malarial Only -Immunosuppressant and Anti-malarial Only -Steroid and Immunosuppressant and Anti-malarial

Listings will be provided for current and past medical conditions [L11.10, L21.05].

The summary of demographic and baseline characteristics, baseline disease activity and allowable SLE medication will be repeated for the following subgroups:

- Age (<65 years, ≥65 years) [T11.40, T11.41, T11.42]
- Race (Black vs. Non-Black) [T11.43, T11.44, T11.45]
- Baseline SLEDAI-2K score (≤ 9 vs. ≥ 10) [T11.46, T11.47, T11.48]
- Baseline Immunosuppressant use (use vs. non-use) [T11.49, T11.50, T11.51]
- Baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day) [T11.52, T11.53, T11.54]
- Gender (Male vs Female) [T11.55, T11.56, T11.57]
- Country Region (USA/Canada, Europe, Rest of World) [T11.58, T11.59, T11.60]
- Baseline complement level (At least one low C3/C4 vs. No low C3/C4) [T11.61, T11.62, T11.63]
- Anti-dsDNA (≥ 30 IU/mL vs < 30 IU/mL) [T11.64, T11.65, T11.66]
- Baseline C3/C4 levels & anti-dsDNA (At least one low C3/C4 & anti-dsDNA ≥30 IU/mL vs. Not (At least one low C3/C4 & anti-dsDNA ≥ 30 IU/mL)) [T11.67, T11.68, T11.69]
- Baseline BLyS Protein (>=75th Percentile vs <75th Percentile) [T11.70, T11.71, T11.72]
- RNA Interferon Signature (Low vs. High) [T21.17, T21.18, TT21.19]

6.4. Concomitant Medications

Concomitant medications will be coded according to drug name as defined in the GSK Drug Dictionary, and classified according to the GSK-Drug ATC classification level 1 and ATC level 4. Concomitant medications are defined as medications that start on or before the first dose date of study treatment and end on or after the first dose date of study treatment, or medications that start after the first dose date of study treatment (see Section 15.4.1 for further details). Note that medications with partial or missing start and/or stop dates will be assumed to be concomitant unless there is evidence through comparison of partial dates to suggest otherwise, for example if the day is missing, then the month and year will be compared to the month and year of the first dose date of study treatment and if the month and year are the same or later, then the medication will be considered concomitant (see Section 15.7.2.1 for further details).

A summary of the number and percentage of subjects with concomitant medications by ATC level 1 term and ATC level 4 term will be displayed for both Year 1 and Year 2 separately [T11.35, T21.11]. A further summary of concomitant medications by ATC level 4 term and preferred term will be provided for both Year 1 and Year 2 [T11.36, T21.12]. A listing of all concomitant medication data will be displayed by treatment and subject [L11.11, L21.06].

Protocol-prohibited medication and allowable medication that results in treatment failure designation (see Section 7.7 of the protocol) will be summarized by treatment group. [T11.37, T21.13].

A listing of protocol-prohibited medication and allowable medication that result in treatment failure designation will be displayed by treatment and subject [L11.12, L21.07].

6.5. Extent of Exposure to Study Treatment

Exposure listings detail the amount of planned study medication that was taken, and re-start medication (belimumab taken in Year 2 for Arms A and B). However they do not include concomitant medication of non-study belimumab or rituximab.

Exposure data for both belimumab and rituximab will be listed for:

- Year1: Arm A, B, and C for belimumab; and Arms A and B for rituximab/placebo in Year 1 [L11.13].
- Year 2: Arm A&B: Includes late Year 1 doses (taken in year 2) for Belimumab and re-start Belimumab; Arm C belimumab in Year 2 [L21.08].

See Section 15.6.2 for further details.

Belimumab

The extent of exposure to belimumab through Week 52 for Arm A and Arm B and through Week 104 for Arm C will be assessed by examining the duration of exposure to belimumab in days and the total number of injections a subject receives. Duration of exposure in days will be calculated as:

Duration of exposure (days) = (Last injection date – First injection date + 7).

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

Percent compliance will be calculated as:

100* (Number of injections prescribed – Number of injections missed)/Number of injections prescribed.

The duration of exposure, the total number of injections, and the percent compliance will be summarized using descriptive statistics for the treatment phase. The total number of injections will also be summarized using counts and percentages using the following categories: 1 – 12 doses, 13 – 24 doses, 25 – 36 doses, 37 - 52 and > 52 doses (if applicable). [T11.38]. Similarly, exposure to belimumab in Arm C from Baseline to Week 104 will also be summarized using the following categories: 1 – 12 doses, 13 – 24 doses, 25 – 36 doses, 37 - 52 doses, 53 - 64 doses, 65 - 76 doses, 77 – 88 doses, 89 - 104 doses, and >104 doses (if applicable) [T21.14].

Exposure to belimumab will also be summarized for subjects during Year 2 only. For subjects in Arms A and B this will include incorrectly taken Year 1 medication after

Week 52 and re-start medication [T21.15]. The first dose in Year 2 will be the 1st dose the subject took on the day of or after the Week 52 visit date.

Duration of exposure (days) = (Last injection date – First injection date + 7).

Rituximab

For subjects randomized to Arms A and B, the extent of exposure to rituximab/rituximab-placebo will be assessed by examining the dose intensity and the total number of infusions, i.e. 0, 1 or 2. Dose intensity in mg will be calculated as the cumulative actual dose divided by 2. If the total volume of an infusion is not administered, the actual dose infused for that visit will be calculated as:

Actual Dose infused (mg) = Planned Dose (mg) * Percentage of volume infused

Dose intensity and total number of infusions will be summarized using descriptive statistics [T11.39].

Data Listings

Subjects for whom the treatment blind was broken [L11.14], or potentially the treatment blind broken (29 subjects inappropriately identified on a lab report) will be provided [L11.02].

6.6. Time to Study Treatment Discontinuation

This only includes the belimumab study medication as prescribed in Year 1 (and Year 2 for Arms C) i.e. this does not include re-start belimumab for subjects in Arms A&B in Year 2.

Year 1 (all arms) and Year 1&2 for Arms A&B only

- If the last dose of belimumab+10 days is prior to the Week 52 visit date (where Week 52 visit date is as observed, or predicted as day1+364 for subjects who do not have a Week 52 visit) then the subject has discontinued treatment (had the event / CENSOR=NO=0) at the earliest non-missing date of (last dose date +7, date of death, withdrawal date, LTFU date)
- If the last dose of belimumab + 10 days is on or post the Week 52 visit date (where Week 52 visit date is as observed, or predicted as day1+364 for subjects who do not have a Week 52 visit) then the subject has a censored time to discontinued treatment (does not have the event / CENSOR=Yes=1) at the earliest non-missing date of (observed or predicted Week 52 visit date, death date, withdrawal date, LTFU date)

Year 1&2 for arm C only

- If the last dose of belimumab + 10 days is prior to the Week 104 visit date (where Week 104 visit date is as observed, or predicted as day1+728 for subjects who do not have a Week 104 visit) then the subject has discontinued treatment (had the event / CENSOR=NO=0) at the earliest non-missing date of (last dose date +7, date of death, withdrawal date, LTFU date)
- If the last dose of belimumab + 10 days is on or post the Week 104 visit date (where Week 104 visit date is as observed, or predicted as day1+728 for subjects who do not have a Week 104 visit) then the subject has a censored time to discontinued treatment (does not have the event / CENSOR=Yes=1) at the earliest non-missing date of (observed or predicted Week 104 visit date, death date, withdrawal date, LTFU date)

A KM plot of time to belimumab treatment discontinuation will also be generated [F11.02]. The figures will be repeated for the Week 104 reporting with all data from Year 1 and 2 combined [F21.02]. Due to the design of the study Arms A & B will be truncated at the end of Year 1. A listing of subjects who discontinued belimumab or Rituximab treatment, including reason will be produced [L11.04, L11.05 , L21.03].

7. EFFICACY ANALYSES

The primary objective of the study is to demonstrate superiority (improvement in response rate) of co-administration of belimumab plus rituximab (Arm B: Combination) over belimumab monotherapy (Arm A: Control), when comparing the primary efficacy endpoint at Week 52 in subjects with SLE.

An exploratory summary of Arm B (Combination) vs Arm C (Reference) will also be shown.

SLEDAI-2K score has been measured by both the principal investigator (PI) and the independent blinded assessor (IBA). The key differences between these assessments is the frequency of assessment and awareness of the treatment allocation for Arm C:

- The principal investigator conducts a SLEDAI-2K assessment every 4 weeks in Year 1 (at least every 8 weeks in Year 2), whereas the independent blinded assessor conducts a SLEDAI-2K assessment at a reduced set of key time points (weeks baseline, 12, 26, 40, 52, 64, 80, and 104).
- The principal investigator knows which of their subjects are randomised to treatment arm C, but does not know if their remaining subjects are randomised to arm A or arm B. The independent blinded assessor however is not aware of any MITT population subject's treatment randomisation (Section 4).

Due to the level of blinding the primary and major secondary efficacy endpoints will be conducted using the independent blinded assessors' SLEDAI-2K assessment. Note however the PI assessment of SLEDAI-2K at baseline, is used as the baseline covariate in all adjusted analysis (the baseline SLEDAI-2K assessment is conducted prior to randomisation).

The other secondary endpoints analysis utilises the greater visit frequency of the principal investigator assessment. This is particularly pertinent for differentiating between treatments when considering time to response or duration of response. In by visit summaries, it also allows for the assessment of fluctuating response.

The primary and major secondary efficacy endpoints are repeated using the principal investigator assessment.

Details of the planned displays are provided in Section 15.11 and are based on GSK data standards and statistical principles. Listings of all key efficacy endpoints will be provided [L12.01 – L12.02, and L22.01-L22.02].

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The protocol defined primary endpoint is the proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 52 (Protocol Section 4).

The protocol Section 10.4.1 Efficacy analysis then clarifies that:

> For participants who withdraw prematurely from study treatment and for who subsequent collection of data is not possible, it will be assumed for the primary analysis that they are treatment failures. A dropout/treatment failure = non-responder (DO/TF=NR) analysis will be used .

Hence when adopting the ICH Estimands and Sensitivity Analysis in Clinical Trials E9 R1 addendum terminology, this endpoint is defined as:

Disease Control
Responder: • SLEDAI-2K score ≤2 (IBA); and • Not a TF at the current or any prior visit (TF includes consideration of corticosteroids and immunosuppressants); and • Did not withdraw from the study prior to the visit Non-Responder: • SLEDAI-2K score >2 (IBA); or • TF at the current or any prior visit (TF includes consideration of corticosteroids and immunosuppressants); or • Withdrew from the study prior to visit (which includes study withdrawal, lost to follow-up and death)
The derivation of SLEDAI-2K score is provided in Section 15.6.3, treatment failures are defined in Section 15.6.15. and withdrawal from the study prior to Week 52 in Section 5.9.
Note: Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint, subjects who discontinue investigational product will only be non-responders if they also meet one of the criteria above.

Note this clarification of notation does not change the protocol-specified primary analysis.

The analysis of the primary endpoint of Arm A vs Arm B will use data from treatment Arms A, and B only.

An exploratory analysis of the relative performance of Arm B vs. Arm C will also be conducted, using data from Arms B and C only.

7.1.2. Summary Measure

The odds ratio at Week 52 between Arm B (Combination) vs Arm A (Control).

7.1.3. Population of Interest

The primary efficacy analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

There are 5 potential types of intercurrent events considered for this study:

- Treatment Failure
- Study Withdrawal
- Lost to Follow-up
- Death
- Investigational Product (IP) Discontinuation .

Whilst study withdrawal and lost to follow-up (LTFU) are not true intercurrent events per ICH Estimands and Sensitivity Analysis in Clinical Trials E9 R1 addendum terminology; they are included in the reporting here to allow for backward compatibility to the study Protocol (see Section 7.1.1).

Four intercurrent event strategies are employed:

- Hybrid strategy considers all data while the subject is continuing in the study irrespective of IP discontinuation. Treatment failure and study withdrawal (including LTFU and death) are components of the endpoint definition. Subjects who discontinue investigational product (belimumab) are encouraged to continue in the study.
- Composite strategy considers data collected only while the subject is continuing to receive study treatment. Treatment failure and study withdrawal (including LTFU and death), and IP discontinuation are components of the endpoint definition.
- Hybrid on treatment strategy considers data collected only while the subject is receiving study treatment. Treatment failure and study withdrawal (including LTFU and death), are components of the endpoint definition. IP discontinuation are excluded (unless already experienced treatment failure).
- Treatment Policy strategy considers all data while the subject is continuing in the study irrespective of IP discontinuation or Treatment Failure. Study withdrawal (including LTFU and death), are components of the endpoint definition

The main estimand of this endpoint, is a Hybrid strategy, subjects who discontinue investigational product will continue in the study, assessments after treatment discontinuation will be included in the main estimand. Subjects who are a treatment failure or withdraw from the study will be a non-responder for this estimand.

An analysis of 3 supportive estimands will also be conducted using the alternative intercurrent event strategies, namely:

- Composite,

  This will include IP discontinuation as an intercurrent event resulting in the subject being a non-responder.
- Hybrid On treatment,

  This will only include subjects whilst they are on treatment, or if they have met the definition of a non-responder prior to discontinuing treatment.
- Treatment Policy,

  Assessments after IP discontinuation and assessments after Treatment Failure will be included. Subjects who withdraw from the study will be non-responders.

The impact of the different IP discontinuation components of the endpoint for the Hybrid and composite estimands is summarised by considering 6 hypothetical scenarios:

Table 2 Scenarios for the components of the Hybrid and composite endpoint

Example Subject	SLEDAI-2K score at Week 52	Study Withdrawal(including Lost to Follow-up, or Death) prior to Week 52	Treatment Failure prior to Week 52	IP Discontinuation prior to Week 52	Main Estimand Hybrid	Supplemental Estimand Composite
1	>2	N	N or Y	N or Y	NR	NR
2	<=2	N	N	N	R	R
3	<=2	N	N	Y	R	NR
4	<=2	N	Y	N or Y	NR	NR
5	Incomplete* or entirely missing	N	N or Y	N or Y	NR	NR
6	Missing - does not exist due to study withdrawal	Y	N or Y	Y	NR	NR

R = Responder; NR = Non-Responder
*Incomplete: does not include partial scores where it is possible to determine that the total score must be >2, or that the maximum possible score (assuming worst case for missing data) is <=2 (see Section 15.6.4 Partial but informative SLEDAI-2K score).

A full breakdown of scenarios 'by subject type' and including Hybrid On Treatment and Treatment Policy is provided in Section 15.6.4

7.1.5. Statistical Analyses / Methods

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without treatment failure or study withdrawal
Derivation
• Derivation of the endpoint for Arms A, B and C is provided in Section 15
Model Specification

• Logistic regression model.
• Terms in the model:
  • **Dependent:** response (yes/no)
  • **Categorical:** treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day).

Model Checking & Diagnostics
• If any factor fails to converge it will be removed from the logistic model. • If the logistic model fails to converge, e.g., due to a small number of responders, the primary endpoint will be analyzed using a Fishers exact test. • If the model diagnostics raise questions about the validity of the analysis additional non-parametric analysis will also be conducted.
Model Results Presentation

• The table [T12.01] will display:
  • the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group,
  • the observed difference in percentage of responders for the comparison of Arm B vs Arm A; and Arm B vs Arm C,
  • the stratified (baseline SLEDAI-2K score, baseline immunosuppressant use, baseline corticosteroid dose) Cochran-Mantel-Haenszel treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
  • the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
  • the p-value for the odds ratio the treatment difference for Arm B vs Arm A.
• A table [T12.02]. showing the details from the logistic regression will also be presented; including:
  • the parameter estimate and standard error for each of the terms in the model
  • the odds ratio and 95% CI and p-value for each covariate in the model
  • the parameter estimate, standard error, odds ratio, 95% CI and p-value for the comparison of Arm B vs Arm A

- the parameter estimate, standard error, odds ratio, and 95% CI for the comparison of Arm B vs Arm C
- the odds ratio and 95% CI for the comparison of Arm A vs Arm C

- The proportion of participants with a state of disease control at Week 52 will be displayed in a point estimate +/- SE figure, by treatment group [F12.01].

Subgroup Analyses

The comparison of the primary efficacy endpoint between Arm B vs. Arm A will be performed by the following subgroups [F12.02]:

- Age (<65 years vs. ≥65 years) [T12.16].
- Race (Black vs. Non-Black) [T12.17].
- Gender (Male vs. Female) [T12.18]
- Baseline SLEDAI-2K score (≤ 9 vs. ≥ 10) [T12.19].
- Baseline immunosuppressant use (use vs. non-use) [T12.20].
- Baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day) [T12.21].
- Baseline C3/C4 levels & anti-dsDNA (At least one C3/C4 low & anti-dsDNA >= 30 IU/mL vs. NOT (At least one C3/C4 low & anti-dsDNA >= 30 IU/mL)) [T12.24].
- BLyS Protein at baseline (>= 75th Percentile vs. < 75th Percentile) [T12.25].
- Country Region (USA/Canada vs. Europe vs. Rest of World) [T12.26].
- Baseline complement level (At least one low C3/C4 vs. No low C3/C4) [T12.22].
- Anti-dsDNA (<30 IU/mL vs. >=30 IU/mL) [T12.23]
- RNA Interferon Signature at baseline (Low vs. High) [T22.34] (note this assessment of subgroups for the primary endpoint will be reported at the end of the study).

Each of the subgroups will be analysed separately using a logistic regression model with adjustment for the stratification factors, using the Intercurrent event strategy: Hybrid . If the model fails to converge the relevant stratification factor(s) will be removed from the model.

To further assess each subgroup, the interaction between treatment and the subgroup will be tested by fitting a logistic regression model to the data (all subgroups combined). The model, will include the stratification factors, the variable for the subgroup, and the interaction term between treatment group and the subgroup. The summary table will include the p-value for the interaction that tests the of stability of Arm B vs Arm A over the 2 (or more) levels of the subgroup. If the logistic model fails to converge then the interaction p-value will not be presented.

Supportive Analyses

- The disposition of the primary endpoint, detailing the reasons why a subject was a non-responder will be summarized (n,%) [T12.03, T12.04].
- The components of the primary endpoint will be summarized [T12.05]. i.e. proportion of participants with:
  - SLEDAI 2K-score ≤2 (IBA)
  - Treatment failure due to corticosteroid use
  - Treatment failure due to immunosuppressant use
  - Treatment failure due to anti-malarial, NSAID, Aspirin or other prohibited medication use
  - Study withdrawal
- The table will include

    - the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group
    - the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
    - the p-value for the odds ratio the treatment difference for Arm B vs Arm A
- The primary efficacy analysis at Week 52 will be repeated to assess the robustness of the primary efficacy results:
    - ITT population –Including subjects where the independent blinded assessor was potentially unblinded at Week 52 . Intercurrent event strategy: Hybrid [T12.06].
    - Unadjusted for covariates. the only independent variable in the model will be treatment group. Intercurrent event strategy: Hybrid [T12.07].
    - Composite. Intercurrent event strategy: Composite [T12.08].
    - Hybrid On treatment. Intercurrent event strategy: Hybrid On Treatment [T12.10].
    - Treatment Policy. Intercurrent event strategy: Treatment Policy [12.11].
    - Per Protocol population. Intercurrent event strategy: Hybrid[T12.09].
    - Ongoing on study treatment at Week 52 population. Intercurrent event strategy: Hybrid on Treatment [T12.12].
- A supportive analysis that considers all the data from Arms A, B, and C in the same model will also be conducted. Estimates of the treatment effect will be made for comparison of Arms A vs B and Arms B vs C. Intercurrent event strategy: Hybrid (T12.13)
- Two tipping point analyses may be performed if there is a significant treatment difference, including all recorded data up to the time of study withdrawal, and using differing assumptions regarding data missing following study withdrawal (Section 7.1.6). Intercurrent event strategy: Hybrid [T12.14, F12.03]. Intercurrent event strategy: Treatment Policy [T12.15, F12.04].

7.1.6. Tipping Point Analysis

Tipping point analyses will be performed for the primary endpoint if the endpoint is statistically significant and it is plausible that missing data caused by study withdrawal could alter the conclusions of the analysis (treatment p-value is ≤ 0.05 and > 0.001). If the tipping point analyses are needed, they will be performed shortly after the Statistical Analysis Complete milestone has been met and will be presented in the clinical study report.

The tipping point analyses will be based on the Intent-to-Treat population. Only the subjects in the belimumab plus placebo, and belimumab plus rituximab arms will be considered.

For the primary analysis, subjects for whom the Week 52 disease control status cannot be determined due to study withdrawal (including lost to follow-up, and death) are imputed as non-responders. In contrast, the missing data due to study withdrawal in the tipping point analysis is evaluated using multiple imputation methods, by simulating all combinations of response probability in the treatment arms independently.

The first tipping point analysis will use the Hybrid strategy (as described in Section 7.1.4 as per the primary estimand). If a subject's study withdrawal is subsequent to treatment failure the subject will still be considered as a non-responder, i.e. the non-responder assumption will only be varied for withdrawn subjects that were not treatment failures.

The second tipping point analysis will use the treatment policy strategy (Section 7.1.4). In this approach, treatment failure data is ignored, i.e. the non-responder assumption is varied for all withdrawn subjects regardless of treatment failures.

The tipping point analyses will not consider covariates. However, if the conclusions of the primary analysis adjusting for covariates differ from the conclusions of the unadjusted analysis, a post hoc analysis assessing the impact of covariate adjustment in the tipping point analyses may be performed.

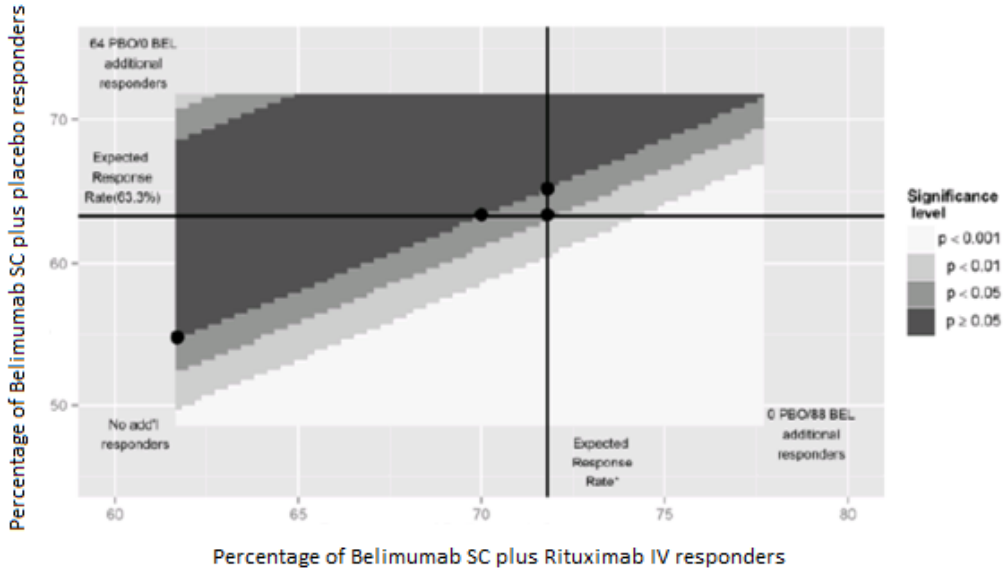
The following multiple imputation method will be implemented:

1. For subjects in Arm A (belimumab plus placebo) and Arm B (belimumab plus rituximab) with missing Bernoulli outcomes, a grid of the probability of response varying from 0.025 to 0.975 by 0.025 will be created. This will create all combinations, from low to high response probability, for subjects with a missing response.
2. For a given of probability (e.g., 0.025 for Arm A, 0.500 for Arm B)
    a. An incidence of the number of additional responders for Arm A (Arm B) given the number of Arm A (Arm B) subjects with missing outcome and the probability assumed (e.g., 0.025 (e.g., 0.500)) will be simulated using the binomial distribution.
    b. The statistics (sample mean and standard error) will be calculated and used to construct the Mantel-Haenszel Chi-Square test.

Steps 2a and 2b will be repeated 1000 times, and Rubin's rules applied to combine them, in order to obtain a single p-value for each given probability combination.

Heat maps will be produced (Figure 2) to show the results of the multiple imputation tipping point analyses for disease control at Week 52. The black lines on each heat map will represent a plausible scenario whereby the probability of response for the missing data in Arms A and B will be equal to the observed case response rate on the control arm (Arm A: belimumab plus placebo).

Figure 2 Tipping Point for Disease Control at Week 52



A tipping point analysis will also be performed for the key secondary endpoints if there is hierarchical significance for the endpoint, and it is plausible that the imputation strategy for missing data could alter the conclusions of the analysis (treatment p-value is ≤ 0.05 and > 0.001).

7.1.7. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the Primary Endpoint

Additional analyses will be carried out to assess the impact of the COVID-19 pandemic on the primary endpoint. The additional analyses will utilise the COVID-19 environment onset date (Section 15.6.16) to establish which data might be affected by COVID-19.

7.1.7.1. COVID Attributed – Observed Data until Intercurrent Events That Could be Attributable to the COVID-19 Pandemic

The first additional analysis (T12.40) uses the observed SLEDAI-2K data, as long the subject has not experienced a treatment failure or study withdrawal that could have been attributable to COVID-19 (i.e. after the COVID-19 environment onset date).

A Hypothetical estimand will be used to estimate the treatment effect had the COVID-19 pandemic not occurred. The difference in response rates between Arm A and Arm B at Week 52 will be assessed for subjects who:

- achieve a SLEDAI 2K-score ≤2 (IBA),
- without immunosuppressants that could be attributable to the COVID-19 pandemic and
- with corticosteroids at a prednisone equivalent dose of ≤5mg/day, in the absence of higher doses that could be attributable to the COVID-19 pandemic

The full MITT population will be used, with the following attributes:

- A strategy that matches the primary analysis (Hybrid) will be used for the following Intercurrent Events to classify the subject as a Non-Responder:
    - Study Withdrawal (includes Lost to Follow Up) that occurs prior to the COVID-19 environment onset date
    - Treatment Failure (includes consideration of corticosteroids and immunosuppressants) that occurs prior to the COVID-19 environment onset date
    - Death that occurs at any time
- A hypothetical strategy will be used for any subject who has their Week 52 assessment scheduled to be on or after the COVID-19 environment onset date, who has not been classified as a Non-Responder using the strategy above, and has any of the following Intercurrent Events on or after the COVID-19 onset date:
    - Study Withdrawal (includes Lost to Follow Up)
    - Treatment Failure (includes consideration of corticosteroids and immunosuppressants)
    - Missing SLEDAI-2K score (IBA)

  The response status for these subjects will be treated as a missing value and will be assumed to be Missing At Random (MAR). It will be imputed using Multiple Imputation methods, which take into account the subjects baseline characteristics and their existing pre-COVID-19 data.
- Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint.

Imputation of Missing Data
• A bayesian repeated measures logistic regression model will be fitted to the observed data, using a Markov Chain Monte Carlo (MCMC) approach, adjusting for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). Non-informative priors will be used. • Samples will be drawn from the posterior distribution of the model parameters of the Bernoulli distribution for each treatment group and each missingness pattern. • Each sample leads to a separate imputed dataset, in which the missing values are replaced by values drawn randomly from their conditional distribution. This distribution is based on the observed data and the covariates for that subject using the imputation model and the sampled parameter values. • These steps will be repeated at least 1000 times.
Model Specification
• Each imputed dataset will be analyzed using logistic regression to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). • The resulting Odds Ratios and their Standard Errors will be combined across imputations using Rubin's rules.

7.1.7.2. COVID Environment – Observed Data Until the COVID-19 Pandemic

The second additional analysis assumes that all data after the COVID-19 environment onset date may either be missing due to the pandemic or affected by the pandemic. There may be intangible ways that

the data may have been affected even if it has been collected, therefore this analysis accepts that we cannot distinguish between affected and unaffected data after the COVID-19 environment onset date.

A Hypothetical estimand will be used to estimate the treatment effect had the COVID-19 pandemic not occurred. The difference in response rates between Arm A and Arm B at Week 52 will be assessed for subjects who:

- achieve a SLEDAI 2K-score ≤2 (IBA),
- without immunosuppressants and
- with corticosteroids at a prednisone equivalent dose of ≤5mg/day and
- in the absence of any Intercurrent Events that could be attributable to the COVID-19 pandemic, based on the COVID-19 environment onset date.

The full MITT population will be used, with the following attributes:

- A strategy that matches the primary analysis (Hybrid) will be used for the following Intercurrent Events to classify the subject as a Non-Responder:
    - Study Withdrawal (includes Lost to Follow Up and death) that occurs prior to the onset date
    - Treatment Failure (includes consideration of corticosteroids and immunosuppressants) that occurs prior to the onset date
    -
- A hypothetical strategy using the COVID-19 environment onset date as the Intercurrent Event will be used for any subject who has their Week 52 assessment scheduled to be on or after the COVID-19 environment onset date, who has not already been classified as a Non-Responder using the strategy above. The response status for these subjects will be treated as a missing value and will be assumed to be Missing At Random (MAR). It will be imputed using Multiple Imputation methods, which take into account the subjects baseline characteristics and their existing pre-COVID data.
- Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint.

The statistical methods will match the first additional analysis (Section 7.1.7.1) [T12.41].

7.1.7.3. Pre-COVID – MITT Population Prior to the COVID-19 Pandemic

The third additional analysis will use the "MITT Week 52 prior to COVID-19" analysis population. This will assess the treatment difference on the subset of subjects who completed Week 52 before the COVID-19 environment onset date and hence have no possible COVID-19 impact on any of their assessments.

A Hybrid estimand will be used to estimate the treatment effect in the population of subjects for which the COVID-19 pandemic not occurred. The difference in response rates between Arm A and Arm B at Week 52 will be assessed for subjects who complete Week 52 prior to the COVID-19 environment onset date and who:

- achieve a SLEDAI 2K-score ≤2 (IBA),
- without immunosuppressants and
- with corticosteroids at a prednisone equivalent dose of ≤5mg/day.

The “MITT Week 52 prior to COVID-19” population will be used, with the following attributes:

- A strategy that matches the primary analysis (Hybrid) will be used for the following Intercurrent Events to classify the subject as a Non-Responder:
    - Study Withdrawal (includes Lost to Follow Up and Death)
    - Treatment Failure (includes consideration of corticosteroids and immunosuppressants)
- Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint.

The statistical methods will match the primary analysis (Section 7.1.5) for the endpoint definition, derivation, model specification, model checking and diagnostics and the model results presentation [T12.42].

7.1.7.4. Graphical Representation of the Additional Analyses

Table 3 shows a graphical representation of specific scenarios for individual subjects, in terms of their completion status or any Intercurrent Events, and the timing of them in relation to the COVID-19 environment onset date (Section 15.6.16). The way in which the data for subjects in each scenario will be used is presented for the primary analysis, plus each of the three pre-specified additional analyses to investigate the COVID-19 pandemic.

Table 3 Graphical Representation of the Additional Analyses

COVID-19 environment Onset **date**	**Description**	**Primary Analysis Hybrid**	**COVID Attributed**	**COVID Environment**	**Pre-COVID**
X——————————0 Comp.	Subject Completes Week 52 prior to onset date	R/NR	R/NR	R/NR	R/NR
X————0 WD/Death	Subject had scheduled Week 52 prior to COVID-19 environment onset date, but Withdraws / LTFU / Dies prior to COVID-19 environment onset date	NR	NR	NR	NR
X————0 TF	Subject had scheduled Week 52 prior to onset date, but has Treatment Failure prior to onset date	NR	NR	NR	NR
X——————————0 Comp.	Subject Completes on or after COVID-19 environment onset date	R/NR	R/NR	Imputed	Excluded
X———0 WD/Death	Subject had scheduled Week 52 on or after onset date, but Withdraws/Dies prior to onset date	NR	NR	NR	Excluded
X————0 TF	Subject had scheduled Week 52 on or after onset date, but has Treatment Failure prior to onset date	NR	NR	NR	Excluded

X———	0 WD	Subject Withdraws on or after onset date	NR	Imputed	Imputed	Excluded
X———	0 Death	Subject Dies on or after onset date	NR	NR	Imputed	Excluded
X———	0 TF	Subject has Treatment Failure on or after onset date	NR	Imputed	Imputed	Excluded

Comp. = Completed; WD = Study Withdrawal (includes Lost to Follow Up); TF = Treatment Failure (includes consideration of corticosteroids and immunosuppressants); R/NR = Responder/Non-Responder based on SLEDAI-2K criteria; NR = Non-Responder

7.2. First Major Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

The proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score =0 (IBA) (Section 15.6.3), achieved without immunosuppressants and corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64.

The protocol Section 10.4.1 Efficacy analysis then clarifies that:

> For participants who discontinue prematurely from study treatment and for who subsequent collection of data is not possible, it will be assumed for the primary analysis that they are treatment failures. A dropout/treatment failure = non-responder (DO/TF=NR) analysis will be used .

Hence when adopting the ICH Estimands and Sensitivity Analysis in Clinical Trials E9 R1 addendum terminology, this endpoint is defined as:

Clinical Remission
Responder: • Clinical SLEDAI-2K score =0 (IBA); and • 7-day average prednisone equivalent dose of 0mg/kg at the visit; and • Not a TF at the current or any prior visit (TF includes consideration of corticosteroids and immunosuppressants); and • Did not Withdraw from the study prior to the visit Non-Responder: • Clinical SLEDAI-2K score >0 (IBA); or • 7-day average prednisone equivalent dose > 0mg/kg at the visit; or • TF at the current or any prior visit (TF includes consideration of corticosteroids and immunosuppressants); or • Withdrew from the study prior to the visit (includes lost to follow-up and death)
The derivation of Clinical SLEDAI-2K score is provided in Section 15.6.3. Treatment failures are defined in Section 15.6.15. and includes the use of re–start belimumab for Arms A&B. Re-start belimumab is principal investigator prescribed belimumab, it does not include late dosing of Year 1 (prescribed pre Week 52) belimumab injections that were taken incorrectly after Week 52. Withdrawal from the study prior to Week 64 is defined in Section 5.9.
Note: Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint, subjects who discontinue investigational product will only be non-responders if they also meet 1 of the criteria above.

Note this clarification of notation does not change the protocol-specified analysis.

The analysis of Arm A vs Arm B will use data from treatment Arms A, and B only. An exploratory analysis of the relative performance of Arm B vs. Arm C will also be conducted, using data from Arms B and C only.

Note: A subject can be a responder for this key secondary endpoint without being a responder for the primary endpoint.

7.2.2. Summary Measure

The odds ratio at Week 64 between Arm B (Combination) vs Arm A (Control).

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent event strategies used for the primary endpoint (as defined in Section 7.1.4) will be used for this major secondary endpoint.

Subjects in Arms A and B will not receive investigational product post Week 52, these subjects will be considered as on treatment if they completed treatment through Week 52.

The main estimand of this endpoint, is a Hybrid strategy, subjects who discontinue investigational product will continue in the study, assessments after treatment discontinuation will be included in the main estimand.

7.2.5. Statistical Analyses / Methods

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• The proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score = 0 (IBA), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64, and without treatment failure or study withdrawal
Model Specification
• The proposed statistical analyses planned for the primary endpoint will be repeated for this major secondary endpoint.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for this major secondary endpoint.

Model Results Presentation

- The proposed tables and figure for the primary endpoint will be repeated for this major secondary endpoint [T22.01, T22.02, F22.01]. .

Subgroup Analyses

- Subgroup analyses will not be conducted for major secondary endpoints.

Supportive Analyses

- The disposition of the endpoint, detailing the reasons why a subject was a non-responder will be summarized (n,%) [T22.03].
- The components of the endpoint will be summarized [T22.04]. i.e. proportion of participants with
    - Clinical SLEDAI-2K score =0 (IBA)
    - Treatment failure due to corticosteroid use
    - Corticosteroids at a prednisone equivalent dose of >0mg/day and <=5mg/day
    - Treatment failure due to immunosuppressant use
    - Treatment failure due to anti-malarial, NSAID, Aspirin or other prohibited medication use
    - Study withdrawal
- The table will include:
    - the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group,
    - the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
    - the stratified (baseline SLEDAI-2K score, baseline immunosuppressant use, baseline corticosteroid dose) Cochran-Mantel-Haenszel treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
    - the p-value for the odds ratio the treatment difference for Arm B vs Arm A
- This key Secondary efficacy analysis at Week 64 will be repeated to assess the robustness of the results:
    - Including subjects where the independent blinded assessor was potentially unblinded, at Week 64 (i.e. ITT population). Intercurrent event strategy: Hybrid [T22.05].
    - Unadjusted for covariates. The only independent variable in the model will be treatment group. Intercurrent event strategy: Hybrid [T22.06].

Tipping point analyses may be performed, including all recorded data up to the time of study withdrawal, and using differing assumptions regarding data missing following withdrawal from the study as detailed in Section 7.1.6. Intercurrent event strategy: Hybrid [T22.07, F22.12].

7.2.6. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the First Major Secondary Endpoint

Additional analyses will be carried out to assess the impact of the COVID-19 pandemic on the first major secondary endpoint.

7.2.6.1. COVID Attributed – Observed data until Intercurrent Events that could be attributable to the COVID-19 pandemic

The first additional analysis specified for the primary endpoint (Section 7.1.7.1) will be repeated for the first major secondary endpoint [T22.35].

7.2.6.2. COVID Environment – Observed data until the COVID-19 pandemic

The second additional analysis specified for the primary endpoint (Section 7.1.7.2) will be repeated for the first major secondary endpoint [T22.36].

7.2.6.3. Pre-COVID – MITT Population prior to the COVID-19 pandemic

The third additional analysis specified for the primary endpoint (Section 7.1.7.3) will be repeated for the first major secondary endpoint [T22.37] using the "MITT Week 64 prior to COVID-19" population.

7.3. Second Major Secondary Efficacy Analyses

7.3.1. Endpoint / Variables

The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 104.

This endpoint is as defined for the primary endpoint (Section 7.1) but at Week 104.

The primary comparison is Arm B (Combination) vs Arm A (Control), and an exploratory summary of Arm B (Combination) vs Arm C (Reference) will also be shown.

Note: A subject can be a responder for this key secondary endpoint without being a responder for the primary endpoint or the first major secondary endpoint.

7.3.2. Summary Measure

The odds ratio at Week 104 between Arm B (combination) vs Arm A (control).

7.3.3. Population of Interest

The secondary efficacy analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent event strategies used for the primary endpoint (see as defined in Section 7.1.4) will be used for this major secondary endpoint.

Subjects in Arms A and B will not receive investigational product post Week 51, these subjects will be considered as on treatment if they completed treatment through Week 52.

The main estimand of this endpoint, is a Hybrid strategy, subjects who discontinue investigational product will continue in the study, assessments after treatment discontinuation will be included in the main estimand.

7.3.5. Statistical Analyses / Methods

7.3.5.1. Statistical Methodology Specification

Endpoint / Variables
• The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), without treatment failure or study withdrawal
Model Specification
• The proposed statistical analyses planned for the primary endpoint will be repeated for this major secondary endpoint.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for this major secondary endpoint.
Model Results Presentation
• The proposed tables and figure for the primary endpoint will be repeated for this major secondary endpoint [T22.10, T22.11, F22.04].
Subgroup Analyses
• Subgroup analyses will not be conducted for major secondary endpoints.
Supportive Analyses
• The disposition of the endpoint, detailing the reasons why a subject was a non-responder will be summarized (n,%) [T22.12]. The components of the endpoint will be summarized [T22.13]. i.e. proportion of participants with: ○ SLEDAI-2K score <=2 (IBA) ○ Treatment failure due to corticosteroid use ○ Treatment failure due to immunosuppressant use

- Treatment failure due to anti-malarial, NSAID, Aspirin or other prohibited medication use
- Study withdrawal

- The table will include:
  - the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group,
  - the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
  - the stratified (baseline SLEDAI-2K score, baseline immunosuppressant use, baseline corticosteroid dose) Cochran-Mantel-Haenszel treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
  - the p-value for the odds ratio the treatment difference for Arm B vs Arm A
- This key Secondary efficacy analysis at Week 104 will be repeated to assess the robustness of the results:
  - Including subjects where the independent blinded assessor was potentially unblinded, at Week 104 (i.e. ITT population). Intercurrent event strategy: Hybrid [T22.14].
  - Unadjusted for covariates. The only independent variable in the model will be treatment group. Intercurrent event strategy: Hybrid [T22.15].

Tipping point analyses may be performed, including all recorded data up to the time of study withdrawal, and using differing assumptions regarding data missing following withdrawal from the study, as detailed in Section 7.1.6. Intercurrent event strategy: Hybrid [T22.16, F22.13].

7.3.6. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the Second Major Secondary Endpoint

Additional analyses will be carried out to assess the impact of the COVID-19 pandemic on the second major secondary endpoint. It may not be possible to conduct all the proposed analysis, the feasibility of the analysis is dependent on the number of observed intercurrent events after the COVID-19 environment onset date or quantity of missed assessments.

7.3.6.1. COVID Attributed – Observed Data Until Intercurrent Events That Could be Attributable to the COVID-19 Pandemic

The first additional analysis specified for the primary endpoint (Section 7.1.7.1) will be repeated for the second major secondary endpoint [T22.38].

7.3.6.2. COVID Modified – SLEDAI 2K-Score ≤2 (IBA), Without Current Immunosuppressants, Without Current Belimumab (arms A&B), and prednisone equivalent dose of ≤5mg/day at Week 104

This is an additional endpoint to that specified in the protocol, using a modified definition of disease control. It will be defined as a SLEDAI-2K score ≤2 (IBA), without **Current** Immunosuppressants

or **Current** Belimumab dosing (Arms A and B) and corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 104.

It is possible that subjects may take extra immunosuppressants/corticosteroids/Belimumab during the COVID-19 environment, which would class them as a Treatment Failure and therefore a Non-Responder for the main analysis. This additional analysis will allow the subjects to take these concomitant medications / re-start Belimumab during the study, as long as their dose is back to the pre-defined levels for an adequate period prior to Week 104. Therefore, these subjects will not automatically be classed as a Treatment Failure (Non-Responder) for this additional analysis.

Disease Control without Treatment Failure
Responder: • SLEDAI 2K-score ≤2 (IBA); and • Did not withdraw from the study prior to the visit; and • Did not receive a protocol non-allowed immunosuppressant or change in immunosuppressant on the day of the visit or the 55 days prior; and • Did not receive corticosteroids at a prednisone equivalent dose of >5mg/day (7day average) on the day of the visit or the 6 days prior; and • Did not have a Belimumab dose on the day of the visit or the 112 days (16 weeks) prior (Arms A and B). Non-Responder: • SLEDAI 2K-score >2 (IBA); or • Withdrew from the study prior to Week 104 (which includes study withdrawal, lost to follow-up and death); or • Received a protocol non-allowed immunosuppressant or change in immunosuppressant on the day of the visit or the 55 days prior; or • Received corticosteroids at a prednisone equivalent dose of >5mg/day (7day average) on the day of the visit or the 6 days prior; or • Had a Belimumab dose on the day of the visit or the 112 days (16 weeks) prior (Arms A and B).
The derivation of SLEDAI-2K score is provided in Section 15.6.3 and withdrew from the study prior to Week 104 in Section 5.9.
Note: Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint, subjects who discontinue investigational product will only be non-responders if they also meet one of the criteria above.

The statistical methods will match the primary analysis (Section 7.1.5 Hybrid strategy) for the model specification, model checking and diagnostics and the model results presentation at Week 104 [T22.39].

7.4. Lupus Low Disease Activity State (LLDAS)

7.4.1. Endpoint / Variables

The LLDAS endpoint is derived based on [Franklyn, 2016] and [Oon, 2019] given the available data in this study, namely:

- SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity;
- no new features of lupus disease activity compared with the previous assessment;
- PGA (scale 0-3) ≤1;
- current prednisolone (or equivalent) dose ≤7.5 mg daily; and
- well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs.
- Not study withdrawal (including death and lost to follow-up)

Further details of the derivation that is applied to this study is provided in Section 15.6.9 Lupus Low Disease Activity State (LLDAS). The principal investigators assessment of the SLEDAI-2K is used in the derivation of LLDAS. Treatment Failures (TF) is not a component of the endpoint.

7.4.2. Summary Measure

The odds ratio between Arm B (Combination) vs Arm A (Control).

7.4.3. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.4.4. Strategy for Intercurrent (Post-Randomization) Events

The definition of the endpoint includes consideration for the intercurrent events of study withdrawal (including LTFU and death)(as defined in Section 7.1.4). Treatment failure is not a component of the endpoint and is not considered as an intercurrent event. Data from subjects who discontinue IP is included in this secondary endpoint.

Subjects in Arms A and B will not receive investigational product post Week 52, these subjects will be considered as on treatment if they completed treatment through Week 52.

Subjects who discontinue investigational product will continue in the study, assessments after treatment discontinuation will be included in the estimand.

7.4.5. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.4.6. Statistical Methodology Specification

Endpoint / Variables
• Proportion of participants that meet the Lupus Low Disease Activity State (LLDAS) response criteria by Visit [T12.37, T22.31] • Proportion of participants for each component of the Lupus Low Disease Activity State (LLDAS) response criteria at Weeks 52, 64, and 104 [T12.38,T22.32]
Model Specification
• The proposed statistical analyses planned for the primary endpoint will be repeated for LLDAS.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for the LLDAS endpoints.
Model Results Presentation

• The table will display:
  ◦ the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group
  ◦ the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104.
  ◦ the p-value for the odds ratio the treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

7.5. Other Secondary Efficacy Analyses - Proportion Endpoints (Hybrid)

7.5.1. Summary Measure

The odds ratio between Arm B (combination) vs Arm A (control).

7.5.2. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.5.3. Strategy for Intercurrent (Post-Randomization) Events

The same intercurrent event strategy as used for the primary endpoint (Section 7.1.4) will also be used for other secondary endpoints.

7.5.4. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.5.5. Statistical Methodology Specification

Endpoint / Variables
• The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without treatment failure or study withdrawal by visit (T12.27, T22.17, F12.05, F22.05). • Proportion of participants with a state of clinical remission, defined as a Clinical SLEDAI-2K score = 0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit. (T22.08, F22.02) • Proportion of participants with a state of complete remission, defined as SLEDAI-2K score = 0 (PI), achieved without treatment failure or study withdrawal, and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks.(T22.19) • Proportion of participants with a state of clinical remission, defined as Clinical SLEDAI-2K score =0 (PI) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks. (T22.20) • Proportion of participants with a state of complete remission, defined as a SLEDAI-2K score =0 (PI), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit (T22.21,F22.08) • The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (PI), achieved without treatment failure or study and with corticosteroids at a prednisone equivalent dose of ≤5mg/day by visit (T12.28, T22.18, F12.06). • The proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score =0 (PI) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit (T22.18,F22.03).
Model Specification
• The proposed statistical analyses planned for the primary endpoint (Hybrid) will be repeated for the other binary secondary endpoints.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for the other binary secondary endpoints.
Model Results Presentation
• For each endpoint a table will display:

- the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group
- the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104.
- the p-value for the odds ratio the treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

7.6. Other Secondary Efficacy Analyses - Proportion Endpoints (Observed Case)

7.6.1. Summary Measure

The odds ratio between Arm B (combination) vs Arm A (control).

7.6.2. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.6.3. Strategy for Intercurrent (Post-Randomization) Events

Treatment failure and study withdrawal will not be considered as components of the endpoint and an observed case analysis will be conducted.

7.6.4. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.6.5. Statistical Methodology Specification

Endpoint / Variables
• Proportion of participants with SLEDAI-2K (PI) organ improvement by visit (T12.31, T22.27)
• Proportion of participants with SLEDAI-2K (PI) organ worsening by visit (T12.32,T22.28)
• Proportion of participants with any SLICC Damage Index worsening (change >0) compared with baseline at Week 52 and Week 104 (Worst Observation Carried Forward for observed visits) (T12.36, T22.30). Note: The scoring of the SLICC Damage Index is such that it should not be possible for a subject to improve. Hence the WOCF is used to ensure the correct scoring has been applied the highest score for an individual item is carried forward to subsequent observed visits, it does not impute missing visits. Only observed (but potentially corrected by WOCF) data will be analysed, irrespective of treatment failure or IP discontinuation (all data reported will be included).

Model Specification
• The proposed statistical analyses planned for the primary endpoint will be repeated for the other binary secondary endpoints. The SLICC Damage Index worsening will also include SLICC DAMAGE index score at baseline as a covariate.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for the other binary secondary endpoints.
Model Results Presentation

• For each endpoint a table will display:
  ◦ the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group
• For the SLICC analysis (T12.36, T22.30) the table will also display:
  ◦ the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
  ◦ the p-value for the odds ratio the treatment difference for Arm B vs Arm A at weeks 52, 64 and 104.

7.7. Other Secondary Efficacy Analyses - Time to Event Endpoints

7.7.1. Summary Measures

The hazard ratio of Arm B (combination) and Arm A (control).

7.7.2. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.7.3. Strategy for Intercurrent (Post-Randomization) Events

Subjects without an event will be considered censored at the last observed timepoint.

7.7.4. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.7.5. Statistical Methodology Specification for Time to Event Endpoints

Endpoints
• Time to first severe flare (as measured by the modified SLE Flare Index) [T12.33, T22.22, F12.12,F22.06]

- Time to first flare (as measured by the modified SLE Flare Index) [T12.34, T22.23,F12.09,F22.07]
- Time to disease control sustained to Week 104, defined as SLEDAI-2K score ≤2 (PI), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day.[T22.24,F22.09].
- Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score=0 (PI) (Section 15.6.3), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day [T22.33].

Derivation

Flare Endpoints

Subject	Time to defined as:	Censored
Flare	Date of 1st flare – trt start date +1	No = 0
TF before or without flare	Date of 1st TF – trt start date +1	No = 0
Subjects without a Flare or TF who have an intercurrent event:		
Withdraw Lost to Follow-up	Date of last Flare assessment prior to intercurrent event – trt start date +1	Yes =1
Die	Date of Death – trt start date +1	Yes =1
For Year 1 reporting:		
Subject completes Week 52	Date of Week 52 visit – trt start date +1	Yes =1
For Year 2 reporting:		
Subject completes Week 104	Date of Week 104 visit – trt start date +1	Yes =1

- The flare criteria will be programmed from the SLEDAI-2K irrespective of data recorded on the SFI form
- Flares recorded as severe on the SFI form will be downgraded to not severe in the programmed endpoint if the only cause of the severe flare was SLEDAI-2K>12
- Only post baseline flares will be included in the analysis (Flares on Day 1 will not be considered)
- Treatment failure is considered as a severe flare.
- Subjects who do not have a flare assessment post baseline will be censored at Day 1 and hence reported as 'time to' defined as 1 and censor =Yes = 1

Time to Response Endpoints

Subject	Time to defined as:	Censored
Sustained response	Date of 1st sustained response – trt start date +1	No = 0
Subjects without a sustained response		

Withdraw	Date of last visit prior to intercurrent event – trt start date +1	Yes =1
Lost to Follow-up		
Treatment Failure		
Die	Date of Death – trt start date +1	Yes =1
For Year 1 reporting:		
Subject completes Week 52 without treatment failure	Date of Week 52 visit – trt start date +1	Yes =1
For Year 2 reporting:		
Subject completes Week 104 without treatment failure	Date of Week 104 visit – trt start date +1	Yes =1

Further detail is provided in Section 15.6.7.

Model Specification

A Cox proportional hazards model controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day) will be used to evaluate time to event endpoints.

Ties will be managed using Efron's approximation.

Model Checking & Diagnostics

Overall model Goodness of fit tests using the -2 Log Likelihood, Akaike's Information Criterion (AIC), and Schwarz Bayesian criterion (SBC) tests will be performed. The AIC and SBC statistics offer two different ways of adjusting the -2 log likelihood statistic for the number of terms in the model and the number of observations used. Lower values in these statistics represent a more desirable model. These tests will aid in the assessment of model fit but the final decision regarding goodness of fit will be based on statistician review. If the model fit is considered inadequate additional analysis will be conducted.

Model Results Presentation

A table for each endpoint [as above] will present:

- The number and percentage of subjects with an event and the median, 25th percentile, and 75th percentile of days to event by treatment group,
- the hazard ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C.
- the p-value for the hazard ratio for Arm B vs Arm A.
- the median, 25th percentile, and 75th percentile of days, min and max for the study day of 1st event

A Kaplan-Meier plot of time to event for each endpoint will be displayed by treatment group.

Subgroup Analyses

Subgroup analyses will not be conducted for secondary endpoints.

7.8. Other Secondary Efficacy Analyses - Duration Endpoints

7.8.1. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.8.2. Strategy for Intercurrent (Post-Randomization) Events

A Hybrid strategy will be adopted

7.8.3. Endpoint / Variables

The endpoint points are defined as per the primary (Section 7.1) and secondary (Section 7.2) endpoints. The duration is defined as the longest period between any 2 assessments that the subject remains a responder throughout (missing assessments are not considered).

7.8.4. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.8.5. Statistical Methodology Specification for Duration Endpoints

Endpoints
• Duration of disease control, defined as SLEDAI-2K score ≤2 (PI), achieved without treatment failure or study withdrawal [T12.29]. • Duration of clinical remission, defined as Clinical SLEDAI-2K score =0 (PI) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day. [T22.25].
Imputation of Missing Data
Duration endpoints: There will be no imputation of missing data, only observed data will be considered. Duration will be derived based on the date of the assessment as: Date of last visit meeting criteria - Date of first visit meeting criteria +1
Model Specification
• Duration endpoints will be analyzed using ANCOVA to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day).
Model Checking & Diagnostics
• The Kolmogorov-Smirnov D statistic will be used to test the assumption of normality. Residuals will be reviewed to assess the homogeneity of variance assumption. If the model fit is inadequate additional analysis will be conducted.

Model Results Presentation
The tables will display: • Baseline: the number of subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, maximum for each arm • At each visit: o the number subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum, o LS Mean, and standard error of the LS Mean for each arm at Weeks 52, 64 and 104. o the treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104. o the p-value for treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

7.9. Other Secondary Efficacy Analyses Continuous Endpoints

7.9.1. Endpoint / Variables

Change from baseline in SLEDAI-2K (PI) score and change from baseline in Physician Global Assessment (PGA) by visit.

7.9.2. Summary Measure

The difference in mean change from baseline between Arm B (Combination) vs Arm A (Control).

7.9.3. Population of Interest

The secondary efficacy analyses will be based on the modified Intent-To-Treat population, unless otherwise specified.

7.9.4. Strategy for Intercurrent (Post-Randomization) Events

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subjects not withdrawn from the study . Data collected after TF will be used in the analysis.

7.9.5. Subgroup, Supportive and Sensitivity Analyses

There are no planned subgroup, supportive or sensitivity analyses for other secondary endpoints.

7.9.6. Statistical Methodology Specification for Continuous Endpoints

Endpoints

- Change from baseline in SLEDAI-2K (PI) score by visit.[T12.30, T22.26,F12.07, F22.10].
- Change from baseline in Physician Global Assessment (PGA) by visit [T12.35,T22.29, F12.08, F22.11].

Imputation of Data for Missed Visits and Following Study Withdrawal

- A bayesian repeated measures normal model will be fitted to the data collected prior to study withdrawal, using a Markov Chain Monte Carlo approach, adjusting for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). Non-informative priors will be used.
- Quasi-independent samples will be drawn from the posterior distributions for the parameters of the multivariate normal distribution for each treatment group and each missingness pattern.
- Each sample leads to a separate imputed dataset, in which the missing values are replaced by values drawn randomly from their conditional distribution. This distribution is based on the observed data and the covariates for that subject using the imputation model and the sampled parameter values.
- These steps will be repeated at least 1000 times.

Imputation of Data Following Partially Missing SLEDAI-2K

The same imputation approach will be used for subjects with partially completed SLEDAI-2K scores (i.e. some missing items) however imputed values that are below the minimum possible score (determined from the completed items) will be replaced with the known minimum score. Similarly, imputed values that are above the maximum possible score will be replaced with the known maximum score

Minimum and maximum possible SLEDAI-2K scores are detailed in Section 15.6.3.

Model Specification

- Each imputed dataset will be analyzed using ANCOVA to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day).
- The resulting treatment differences and their SEs will be combined across imputations using Rubin's rules.
- The models for the SLEDAI-2K endpoints will include the baseline (PI) SLEDAI-2K score (continuous) rather that the stratification factor (≤9 vs. ≥10).
- The model for PGA endpoints will also include the baseline PGA score (continuous).

Model Checking & Diagnostics

The Kolmogorov-Smirnov D statistic will be used to test the assumption of normality. Residuals will be reviewed to assess the homogeneity of variance assumption. If the model fit is inadequate additional analysis will be conducted

Model Results Presentation

The tables will display:

- Baseline: the number of subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, maximum for each arm
- At each visit:
  - the number subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum
  - LS Mean, and standard error of the LS Mean for each arm at Weeks 52, 64 and 104.
  - the treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104.
  - the p-value for treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

For change from baseline endpoints, a plot of LS means +/- SE by visit and treatment group will be provided.

7.10. Other Secondary Efficacy Analyses: SLEDAI-2K Score ≤2 (IBA), Without Current Immunosuppressant and Corticosteroids <=5mg/day

7.10.1. Endpoint / Variables

This is an additional endpoint to that specified in the protocol. The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without current immunosuppressants and with current corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 52. Immunosuppressant use and corticosteroid reduction are key components of the endpoint in the protocol and are included in the synopsis definition without referring to treatment failure. Hence a supportive analysis that considers immunosuppressant use and corticosteroids without other treatment failure criteria will be conducted.

Disease Control without Treatment Failure

Responder:

- SLEDAI-2K score ≤2 (IBA); and
- Did not withdraw (including LTFU and death) from the study prior to the visit; and
- Did not receive a protocol non-allowed immunosuppressant or change in immunosuppressant on the day of the visit or the 55 days prior; and
- Did not receive corticosteroids at a prednisone equivalent dose of >5mg/day (7day average) on the day of the visit or the 6 days prior.

Non-Responder:

- SLEDAI-2K score >2 (IBA); or
- withdrew from the study prior to Week 52 (including, LTFU and death); or
- Received a protocol non-allowed immunosuppressant or change in immunosuppressant on the day of the visit or the 55 days prior; or

• Received corticosteroids at a prednisone equivalent dose of >5mg/day (7day average) on the day of the visit or the 6 days prior.
The derivation of SLEDAI-2K score is provided in Section 15.6.3 and withdrawal from the study prior to Week 52 in Section 5.9.
Note: Discontinuation of study investigational product (belimumab or rituximab) is NOT a component of this endpoint, subject who discontinue investigational product will only be non-responders if they also meet 1 of the criteria above.

7.10.2. Summary Measure

The odds ratio at Week 52 between Arm B (Combination) vs Arm A (Control).

7.10.3. Population of Interest

The efficacy analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

7.10.4. Strategy for Intercurrent (Post-Randomization) Events

The definition of the endpoint includes consideration for the intercurrent events of study withdrawal (including LTFU and death)(as defined in Section 7.1.4). Treatment failure is not a component of the endpoint and is not considered as an intercurrent event. Data from subjects who discontinue IP is included in this secondary endpoint.

7.10.5. Statistical Analyses / Methods

7.10.5.1. Statistical Methodology Specification

Endpoint / Variables
• The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2 (IBA), achieved without study withdrawal, without current immunosuppressants, and with current corticosteroids at a prednisone equivalent dose of ≤5mg/day
Derivation
• Derivation of the endpoint for Arms A, B and C is provided in Section 15.6.4
Model Specification

• Logistic regression model.
• Terms in the model:
  • **Dependent:** response (yes/no)
  • **Categorical:** treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day).

Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for the other binary secondary endpoints.
Model Results Presentation (T12.39)
• the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group • the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Week 52. • the p-value for the odds ratio the treatment difference for Arm B vs Arm A at Week 52.

7.11. Additional Efficacy Analyses

A scatter plot will be produced to assess the degree to which the Principal Investigators assessment of SLEDAI-2K differs from that of the Independent Blinded Assessor at Week 52 [F12.10].

This will only include subjects who have both a PI and IBA SLEDAI-2K total score at Week 52. The scatter plot will show the PI SLEDAI-2K total score on the x-axis and IBA SLEDAI-2K total score on the y-axis. No formal statistical testing will be conducted. Different colours (and symbols) will be used for the following groups of subjects:

- Arm A
- Arm B
- Arm C included in MITT population
- Arm C excluded from MITT population

A Bland-Altman plot of the differences between the IBA and PI scores against the mean of the IBA and PI scores will also be produced at Week 52 [F12.11].

If the conclusions of the analysis of the comparison between Arm A and Arm B for disease control differ between SLEDAI-2K score based on the IBA assessment and the PI assessment at Week 52, then additional analysis may be performed. Additional analysis of endpoints at Week 52 will be performed after the Week 52 Statistical Analysis Complete milestone has been met and will be presented in the Week 52 clinical study report. Analysis of endpoints post Week 52 will be performed as part of the Week 104 reporting.

A difference in conclusion will be determined by the study team after reviewing the complete Week 52 SAC outputs. Consideration will be given to the comparison of the magnitude of the odds ratio in the analysis of:

- The proportion of participants with a state of disease control (IBA)
- The proportion of participants with a state of disease control (PI)

with consideration to the related C.I.s and p-values for the comparison between Arms A and B.

The additional analyses will consider some or all of the following endpoints depending on the results by endpoint for the Week 52 reporting:

- Proportion of participants with a state of clinical remission, defined as a Clinical SLEDAI-2K score =0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit.
- Proportion of participants with a state of complete remission, defined as SLEDAI-2K score=0 (IBA), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks.
- Proportion of participants with a state of clinical remission, defined as Clinical SLEDAI-2K score =0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks.
- Proportion of participants with a state of complete remission, defined as a SLEDAI-2K score =0 (IBA), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit
- Proportion of participants with SLEDAI-2K (IBA) organ improvement by visit (TP, Observed)
- Proportion of participants with SLEDAI-2K (IBA) organ worsening by visit (TP, Observed)
- Time to disease control sustained to Week 104, defined as SLEDAI-2K score ≤2 (IBA), achieved without treatment failure or study withdrawal.
- Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score=0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day.
- Duration of disease control, defined as SLEDAI-2K score ≤2 (IBA), achieved without treatment failure or study withdrawal..
- Duration of clinical remission, defined as Clinical SLEDAI-2K score =0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day.
- Change from baseline in SLEDAI-2K (IBA) score by visit.
- Duration of disease control, defined as SLEDAI-2K score ≤2 (IBA), achieved without treatment failure or study withdrawal.
- Duration of clinical remission, defined as Clinical SLEDAI-2K score =0 (IBA) (Section 15.6.3), achieved without treatment failure or study withdrawal and with corticosteroids at a prednisone equivalent dose of 0 mg/day.
- Change from baseline in SLEDAI-2K (IBA) score by visit.
- Proportion of participants that meet the Lupus Low Disease Activity State (LLDAS) response criteria by Visit based on the IBA assessment.

The analysis will be based on the modified Intent-To-Treat population and use the same intercurrent event strategy (Hybrid as used for the primary endpoint (Section 7.1.4). The analysis will be conducted as specified in Section 7.4.4, Section 7.4.5, Section 7.4.6)

Similarly if there is a difference in the conclusions of the analysis of clinical remission based on the IBA and PI assessment at Week 64, or analysis of disease control based on the IBA and PI assessment at Week 104; then additional analyses will be performed shortly after the Week 104 Statistical Analysis Complete milestone has been met and will be presented in the Week 104 clinical study report. The additional post Week 104 SAC analysis will repeat the analysis of the other secondary endpoints but utilising the IBA assessment instead of the PI assessment. The endpoints to be assessed will potentially include all those previously listed in the Section 7.11.

Note that in the event that the Week 52 reporting does not identify a treatment benefit an abridged set of analysis may be conducted at the end of the study (Week 104).

7.12. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the Secondary Efficacy Endpoints

There will not be any prospective additional analyses carried out to assess the impact of the COVID-19 pandemic on the secondary (non-major) endpoints. However, if the additional analysis of the primary endpoint indicates a major impact of the COVID-19 pandemic, then additional post-SAC analyses will be performed on the secondary endpoints after the Week 52 Statistical Analysis Complete milestone has been met and will be presented in the Week 52 clinical study report.

Similarly, if the additional analysis of the key secondary endpoints indicates a major impact of the COVID-19 pandemic, then additional post-SAC analyses will be performed on the other secondary endpoints after the Week 104 Statistical Analysis Complete milestone has been met and will be presented in the Week 104 clinical study report.

8. SAFETY ANALYSES

The safety analyses will be based on the ITT population. However, if there are more than 5% of subjects who receive a rituximab/placebo infusion that is different from the randomized treatment for one or both doses, safety analysis will be performed on the As Treated population.

8.1. Adverse Events

8.1.1. Reporting Phases

Adverse events will be reported for Year 1 and Year 2 study period:

8.1.1.1. Pre Treatment

Adverse events starting prior to the 1st dose of belimumab.

8.1.1.2. On Treatment (Year 1 only)

As defined in Section 5.12

8.1.1.3. On Study

As defined in Section 5.11

Year 2 reporting will include all events starting on or after Week 52 visit + 1 day and at or prior to the Week 104 visit.

Year 1&2 reporting will include all events starting on or after the 1st dose of belimumab and at or prior to the Week 104 visit.

The tabular summary for each category of AE listed below will include the number of events, number of subjects who reported at least one event, and percentage of subjects who reported at least one AE (incidence) by treatment group for each SOC (where applicable), each PT, and overall.

8.1.1.4. Post Withdrawal/Completion

Adverse events starting after the on study period (Section 5.11 / Section 8.1.1.3) will be reported separately.

8.1.2. Adverse Events Analyses

- Adverse events analyses including the analysis of adverse events (AEs), Serious Adverse Events (SAEs) and AEs of special interest (AESIs) will be based on GSK Core Data Standards.
- All subjects will be followed for safety through at least 8 weeks post-treatment.

- A table summarizing AEs that occurred prior to treatment start date will be presented, for each system organ class (SOC) and preferred term (PT) by treatment group [T13.01].
- All AEs will be classified using the current standard GSK Medical Dictionary for Regulatory Activities (i.e. MedDRA version in use at the time of reporting), and grouped by SOC and PT, unless otherwise stated. MedDRA version is detailed on every table that uses MedDRA . The Year 1 report will be based on MedDRA dictionary version 23. The Year 2 report will use the MedDRA dictionary current at the time of reporting the Year 2 data (anticipated to be version 25) and hence will be different to Year 1. Dictionary coding changes between Year 1 and Year 2 will be listed (L23.13) and any impact on the interpretation will be detailed in the Year 2 clinical study report (CSR). The investigator will evaluate all AEs with respect to seriousness, severity, and causality. The severity of an AE is to be determined using the Assessment of Intensity provided in Appendix 7 of the protocol, if a grade is provided for the AE of interest.
- AEs during Year 1 that are not reported until Year 2; and AEs that have their reporting details (e.g. onset date, severity etc) changed after Year 1, will be reported in Year 2 with the latest details. Changes will be listed and summarised as appropriate.
- All treatment-emergent AEs will be summarized for both the double-blind phase (Year 1) and the observational phase (Year 2) separately. Selected tables will also be produced for Years 1 and 2 combined. See Section 8.1.1 for definitions of phases.
- 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 treatment discontinuation, and deaths [On Treatment:T13.02, and On Study: T13.03, T23.01,T23.02, L13.05, L13.06, L23.12].
- Common AEs will be defined as ≥ 5% incidence in any treatment group.
- 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 and PT) [On Treatment: T13.04; On Study: T13.05, T23.03, T23.04].
    - AEs (by PT) [On Treatment:T13.06; On Study: T23.05]. (ordered on total incidence – Arms A+B+C)
    - Study treatment Related AEs (by SOC and PT) – belimumab only [on Treatment:T13.07; on Study: T23.06].
    - Study treatment Related AEs (by SOC and PT) – rituximab only [on Treatment:T13.08; on Study: T23.07].
    - Study treatment Related AEs (by SOC and PT) – Both belimumab and rituximab [on Treatment:T13.09; on Study: T23.08].
    - Severe AEs (by SOC and PT) [On Treatment:T13.11, on Study T23.27].
    - Serious AEs (by SOC and PT) [On Treatment:T13.21, and on Study:T13.22, T23.19, T23.20]

  - AEs leading to permanent discontinuation of study treatment (by SOC and PT) [on Study:T13.26, T13.27; on Study: T23.21, T23.22].
  - Deaths (by Category and PT) [on Study: T13.20, T23.18].
  - Common Non-Serious AEs (by SOC and PT) [on Study: T13.28; T23.23].
  - Study treatment Related Serious AEs (by SOC and PT) [On Treatment:T13.23, T13.24, T13.25; on Study: T23.24, T23.25, T23.26].
  - Fatal Serious AEs (by SOC and PT) and Study treatment Related Fatal Serious AEs (by SOC and PT) [On Treatment:T13.29; on Study:T23.28].
- 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.
- The table for all AEs by SOC and PT will be repeated for the following subgroups:
  - Age group (<65, >=65), [On Treatment: T13.12; On Study: T23.10].
  - Race (Black, non-Black), [On Treatment: T13.13; On Study: T23.11].
  - Country region, [On Treatment: T13.14; On Study: T23.12].
  - Baseline C3/C4 levels & anti-dsDNA subgroup [On Treatment: T13.15; On Study: T23.13].
  - Baseline SLEDAI-2K (<=9, >=10) [On Treatment: T13.16; On Study: T23.14].
  - Baseline Immunosuppressant use (Y,N))[On Treatment: T13.17; On Study: T23.15].
  - Baseline Corticosteroid dose (<=10 mg/day, >10 mg/day))[On Treatment: T13.18; On Study: T23.16].
  - Gender, [On Treatment: T13.19; On Study: T23.17].
- For Year 1 reporting, the table of deaths by category and PT will include deaths that occurred during Year 1 and fatal SAEs that started during Year 1 and resulted in death during Year 2 by the time of the data cut [On Treatment:T13.20]. For Year 2 reporting, the table of deaths by category and PT will include deaths that occurred during Year 2 (and 8-week Follow-up) that have not been previously reported in Year 1 as a result of a fatal SAE [On Study: T23.22].
- A summary of AEs by SOC, PT and severity will also be provided by treatment group. The number and percentage of subjects will be summarized as mild, moderate or severe based on the maximum severity observed within each PT, and within each SOC [On Treatment: T13.10; On Study: T23.09].
- The hierarchical relationship between MedDRA SOCs, PTs, and verbatim text will be displayed in a listing for all AEs [L13.01, L23.01].
- A listing of all AEs [On Study: L13.02, L23.02], study treatment related AEs [On Study: L13.03, L13.04, L23.03, L23.04], and AEs resulting in study treatment

discontinuation [On Study: L13.05, L13.06, L23.05] and post withdrawal [L13.07,23.06] will be presented, including duration, study day of onset/resolution and days since 1st / last belimumab dose.

- If a Year 1 adverse events is reported after year 1 database lock it will be reported in year 2 (L23.07].
- A summary of Adverse Events including Exposure-Adjusted Incidence Rates will be produced for Year 1 On Treatment (Section 5.12) [T13.44] and Years 1&2 combined On Study (Section 5.11) [T23.37]. These will present Adverse Events Overall and by System Organ Class and Preferred Term and will display:
  - the number of subjects experiencing the event (n);
  - For Year 1: the sum of the total time to the first event or total on treatment time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On Treatment Exposure (Year 1);
  - For Years 1&2 combined: the sum of the total time to the first event or total on-study time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On-Study Exposure (Years 1&2 Combined);
  - the exposure adjusted subject rate per 100 subject years (r = (n/e)*100).
- A summary of Adverse Events leading to Permanent Discontinuation of Belimumab Study Drug including Exposure-Adjusted Incidence Rates will be produced for Year 1 On Treatment (Section 5.12) [T13.45] and Years 1&2 combined On Study (Section 5.11) [T23.39]. These will present Adverse Events Overall and by System Organ Class and Preferred Term and will display:
  - the number of subjects experiencing the event (n);
  - For Year 1: the sum of the total time to the first event or total on treatment time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On Treatment Exposure (Year 1);
  - For Years 1&2 combined: the sum of the total time to the first event or total on-study time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On-Study Exposure (Years 1&2 Combined);
  - the exposure adjusted subject rate per 100 subject years (r = (n/e)*100).

8.1.3. Deaths, Serious Adverse Events, and Survival Status

In addition to the tabular summaries of AEs described in Section 8.1.2, listings for all SAEs [L13.08, L23.08], all deaths [L13.09, L23.09] and all non-fatal SAEs [L13.10, L23.10] will be produced (which will also identify on study events). The categorization of the cause of death will be adjudicated by GSK.

A listing of reasons for considering an AE as serious will be provided [L13.11, L23.11].

A summary of Serious Adverse Events including Exposure-Adjusted Incidence Rates will be produced for Year 1 On Treatment (Section 5.12) [T13.46] and Years 1&2 combined

On Study (Section 5.11) [T23.38]. These will present Serious Adverse Events Overall and by System Organ Class and Preferred Term and will display:

- the number of subjects experiencing the event (n);
- For Year 1: the sum of the total time to the first event or total on treatment time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On Treatment Exposure (Year 1);
- For Years 1&2 combined: the sum of the total time to the first event or total on-study time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On-Study Exposure (Years 1&2 Combined);
- the exposure adjusted subject rate per 100 subject years (r = (n/e)*100).

A summary of Deaths including Exposure-Adjusted Incidence Rates will be produced for Year 1 On Treatment (Section 5.12) [T13.47] and Years 1&2 combined On Study (Section 5.11) [T23.40]. These will present Deaths Overall and by Category and Preferred Term and will display:

- the number of subjects experiencing the event (n);
- For Year 1: the sum of the total time to the first event or total on treatment time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On Treatment Exposure (Year 1);
- For Years 1&2 combined: the sum of the total time to the first event or total on-study time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On-Study Exposure (Years 1&2 Combined);
- the exposure adjusted subject rate per 100 subject years (r = (n/e)*100)

Survival status will also be summarized at Weeks 52 and 104. The number and percentage of subjects will be summarized for each of the following categories for Year 1 and Year 1&2 [T13.30, T23.29].

- Alive
- Consent Withdrawn
- Lost to Follow-up
- All Deaths based on the date of death relative to the planned or actual Week 52 visit.
    - For Year 1 reporting, include deaths that occur at or prior to the observed Week 52 visit.
    - For Year 2 reporting (after the actual Week 52 visit):
        - Include all deaths

8.1.4. Adverse Events of Special Interest Analyses

To ensure consistency across belimumab studies, AESI will be defined per the version of the PSAP and MedDRA in effect at the time of DBR.

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 are defined in the PSAP.

The milestone defined in the PSAP (i.e. before database release) for adjudications will be "primary analysis database release" (Year 1) and "end of study database release" (Year 2).

Events with a start date on or prior to the week 52 visit date will be attributed to Year 1; otherwise events will be attributed to Year 2. Events will only be reported once even if the event does not resolve by the Week 52 visit.

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 [On Treatment: T13.31; On Study: T23.30].

A summary of AESI including Exposure-Adjusted Incidence Rates will be produced for Year 1 On Treatment (Section 5.12) [T13.48] and Years 1&2 combined On Study (Section 5.11) [T23.xxx]. These will present AESI Overall and by each specific category and Preferred Term and will display:

- the number of subjects experiencing the event (n);
- For Year 1: the sum of the total time to the first event or total on treatment time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On Treatment Exposure (Year 1);
- For Years 1&2 combined: the sum of the total time to the first event or total on-study time* if no event (years) across all subjects (e), * defined in Section 15.6.2: On-Study Exposure (Years 1&2 Combined);
- the exposure adjusted subject rate per 100 subject years (r = (n/e)*100).

The following AESI will be identified and adjudicated as detailed in the PSAP.

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

Adverse Events

Adverse Events of Special Interest (AESI)

- Skin (All)
  - NMSC
  - Excluding NMSC
- Tumours of unspecified malignancy adjudicated as malignant per GSK

Post-Injection 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 Behavior
    - Completed Suicide
  - Suicidal Ideation
  - Self-injurious Behavior 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 [On Treatment: T13.32; On Study: T23.31].

Post-injection systemic reactions and serious post- injection systemic reactions will be presented using nine different definitions as indicated above. These will be presented by category and PT [On Treatment: T13.33, T13.34; On Study: T23.32, T23.33].

Infection AESIs will be presented by Category and PT for all infections and for infections leading to study treatment discontinuation [On Treatment: T13.41, T13.42; On Study: T23.34, T23.35].

Depression, suicide and self-injury as defined in the PSAP will be presented by Category and PT [On Treatment: T13.43; On Study: T23.36].

All AESI will be presented in a listing [L13.12, L23.12]. Post-Treatment AESIs will be summarized and presented by Category.

8.1.5. Post-Injection Systemic Reactions

Summaries of post-injection systemic reactions that occur on the day of an injection or within 3 days after an injection will be presented by treatment group, by the first six injections and over all injections, and PT for the following:

- Post-Injection Systemic Reactions Adverse Events of Special Interest by Category and PT [T13.33, T23.32].
- Serious Post-Injection Systemic Reactions Adverse Events of Special Interest by Category and PT [T13.34, T23.33].
- Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the injection or within 3 days after the Belimumab injection) by PT in the first six injections [On treatment:T13.35].
- Serious Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the injection or within 3 days after the Belimumab injection) by PT in the first six injections [on Treatment: T13.36].
- Serious Acute Post-Injection Systemic Reactions/Hypersensitivity per GSK Adjudication by PT in the First Six Injections [On Treatment: T13.37].
- Serious Delayed Acute Hypersensitivity Reactions per GSK Adjudication by PT in First Six Injections [On Treatment:T13.38].
- Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Adjudication by PT in First Six Injections [On Treatment: T13.39].
- Post-Injection Systemic Reactions per Anaphylactic Reaction CMQ broad search (on the day of the injection or within 3 days after the Rituximab infusion) by PT [On treatment:T13.40].

8.1.6. Additional Adverse Event Summaries to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic

Additional adverse event summaries will be produced to further understand the safety profile and/or impact of the COVID-19 pandemic on safety.

Two listings will be produced to show the number of subjects with a suspected, probable or confirmed COVID-19 infection. The first listing will present data for Year 1 On Treatment (Section 5.12) [L13.26]; the second listing will present data for Years 1 and 2 combined On-Study (Section 5.11) [L23.27]. Both listings will also show the number of subjects who had a COVID-19 diagnosis test performed and the number of subjects with positive, negative, or indeterminate results. The listings will be based on information collected on the COVID-19 Coronavirus Infection Assessment CRF page.

Extra tables will be produced to display the incidence of Adverse Events over the time course of the trial. Event rates will be reported by calendar time defined as either pre or during the COVID-19 pandemic (or post the pandemic if applicable by the Year 2 reporting). The COVID-19 environment onset date will be used to define pre and during the COVID-19 pandemic (Section 15.6.16).

The following Tables will summarise the Year 1 On Treatment (Section 5.12) events for pre or during the COVID-19 pandemic. Event rates will be adjusted for on treatment exposure (Section 15.6.2, On -Treatment exposure in the relevant pandemic phase (Year 1)).

- The overall rates of AEs, SAEs and severe AEs [T13.49]
- The overall rates of AEs, SAEs and severe AEs, presented by Country Region (USA/Canada vs. Europe vs. Rest of World) (Section 5.5.2.) [T13.50]
- The most frequent Adverse Events (≥ 5% incidence in any treatment group) by Preferred Term [T13.51]

The following Tables will summarise the Year 1 and 2 combined On-Study (Section 5.11) events for pre or during the COVID-19 pandemic. Note that if a date is defined prior to the Year 2 reporting for the 'end of the pandemic' then this output will split events into pre, during or post the COVID-19 pandemic. Event rates will be adjusted for on-study exposure in the relevant pandemic phase (Section 15.6.2, On-Study exposure (Years 1&2 combined)).

- The overall rates of AEs, SAEs and severe AEs [T23.42]
- The overall rates of AEs, SAEs and severe AEs, presented by Country Region (USA/Canada vs. Europe vs. Rest of World) (Section 5.5.2.) [T23.43]
- The most frequent Adverse Events (≥ 5% incidence in any treatment group) by Preferred Term [T23.44]

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

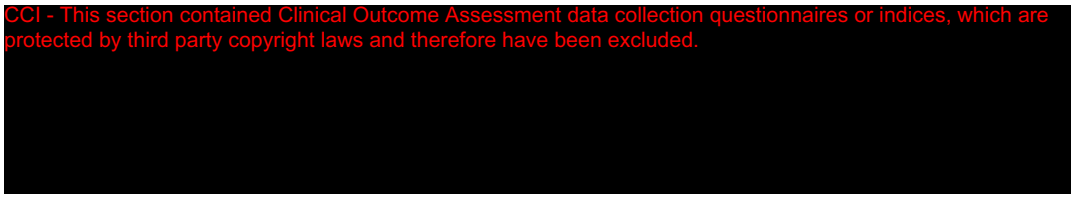
For suicidal ideation, the pre-treatment reference period is the lifetime history, current history and baseline (for further detail refer to the IDSL documentation). For suicidal behavior, the pre-treatment reference period is the lifetime history and baseline (note: suicidal behavior is not re-assessed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

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

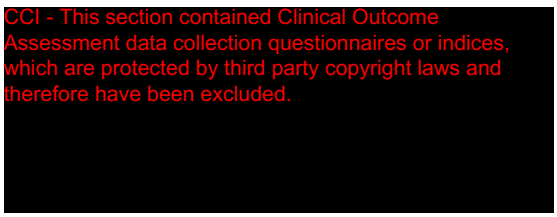
Suicidal ideation will be assessed using responses to C-SSRS ideation questions (categories 1 to 5) only. Suicidal behavior will be assessed using responses to C-SSRS behavior questions (categories 6 to 10) only.

- **Treatment emergent suicidal ideation** will be assessed using the maximum ideation score pre-treatment, compared to the maximum ideation score post-treatment (Year 1 or Year 2 as appropriate). If the maximum ideation score worsens relative to the pre-treatment reference period then this will be considered a treatment emergent suicidal ideation. This is derived from responses to suicidal ideation questions (categories 1 to 5).
- **Treatment emergent suicidal behavior** will be assessed using the maximum behavior score pre-treatment, compared to the maximum behavior score post-treatment (Year 1 or Year 2 as appropriate). If the maximum behavior score worsens relative to the pre-treatment reference period then this will be considered a treatment emergent suicidal behavior. This is derived from responses to suicidal behavior questions (categories 6 to 10).
- **Treatment emergent suicidal ideation or behavior** will be defined as a subject having a treatment emergent suicidal ideation (as defined above) and/or a treatment emergent suicidal behavior (as defined above).

Suicidal Ideation (categories):



Suicidal Behavior (categories):



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

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).

All C-SSRS tables will be presented for subjects whilst on study.

8.2.1. C-SSRS Suicidal Ideation or Behaviour on Study [T13.52, T23.45].

The number and percentage of subjects with each category of suicidal ideation or behavior during treatment (starting after Day 1 assessment) will be presented for Year 1, and Year 2. For suicidal ideation, the maximum ideation score (1-5) at any time during the relevant period will be presented. For suicidal behavior, all behaviors (6-10) present at any time during the relevant period will be presented. This will be regardless of whether the subject had pre-treatment history (up to and including baseline). The categories of suicidal ideation and behavior are presented in increasing order of severity from 1 to 5, and 6-10 respectively.

8.2.2. C-SSRS Suicidal Ideation or Behavior Relative to Pre-Treatment [T13.53, T23.46].

The number and percentage of subjects with treatment-emergent suicidal ideation or behavior -post-baseline will be presented for Year 1 and Year 2.

A subject must have at least one pre-treatment C-SSRS assessment (screening and/or baseline) and at least one Year 1 or Year 2 (respectively) C-SSRS assessment to be included in this display.

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

The following categories will be presented:

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

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

8.2.3. C-SSRS Shift Changes in Categories from Pre-Treatment to On-Study [T13.54, T23.47].

A summary of the shift from maximum pre-treatment C-SSRS category to maximum category during Year 1 and Year 2 separately will be produced by treatment group.

The pre-treatment period for ideation is based on the lifetime, current and baseline history. For behavior, it is based on the lifetime and baseline history. A subject must have at least one pre-treatment assessment and at least one assessment during Year 1 or Year 2 (respectively) in order to be included in these displays.

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

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

8.2.4. C-SSRS Shift Changes in Categories from Year 1 to Year 2 [T23.48].

A summary of the shift from last Year 1 C-SSRS assessment to maximum Year 2 C-SSRS assessment will be produced by treatment group.

The last Year 1 is based on the current assessment. A subject must have at least one Year 1 assessment, and at least one assessment during Year 2 in order to be included in these displays.

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

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

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards.

For laboratory analyses analytes will be analyzed and summaries and analyses will be performed based on the observed data. No imputation will be done for missing data. Baseline is defined as described in Section 5.3. See Protocol Appendix 9 for a list of laboratory parameters. Laboratory toxicity grades will be assigned based on DMID (see Section 15.8 Appendix 8: Laboratory Parameters and Toxicity Grades) by the laboratory,

with the exception of Lymphopenia (as there is no DMID grade). Lymphopenia will be graded as per CTCAE v4.03.

Calcium, will be presented as hypercalcaemia and hypocalcaemia separately (with each subject appearing in both categories) and similarly for sodium (hypernatremia, hyponatremia), potassium (hyperkalemia, hypokalemia), and glucose (hyperglycemia, hypoglycemia).

Listings will be generated for all laboratory results and for Grade 3 or Grade 4 laboratory toxicity results [L13.13 – L13.24, L23.14 - L23.26].

If a numeric laboratory value, has a non-detectable level reported in the database, then typically the numeric value is missing, and a character value starting with '<x' or '>x' is present. A numeric value will be derived using the number of decimal places in the observed character values i.e.

- 2 Decimal Places = '< x ' becomes x – 0.01
- 1 Decimal Place = '> x' becomes x + 0.1
- 0 Decimal Places = '< x' becomes x – 1

8.3.1. Laboratory Descriptive Statistics by Visit

Descriptive statistics for each analyte will be displayed for each visit for both the Year 1 and Year 1&2 reporting separately. The tables will display the mean value, standard deviation, median, 25th and 75th percentiles, minimum and maximum. No statistical tests will be performed [T13.55, T13.59, T13.63, T13.67, T13.74, T23.49, T23.53, T23.57, T23.61, T23.68].

A line graph will be produced for each analyte which displays the mean value (±SE) by visit and treatment group for both Year 1 and Year 1&2 separately [F13.01-F13.05, F23.01-F23.05].

8.3.2. 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) for Year 1 and Year 1&2 separately. 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 [T13.57, T13.61, T13.65, T13.69, T13.72, T13.76, T23.51, T23.55, T23.59, T23.63, T23.66, T23.70].

8.3.3. 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 normal/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. This analysis will be performed for Year 1 and Year 1&2 separately [T13.58, T13.62, T13.66, T13.70, T13.73, T23.52, T23.56, T23.60, T23.64, T23.67].

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

8.3.4. Immunoglobulin Reference Range Shifts from Baseline by Visit

For immunoglobulins (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. This analysis will be performed for Year 1 and Year 1&2 separately [T13.77, T23.71].

8.3.5. Worst Laboratory Toxicity Grade Post-Baseline

Laboratory toxicity will be graded using grades corresponding to mild, moderate, severe, and life-threatening when possible. The worst laboratory toxicity grade for each laboratory parameter within each laboratory category (hematology, liver function, electrolytes, other chemistries, urinalysis and immunoglobulins) during Year 1 and Year 1&2 separately will be presented. Data for both scheduled and unscheduled visits will be included. For calcium, sodium, potassium and glucose, grades associated with hypo- and hyper- conditions will be included [T13.56, T13.60, T13.64, T13.68, T13.71, T13.75, T23.50, T23.54, T23.58, T23.62, T23.65, T23.69].

8.3.6. 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 for Year 1 and Year 1&2 separately. No statistical test will be performed [T13.78, T13.79, T23.72, T23.73].

8.3.7. 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 for Year 1 and Year 2 separately. No statistical test will be performed [T13.80, T13.81, T23.74, T23.75].

8.3.8. Immunogenicity

For the immunogenicity assessment for belimumab, two types of antibody assays will be performed, i.e. a binding assay and neutralizing assay. For the immunogenicity assessment for rituximab only a binding assay will be performed . For the binding assay, there will be 3-testing steps. A screening assessment is performed which produces a result of positive or negative. Confirmed positive samples will be further characterised for a relative level of binding (titre value). Subjects will be viewed as positive for anti-drug antibody (ADA) if the confirmation assay is positive. Subjects, who confirm positive in the anti-belimumab ADA assay, will be evaluated for the presence of neutralising antibody (Nab) response with the NAb assay, which again produces a result of positive or negative.

For incidence of subjects with positive binding antibody during the study period, a table will be produced summarizing results for the binding antibody assay by treatment group and visit. The table will include the number and proportion of subjects in each results category for each visit in the study period (including early withdrawal visit). Binding confirmatory assay results will be categorized as negative, persistent positive (defined as a positive immunogenic response at least two consecutive assessments during the study period or a single result at the final assessment in the study period) or transient positive (defined as a single positive immunogenic response that does not occur at the final assessment in the study period).

Results will be summarized by visit and by treatment group for belimumab (Year 1 and Year 2, separately) and for Arms A and B only for rituximab (Year 1) [T13.82 T13.83, T23.76]. A listing of immunogenicity results will also be presented [L13.33, L23.33].

8.3.9. Further Research Samples

Blood leukocyte analysis and B cell receptor samples collected at selected sites in the USA will be reported separately and are not considered in this RAP.

B Cell subsets collected at selected sites in the European Union (EU) will be reported separately and are not considered in this RAP.

8.4. 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.

8.4.1. Vital Signs

A summary of vital signs and change from baseline in vital signs will be presented by visit for Year 1 and Year 2 separately. Weight will be included in these summaries [T13.84, T13.85, T23.77, T23.780].

8.4.2. Neurological Assessment

Findings consistent with the diagnosis of Progressive Multifocal Leukoencephalopathy (PML) will be recorded as adverse events.

9. HEALTH OUTCOMES ANALYSES

Health outcomes reporting will be conducted on the MITT population, following the principles of the Efficacy analysis.

Additional details for the Health Outcome scales are provided in the appendix: Lupus Qol (Section 15.6.10); WPAI (Section 15.6.11); FACIT-Fatigue Scale (Section 15.6.12).. A listing of all health outcomes endpoints will be presented [L24.01-L24.03].

Exit interviews assessing patients experience of the clinical trial will be databased and reported separately.

The Health Outcome scales are completed by the subject and are very subjective, therefore, all data after the COVID-19 environment onset date (Section 15.6.16) is very likely to be either missing due to the pandemic or affected by the pandemic. It is also expected that the Health Outcomes data collected at different stages of the COVID-19 pandemic may be affected in different ways. As per the second additional analysis for the primary Efficacy endpoint, there may be intangible ways that the data may have been affected even if it has been collected, therefore we cannot distinguish between affected and unaffected data after the COVID-19 environment onset date.

For these reasons, additional analyses defined below have been added for Week 52 and Week 64. A hypothetical strategy was already proposed to deal with missing data due to study withdrawal and this has been expanded to also define the COVID-19 environment onset date as an Intercurrent Event for any subject who has their (scheduled) Week 52 (or Week 64) assessment on or after the onset date. The data for these subjects will be treated as missing values and will be assumed to be Missing At Random (MAR). It will be imputed using Multiple Imputation methods, which take into account the subjects baseline characteristics and their existing pre-COVID data.

The analysis for Week 104 has not been modified as all observed Week 104 data will be collected after the COVID-19 environment onset date, so the Multiple Imputation approach will not be possible. This means that the results should be interpreted with caution.

Additional post-SAC analyses may be carried out to assess the impact of the COVID-19 pandemic on the Health Outcomes data.

9.1. Statistical Methodology Specification for Continuous Endpoints

Endpoints
For all reported timepoints upto Week 52 (Year 1 reporting) and upto week 104 (Year 2 reporting): *Patient Global Assessment (PtGA) of Disease Activity* • Change from baseline in PtGA by visit [T14.01, T24.01].

LupusQoL Domain Scores

- Change from baseline in each of the 8 LupusQoL Domain scores by visit [T14.02, T24.02].

FACIT-Fatigue Scale Score

- Change from baseline in FACIT-Fatigue Scale score by visit [T14.03, T24.03].

Work Productivity and Activity Impairment (WPAI)

- Change from baseline in WPAI percent overall work productivity impairment by visit [T14.05, T24.05].
- Change from baseline in WPAI percent activity impairment score by visit [T14.06, T24.06].

Derivation

Derivation of the endpoints is provided in Section 15: Lupus Qol (Section 15.6.10); WPAI (Section 15.6.11); FACIT-Fatigue Scale (Section 15.6.12).

Strategy for Intercurrent (Post-Randomization) Events

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subjects not had missing data.

Imputation of Data for Missed Visits, and Following Study Withdrawal

- A bayesian repeated measures normal model will be fitted to the observed data, using a Markov Chain Monte Carlo approach, adjusting for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day). Non-informative priors will be used
- Quasi-independent samples will be drawn from the posterior distributions for the parameters of the multivariate normal distribution for each treatment group and each missingness pattern.
- Each sample leads to a separate imputed dataset, in which the missing values are replaced by values drawn randomly from their conditional distribution. This distribution is based on the observed data and the covariates for that subject using the imputation model and the sampled parameter values.
-

These steps will be repeated at least 1000 times.

Model Specification

- Each imputed dataset will be analyzed using ANCOVA to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), and baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day) and baseline value.
- The resulting treatment differences and their SEs will be combined across imputations using Rubin's rules.

Model Checking & Diagnostics
The Kolmogorov-Smirnov D statistic will be used to test the assumption of normality. Residuals will be reviewed to assess the homogeneity of variance assumption.
Model Results Presentation
The tables will display: • Baseline: the number subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, maximum for each arm • At each visit: o the number subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum o LS Mean, and standard error of the LS Mean for each arm at Weeks 52, 64 and 104. o the treatment difference and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104. o the p-value for treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

9.1.1. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic (Continuous Endpoints upto Week 52 and Week 64)

The analysis will be repeated, but visits that were conducted on or after the COVID-19 environment onset date (Section 15.6.16) will be considered as impacted and hence removed from the analysis, as if the subjects had withdrawn.

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subjects not had missing data (including the missing data from the removal of impacted COVID-19 visits). Weeks 72 and 104 are anticipated to have too much data post the COVID-19 environment onset date and hence will not be included.

Patient Global Assessment (PtGA) of Disease Activity

- Change from baseline in PtGA by visit [T14.08,T24.08].

LupusQoL Domain Scores

- Change from baseline in each of the 8 LupusQoL Domain scores by visit [T14.09,T24.09].

FACIT-Fatigue Scale Score

- Change from baseline in FACIT-Fatigue Scale score by visit [T14.10,24.09]

Work Productivity and Activity Impairment (WPAI)

- Change from baseline in WPAI percent overall work productivity impairment by visit [T14.12, 24.12].
- Change from baseline in WPAI percent activity impairment score by visit [T14.13, 24.13].

For change from baseline endpoints, a plot of LS means +/- SE by visit and treatment group will be provided.[Year 1: F14.01, Year 1 and 2 combined, but only up to Week 64: F24.01-24.06].

9.2. Statistical Methodology Specification for Proportion Endpoints

Endpoint / Variables
• The proportion of participants with an improvement in FACIT-fatigue score exceeding the minimal clinically important difference (MCID is >=4) by visit.
Derivation
Derivation of the FACIT endpoint is provided in Section 15.6.12. A subject is considered to have an improvement exceeding the minimal clinically important difference if they have ≥4 points improvement in their FACIT-Fatigue Scale score from baseline.
Imputation of Data for missed visits, and following study withdrawal..
Missing Data will be imputed as detailed in Section 9.1.1, then categorized as Responder/Non-Responder using the derivation above. For consistency of results, the same seed will be used for the imputation of missing data on the continuous FACIT scale and the imputation on the continuous scale that is then dichotomized into the binary response.
Model Specification
• Each imputed dataset will analyzed using the proposed statistical analyses planned for the primary endpoint. The FACIT-fatigue score at baseline will also be included as a covariate. • The resulting Odds Ratios and their SEs will be combined across imputations using Rubin's rules.
Model Checking & Diagnostics
• The model and diagnostics checks proposed for the primary endpoint will be repeated for this endpoint.
Model Results Presentation

• For each endpoint a table [T14.04, T24.04]. will display:
  ◦ the number, percentage, SE of percentage, and the 95% CI for the percentage of subjects achieving a response by treatment group,
  ◦ the observed difference in percentage of responders for the comparison of Arm B vs Arm A; and Arm B vs Arm C,
  ◦ the odds ratio and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C at Weeks 52, 64 and 104.
  ◦ the p-value for the odds ratio the treatment difference for Arm B vs Arm A at Weeks 52, 64 and 104.

9.2.1. Additional Analyses to Assess the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic

The analysis will be repeated however visits that were conducted on or after the COVID-19 environment onset date (Section 15.6.16) will be considered as impacted and hence removed from the analysis, as if the subjects had withdrawn.

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subjects not had missing data (including the missing data from the removal of impacted COVID-19 visits). Weeks 72 and 104 are anticipated to have too much data post the COVID-19 environment onset date and hence will not be included.

The proportion of participants with an improvement in FACIT-fatigue score exceeding the minimal clinically important difference (MCID is >=4) by visit [T14.11, T24.11].

9.3. Health Care Resource Utilization

The health care resource utilization (HCRU) data will be used to conduct exploratory economic analyses of:

- Number of outpatient/hospital clinic visits
- Number of emergency room/urgent care facility visits
- Number and duration of in-patient hospitalizations (total nights, including duration by wards [intensive care unit vs. general ward])
- Use of over the counter (non-prescription) medication.

These data will be provided by CRF Health, and planned analyses will be described in a separate document

A listing of data will be provided at Year 2 [L24.04]. Health care resource utilization will be summarised at Week 52 for Year 1 (T14.07), and at Week 104 for Year 1&2 (T24.07).

Duration of hospitalization will be summed for subjects with more than 1 hospitalisation. Subjects with ongoing hospitalization at Week 52 will be truncated for the Week 52 (Year 1) summary. Subjects with ongoing hospitalization at Week 104 will be truncated for the Week 104 (Year 2) summary at the last known date of hospitalization (i.e. including post study hospitalization if the hospitalization is ongoing at Week 104).

If subjects are withdrawing due to hospitalization then an additional exploratory analysis will be performed shortly after the Statistical Analysis Complete milestone.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

Biomarker Endpoints, Autoantibodies, complement, and peripheral B lymphocytes (referred to as B cells) will be collected per the study calendar (Section 15.2 Appendix 2: Schedule of Activities). The peripheral B lymphocytes will be measured (using FACS analysis). The specific biomarkers collected and analyzed are listed in Table 4:

Table 4 Biomarkers for Analysis

Autoantibodies	**Immunoglobulin**
aCL (IgA, IgG, IgM)	IgG, IgM, and IgA
ANA	**B cells (present in tables in this order)**
Beta-2-glycoprotein (IgA, IgG, IgM)	CD19+ Total B cells (cells/mL)
Lupus anticoagulant	B cells CD20+ (cells/mL and % of CD19+ Total B cells)
Anti-dsDNA	Naive B cells IgD+ (cells/mL and % of CD19+ Total B cells)
	Naive CD20+ CD27- (cells/mL and % of CD19+ Total B cells)
Extractable nuclear antigens (ENAs)	Activated Total B cells CD95+ (cells/mL and % of CD19+ Total B cells)
Anti-Ribosomal-P ;	Memory CD20+ CD27+ (cells/mL and % of CD19+ Total B cells)
Anti-RNP-70;	Non-switched memory CD27+ IgD+ (cells/mL and % of CD19+ Total B cells)
Anti-SS-A;	Switched memory CD27+ IgD- (cells/mL and % of CD19+ Total B cells)
Anti-SS-B	Plasmablasts CD27b CD38b (cells/mL and % of CD19+ Total B cells)
Anti-Smith	Plasmablasts CD20+ CD27b CD38b (cells/mL and % of CD19+ Total B cells)
Complement	Plasmablasts CD20- CD27b CD38b (cells/mL and % of CD19+ Total B cells)
C3	Transitional CD10+ CD24b CD27- CD38b (cells/mL and % of CD19+ Total B cells)
C4	Transitional CD24b CD27- CD38b (cells/mL and % of CD19+ Total B cells)
T cells	Cytokines
CD3+ Total T cells (/uL)	BLyS (Total and Free)
CD8+ T cells (/uL)	
CD4+ T cells (/uL)	

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 only contain data from the baseline visit (hence not impacted by treatment group). These datasets will

display the format for 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.

10.1. Biomarker Change and Percent Change from Baseline Analyses

Endpoints
The change from baseline and percent change (not for % endpoints) from baseline will be evaluated by visit for each of the biomarkers listed in Table 4 [T15.01-15.02, T15.04-T15.07, T15.09-T15.12, T15.14-T15.15, T25.01-25.02, T25.04-T25.07, T25.09-T25.12, T25.14-T25.15,]. Tables of descriptive statistics for changes in Year 2 relative to at the end of Year 1 will be summarised for immunoglobulins, auto-antibodies and B-Cells [T25.21, T25.22,T25.23].
Population of Interest
The Intent-to-Treat population will be used for the analysis.
Intercurrent Event Strategy
The Year 1 analyses will be performed on the observed data up to IP discontinuation. No imputation will be done for missing data. The Year 1&2 analyses will be performed on the observed data for subjects who completed Week 52 on treatment (Ongoing and on treatment at Week 52 analysis as defined in Section 7.1.5). No imputation will be performed for missing data (data post re-start Belimumab will not be considered.
Model Specification
Immunoglobulins and Complement An ANCOVA will be used to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day), and baseline value (continuous). If the distribution of the observed data is not consistent with conducting ANCOVA then a non-parametric rank ANCOVA will also be conducted. Auto-Antibody, B-Cells, T-Cells, and BLyS (Total and Free): A Rank ANCOVA will be used to evaluate the treatment effect controlling for treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10), baseline immunosuppressant use (use vs. non-use), baseline corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day), and rank baseline value (continuous).
Model Checking & Diagnostics
For the ANCOVA analysis the Kolmogorov-Smirnov D statistic will be used to test the assumption of normality. Residuals will be reviewed to assess the homogeneity of variance assumption.

Model Results Presentation
The tables will display: • Baseline: the number subjects, number of subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, maximum for each arm • the number of subjects, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum, for each arm at each visit • For ANCOVA analysed endpoints the LS Mean, standard error of the LS Mean, treatment difference for each arm, and 95% confidence interval (CI) for the comparison of Arm B vs Arm A; and Arm B vs Arm C will be presented at Weeks 52, 64, and 104 • For all endpoints the p-value for treatment difference for Arm B vs Arm A will be presented at Weeks 52, 64, and 104. For change from baseline endpoints, a plot of LS means +/- SE or Median +/- Quartiles (dependent on observed data distribution) by visit and treatment group will be provided.

There will also be additional reporting of lab parameters (Haematology, chemistry, urinalysis and other chemistries) to explore the changes in Year 2 relative to at the end of Year 1. Descriptive statistic tables considering the change from Week 52 by visit for Year 2 will be produced [T25.16-25.19].

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

Endpoints [T15.03, T15.08, T15.13, T25.03, T25.08, T25.13].

Shift tables will be used to summarize the changes in immunoglobulins, autoantibodies, and complement by treatment group and visit. Autoantibodies will be evaluated for shifts from positive to negative. Immunoglobulins and complement will be evaluated for shifts from Low to Normal/High.

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.
Beta-2-glycoprotein isotypes: IgA, IgG, IgM	≥21 U/mL	<21 U/mL
Lupus anticoagulant	N/A	
ENAs	> Upper limit of normal range	≤ Upper limit of normal range
Cytokines		
BlyS (Total and Free)	$<75^{th}$ percentile	$>=75^{th}$ percentile
Ig and Complement	**Low**	**Normal/High**
IgG	<6.94 g/L	≥6.94 g/L
IgA	<0.81 g/L	≥0.81 g/L
IgM	<0.48 g/L	≥0.48 g/L
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 at Week 52 only.

Summary Measure

The difference in proportions Arm B (Combination)– Arm A (Control) will be used to measure the treatment effect.

Population of Interest

The 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 plus rituximab=1, belimumab plus placebo=0)
Results Presentation
For IgG, IgA, IgM, C3,C4, and C3 and C4 combined baseline data will be summarized as the number and percent of subjects who are low or normal/high at baseline. For post-baseline visits the data will be summarized by baseline status defined as low or normal/high. Among subjects low at baseline the shifts presented will be low to normal/high and low to low. Among subjects normal/high at baseline, the shifts presented will be normal/high to normal/high and normal/high to low. For anti-dsDNA, ANA, aCL, Beta-2-glycoprotein, Lupus anticoagulant,ENAs and BlyS, 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.
Subgroup Analyses
Subgroup analyses will not be conducted

11. PHARMACOKINETIC ANALYSES

11.1. Primary Pharmacokinetic Analyses

Descriptive statistics for serum belimumab (from all three treatment arms combined) and rituximab concentrations will be displayed for each visit for Year 1 and for Years 1&2 Combined. 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 [T16.01, T16.02, T26.01].

A line graph will be produced which displays the median belimumab or rituximab concentration values along with 25th and 75th percentiles by visit Year 1 and for Years 1&2 Combined [F16.01, F16.02, F26.01].

A listing of serum belimumab and rituximab PK concentration-time data will be presented [L16.01, L16.02, LL26.01].

11.1.1. Endpoint / Variables

11.1.1.1. Drug Concentration Measures

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

11.1.2. Population of Interest

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

11.1.3. Statistical Analyses / Methods

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

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

12. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

12.1. Statistical Analyses / Methods

There will not be a formal requirement to carry out a population pharmacokinetic (PopPK) analysis for this study. However, depending on the study results a PopPK analysis may be performed on a post-hoc basis to quantity the combined effects of belimumab and rituximab in an adult SLE population with respect to belimumab PK, the pharmacological response, and efficacy and safety end-points.

- To develop a PopPK model that characterizes the PK disposition of belimumab following sub-cutaneous administration in adult subjects with SLE.
- Evaluate the potential effect of rituximab administration on belimumab PK parameters.
- Estimate the individual PK parameters for each subject in the study receiving belimumab and summarise across the study.
- Evaluate the effect of belimumab exposure on the response of selected biomarkers, efficacy and safety end-points when dosed alone and in combination with rituximab.

Belimumab serum concentration-time data will be analyzed using a non-linear mixed-effects modelling approach. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

13. 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.

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15. APPENDICES

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

15.1.1. Exclusions from Per Protocol Population

The per protocol population will be based on the review of the important protocol deviations as detailed in PDMP review document

Important protocol deviations in these categories of the PDMP will be assessed as detailed for exclusion from the per protocol population

ELIGIBILITY CRITERIA NOT MET

Subjects who do not meet the following criteria

Did not have a clinical diagnosis of SLE according to the ACR criteria (Inclusion Criterion 2).

Did not have clinically active SLE disease defined as a SLEDAI-2K score ≥ 6 at screening (Inclusion Criterion 3)

Did not have unequivocally positive ANA test results from 2 independent time points (Inclusion Criterion 4)

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

Received an excluded medication prior to Day 0 (Exclusion Criteria 23-26) and adjudicated to have had a reasonable probability of impacting on the assessment of efficacy post Day 1.

ASSESSMENT OR TIME POINT COMPLETION and VISIT COMPLETION

Missed assessment

Missed SLEDAI-2K assessment at Week 52 will be excuded

Out Of Window Assessment

More than 28 days late for Week 52 visit or Week 52 SLEDAI-2K assessment

WRONG STUDY TREATMENT/ADMINISTRATION/DOSE Study treatment not administered per protocol

Subjects randomised to Arms A or B who did not receive all of both scheduled rituximab / rituximab-placebo infusions

Subjects with 4 or more missed consecutive Belimumab doses.

Subjects with 4 or more missed consecutive Belimumab doses irrespective of subject re-initiating Belimuab injections in the presence of the investigator

Wrong study treatment or assignment administered

Subjects who did not receive their assigned treatment will be assessed on a case by case basis.

STUDY PROCEDURES

Study blinding/unblinding procedures

Subjects from whom their Investigator/site staff/GSK Clinical team did not remain blinded to treatment assignment through Week 52/Exit visit efficacy evaluation

OTHER REASONS

As determined during

protocol population review meeting prior to unblinding that are determined to have the potential to impact the efficacy evaluation.

15.2. Appendix 2: Protocol Defined Schedule of Activities

Table 5 Double-blind Treatment Phase Procedures: Year 1, Arms A and B

Double-Blind Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arms A and B (a)												Unsched-uled Visit (l)	Early Withdrawal Visit (b)	Follow-up visit (8 weeks post last dose)
		D1 (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
Informed consent	X															
Inclusion and exclusion criteria	X	X (m)														
Genetics Informed consent	X (r)															
Randomization		X														
Assessments: Clinic																
Full physical exam including height and weight	X															
12-lead ECG	X															
Demography	X															
Medical history (includes substance usage)	X															
Past and current medical conditions including cardiovascular medical history	X															
Vital signs	X															
Symptom-driven physical exam, vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X							X				X		X	
Assessments: Independent Assessor																
SLEDAI-2K: Blinded Assessor (t)		X				X			X		X		X	X	X	
Assessments: Principal Investigator																
SLEDAI-2K: Investigator	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
C-SSRS Baseline/Screening	X															
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Double-Blind Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arms A and B (a)												Unsched-uled Visit (l)	Early Withdrawal Visit (b)	Follow-up visit (8 weeks post last dose)
		D1 (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
Neurological Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLE Flare Index (n)		X	X		X	X	X	X	X	X	X	X	X	X	X	
SLICC-ACR Damage Index		X											X		X	
Physician Global Assessment (PGA)		X	X		X	X	X	X	X	X	X	X	X	X	X	
Survival Assessment (d)													X			
Assessments: Patient Reported Outcomes (PROs)																
Patient Global Assessment (c)		X			X	X			X		X		X		X	
FACIT-Fatigue (c)		X			X	X			X		X		X		X	
Lupus QoL (c)		X			X	X			X		X		X		X	
WPAI: Lupus (c)		X			X	X			X		X		X		X	
Post-treatment interview (o)													X		X	
Central Laboratory Tests																
Drug and alcohol screen	X															
HIV, Hep B and Hep C screen	X															
Pregnancy test (WCBP) (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments (include liver chemistries)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgA, IgM, IgG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-dsDNA/ANA, Complement C3/C4	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Extractable nuclear antigens (ENAs)		X			X				X				X		X	
PT/PTT	X	X			X				X				X	X	X	

Double-Blind Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arms A and B (a)												Unsched-uled Visit (l)	Early Withdrawal Visit (b)	Follow-up visit (8 weeks post last dose)
		D1 (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
Antiphospholipid antibodies (aCL, lupus anticoagulant, ± beta-2-glycoprotein-1)		X			X				X				X	X	X	
Labs and Biomarkers																
B cells subsets		X	X				X		X		X		X		X	X
BLyS Protein		X											X		X	
Immunogenicity: Belimumab		X	X(f)	X(f)	X				X				X	X	X	X
Immunogenicity: Rituximab		X	X(f)	X(f)	X				X				X	X	X	
Pharmacokinetics: Belimumab			X(f)		X				X				X	X	X	X
Pharmacokinetics: Rituximab			X(g)	X(g)	X				X	X(h)				X	X	X
Genetic sample		X														
Exploratory Further Research																
Blood Leukocyte Analysis (PBMC) (p)		X											X		X	
RNA for Interferon Signature		X														
B cell receptor (q)		X												X	X	
B cells subsets – (u)		X	X										X		X	
Study Treatment																
Training on use of Autoinjector	X	X														
Dispense/Train or Collect Electronic Diary		X													X	
Dispense Belimumab for weekly dosing (SC)		X (i)	X (s)		X	X	X	X		X	X	X				
Rituximab or Rituximab-Placebo (IV)			X (j)	X (j)										X (j)		
Discontinue immunosuppressants			X													
Initiate corticosteroid taper						X (k)										

Double-Blind Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arms A and B (a)												Unsched-uled Visit (l)	Early Withdrawal Visit (b)	Follow-up visit (8 weeks post last dose)
		D1 (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
Target for steroid corticosteroid dose to reach prednisone equivalent ≤5 mg/day									X							
Study Visit Review Procedures																
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review (including SLE medications)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review HCRU and Patient Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	

a. Starting at Week 4 and throughout the study period including follow-up, a study visit time window ± 7 days is acceptable. Note: Every effort should be made to schedule the visit in this window, however if the COVID-19 pandemic situation affects the ability to achieve this then, for those COVID-19 specific instances, the visit window can be expanded to ±28 days.
b. Early Withdrawal Visit 1-4 weeks after last dose for participants that withdraw from the study.
c. To be conducted prior to clinical assessments.
d. Survival assessment at Week 52 for participants who withdraw before Week 52.
e. Serum pregnancy test at Screening; Urine pregnancy test at all other visits, including pregnancy test 16 weeks after last dose of belimumab. The pregnancy test 16 weeks after the last dose of belimumab may be done at home, with the results reported by telephone call to the clinic. See Protocol Section 9 for pregnancy test requirements a.
f. At Week 4 and Week 6 pre-rituximab/ rituximab-placebo dose.
g. At Week 4 post-rituximab/rituximab-placebo dose and at Week 6 pre- and post- rituximab/rituximab-placebo dose.
h. At Week 32 only.
i. The first dose of belimumab will be administered at the clinic and the subject needs to stay for 3 hours post dose for observation.
j. Premedication administration will be given 30 minutes prior to each rituximab / rituximab-placebo dose and the subject needs to stay in clinic for 1 hour post dose for observation (i.e., Clinical monitoring including vital signs). If the subject misses the Week 4 dosing visit and dosing will take place during an unscheduled visit, the first dose of rituximab should be scheduled no later than 7 days after Week 4. The second dose of rituximab must be administered at least 2 weeks but not more than 3 weeks after the first rituximab dose. NOTE: Contact Medical Monitor if the date of a) first dose is more than 1 week past week 4, and b) if the date of the second dose of rituximab would exceed 3 weeks after the first dose. During unscheduled visits, procedures for Immunogenicity and PK will follow the schedule for Week 4 and Week 6.
k. It is recommended that the steroid taper be initiated on Week 12 to reach the target prednisone equivalent of ≤5 mg/day at Week 26, but the taper schedule is at the discretion of the investigator.

l. Procedures to be performed at Unscheduled Visits are based on reason for Unscheduled Visit, including adverse event or discontinuation of study agent. Guidance is provided in the Study Reference Manual.
m. The interim medical history, including SLE medications, should be reviewed prior to randomization to assure that the participant's eligibility has not changed.
n. Blood samples for a B cell receptor analysis should be obtained in the event of a suspected SLE Flare (refer to footnote q).
o. To be conducted at US sites only.
p. To be conducted only at US study sites.
q. To be conducted only at US study sites. B-cell receptor samples are also collected when subjects experience a suspected SLE Flare.
r. Separate Genetics informed consent as needed per country specific requirements. Genetics informed consent and sample can be obtained any time after baseline.
s. If a subject happens to be scheduled for an infusion (week 4 and/or 6) on the same day of the week as their normally scheduled belimumab injection, whenever possible, the day of the belimumab injection should be altered within the dosing window to separate the day of the injection from the day of the infusion to allow for appropriate safety monitoring of the infusion. If subject has already self-administered the belimumab dose on the day of IV infusion, contact study Medical Monitor for guidance prior to administering the rituximab/rituximab-placebo dose.
t. Independent assessor will perform symptom-driven physical examination to include, at a minimum, assessments of eyes, mouth, skin, lungs, cardiovascular system, abdomen, and extremities (including joints). Independent assessors must have a source document (paper record in the study file) where the findings in the clinical exam and laboratory analyses supporting the scoring of S2K are described.
u. To be conducted only at selected European sites

Table 6 Double-blind Observational Phase Procedures: Year 2, Arms A and B

	Observational Period – Arms A and B (a)								
Arms A and B Double-blind Observational Phase Procedures (W=Week)	W60	W64	W72	W80	W88, W96	W104	Unscheduled Visit (e)	Early Withdrawal Visit (f)	Follow-up visit (8 weeks post last dose) (j)
Assessments: Clinic									
Symptom-driven physical exam, vital signs	X	X	X	X	X	X	X	X	X
Weight						X		X	
Assessments: Independent Assessor									
SLEDAI-2K: Blinded Assessor (m)		X		X		X	X	X	
Assessments: Principal Investigator									
SLEDAI-2K: Investigator	X	X	X	X	X	X	X	X	
C-SSRS Since Last Visit	X	X	X	X	X	X	X	X	X
Neurological assessment	X	X	X	X	X	X	X	X	X
SLE Flare Index (g)	X	X	X	X	X	X	X	X	
SLICC-ACR Damage Index						X		X	
Physician's Global Assessment (PGA)	X	X	X	X	X	X	X	X	
Survival assessment (c)						X			
Assessments: Patient Reported Outcomes (PROs)									
Patient Global Assessment (b)		X	X			X		X	
FACIT-Fatigue (b)		X	X			X		X	
Lupus QoL (b)		X	X			X		X	
WPAI: Lupus (b)		X	X			X		X	
Exit Interview (h)						X		X	
Central Laboratory Tests									
Urine pregnancy test (WCBP) (d)	X	X	X	X	X	X	X	X	X
Laboratory assessments (include liver chemistries)	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgA, IgM, IgG)	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Anti-dsDNA/ANA, Complement C3/C4	X	X	X	X	X	X	X	X	X
Extractable nuclear antigens (ENAs)	X			X		X		X	
PT/PTT				X		X	X	X	

	Observational Period – Arms A and B (a)								
Arms A and B Double-blind Observational Phase Procedures (W=Week)	W60	W64	W72	W80	W88, W96	W104	Unscheduled Visit (e)	Early Withdrawal Visit (f)	Follow-up visit (8 weeks post last dose) (j)
Antiphospholipid antibodies (aCL, lupus anticoagulant, ± beta-2-glycoprotein-1)	X			X		X	X	X	
Labs and Biomarkers									
B cells subsets	X			X		X		X	X
BLyS Protein	X	X	X	X	X	X		X	
Immunogenicity: Belimumab				X		X	X	X	X
Immunogenicity: Rituximab							X	X	
Pharmacokinetics: Belimumab	X	X	X	X			X	X	X
Pharmacokinetics: Rituximab							X	X	X
Exploratory Research									
Blood Leukocyte Analysis (PBMC) (k)				X		X		X	
B cell receptor (l)						X	X	X	
B cell subsets (n)	X			X		X		X	
Study Treatment									
Collect Electronic Diary						X		X	
Study Visit Review Procedures									
AE/SAE review	X	X	X	X	X	X	X	X	X
Concomitant medication review (including SLE medications)	X	X	X	X	X	X	X	X	X
Review HCRU and Patient Diary (i)	X	X	X	X	X	X	X	X	

a. During this study period including follow-up, a study visit time window ± 7 days is acceptable. Note: Every effort should be made to schedule the visit in this window, however if the COVID-19 pandemic situation affects the ability to achieve this then, for those COVID-19 specific instances, the visit window can be expanded to ±28 days.
b. To be conducted prior to clinical assessments.
c. Survival assessment at Week 104 for participants who withdraw before Week 104.
d. The pregnancy tests 12 months after the last dose of rituximab / rituximab-placebo (Week 58) and 16 weeks after the last dose of belimumab (Week 68) may be done at home, with the results reported by telephone call to the clinic. See Protocol Section 9 for pregnancy test requirements for participants that withdraw.(Argentina only: In addition to pregnancy testing at the specified clinic visits, a urine pregnancy test is to be performed at home at Week 56, Week 68, Week 76, Week 84, Week 92, and Week 100, with the results reported by telephone call to the clinic.)

e. Procedures to be performed at Unscheduled Visits are based on reason for Unscheduled Visit, including adverse event or discontinuation of study agent. Guidance is provided in the Study Reference Manual.
f. Participants who withdraw from the study are required to complete an Early Withdrawal Visit 1-4 weeks after withdrawal from the study.
g. Blood samples for a B cell receptor analysis should be obtained in the event of a SLE Flare (refer to footnote l).
h. To be conducted at US sites only.
i. Diary review is only necessary if the patient receive Belimumab re-start therapy.
j. Follow up visit is required only for subjects who receive belimumab re-start therapy at any time between Week 52 and Week 104.
k. To be conducted only at US study sites.
l. To be conducted only at US study sites. B-cell receptor samples are also collected when subjects experience a SLE Flare.
m. Independent assessor will perform symptom-driven physical examination to include, at a minimum, assessments of eyes, mouth, skin, lungs, cardiovascular system, abdomen, and extremities (including joints). Independent assessors must have a source document (paper record in the study file) where the findings in the clinical exam and laboratory analyses supporting the scoring of S2K are described.
n. To be conducted at select European centers.

Table 7 Open-Label Treatment Phase Procedures: Year 1, Arm C

Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arm C (a)												Unsched-uled Visit (h)	Early Withdrawal Visit (b)	Follow-up Visit (8 weeks post last dose)
		D1, (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
Informed consent	X															
Inclusion and exclusion criteria	X	X (i)														
Genetics Informed consent	X (m)															
Randomization		X														
Assessments: Clinic																
Full physical exam including height and weight	X															
12-lead ECG	X															
Demography	X															
Medical history (includes substance usage)	X															
Past and current medical conditions including cardiovascular medical history	X															
Vital signs	X															
Symptom-driven physical exam, vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X							X				X		X	
Assessments: Independent Assessor																
SLEDAI-2K: Blinded Assessor (n)		X				X			X		X		X	X	X	
Assessments: Principal Investigator																
SLEDAI-2K: Investigator	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
C-SSRS Baseline/Screening	X															
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLE Flare Index (j)		X	X		X	X	X	X	X	X	X	X	X	X	X	

Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arm C (a)												Unsched-uled Visit (h)	Early Withdrawal Visit (b)	Follow-up Visit (8 weeks post last dose)
		D1, (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
SLICC-ACR Damage Index		X											X		X	
Physician Global Assessment (PGA)		X	X		X	X	X	X	X	X	X	X	X	X	X	
Survival Assessment (d)													X			
Assessments: Patient Reported Outcomes (PROs)																
Patient Global Assessment (c)		X			X	X			X		X		X		X	
FACIT-Fatigue (c)		X			X	X			X		X		X		X	
Lupus QoL (c)		X			X	X			X		X		X		X	
WPAI: Lupus (c)		X			X	X			X		X		X		X	
Treatment Interview (k)													X		X	
Central Laboratory Tests																
Drug and alcohol screen	X															
HIV, Hep B and Hep C screen	X															
Pregnancy test (WCBP) (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments (include liver chemistries)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgA, IgM, IgG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-dsDNA/ANA, Complement C3/C4	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Extractable nuclear antigens (ENAs)		X			X				X				X		X	
PT/PTT	X	X			X				X				X	X	X	
Antiphospholipid antibodies (aCL, lupus anticoagulant, ± beta-2-glycoprotein-1)		X			X				X				X	X	X	
Labs and Biomarkers																
B cells subsets		X	X				X		X		X		X		X	X

Treatment Phase Procedures (D=Day, W=Week)	Screening (35 to 1 day(s) before D1)	Treatment Period – Arm C (a)												Unsched-uled Visit (h)	Early Withdrawal Visit (b)	Follow-up Visit (8 weeks post last dose)
		D1, (Base-line)	W4	W6	W8	W12	W16	W20, W24	W26	W28, W32, W36	W40	W44, W48	W52			
BLyS Protein		X											X		X	
RNA for interferon signature		X														
Immunogenicity: Belimumab		X	X	X	X				X				X	X	X	X
Pharmacokinetics: Belimumab			X		X				X				X	X	X	X
Genetic sample		X														
Exploratory Research																
B cells subsets (o)		X	X												X	
B-cell Receptor (l)		X												X	X	
Study Treatment																
Training on use of Autoinjector	X	X														
Dispense/Train or Collect Electronic patient diary		X													X	
Dispense Belimumab for weekly dosing (SC)		X (f)	X		X	X	X	X		X	X	X	X			
Initiate corticosteroid taper						X (g)										
Target for corticosteroid dose to reach prednisone equivalent ≤5 mg/day									X							
Study Visit Review Procedures																
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review (including SLE medications)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review HCRU and Patient Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	

a. Starting at Week 4and throughout the study period including follow-up, a study visit time window ± 7 days is acceptable. Note: Every effort should be made to schedule the visit in this window, however if the COVID-19 pandemic situation affects the ability to achieve this then, for those COVID-19 specific instances, the visit window can be expanded to ±28 days.
b. Early Withdrawal Visit 1-4 weeks after last dose for participants that discontinue study and withdraw from the study.
c. To be conducted prior to clinical assessments.
d. Survival assessment at Week 52 for participants who withdraw before Week 52.
e. For WCBP Serum pregnancy test at Screening; Urine pregnancy test at all other visits, including pregnancy test 16 weeks after last dose of belimumab. The pregnancy test 16 weeks after the last dose of belimumab may be done at home, with the results reported by telephone call to the clinic. See Protocol Section 9 for pregnancy test requirements for participants that withdraw.
f. The first dose of belimumab will be administered at the clinic and the subject needs to stay for 3 hours post dose for observation.
g. It is recommended that the steroid taper be initiated on Week 12 to reach the target prednisone equivalent of ≤5 mg/day at Week 26, but the taper schedule is at the discretion of the investigator.
h. Procedures to be performed at Unscheduled Visits are based on reason for Unscheduled Visit, including adverse event or discontinuation of study agent. Guidance is provided in the Study Reference Manual.
i. The interim medical history, including SLE medications, should be reviewed prior to randomization to assure that the participant's eligibility has not changed.
j. Blood samples for a B cell receptor analysis should be obtained in the event of a SLE Flare (refer to footnote l).
k. To be conducted at US sites only.
l. To be conducted only at US study sites. B-cell receptor samples are also collected when subjects experience a SLE Flare.
m. Separate Genetics informed consent as needed per country specific requirements. Genetics informed consent and sample can be obtained any time after baseline.
n. Independent assessor will perform symptom-driven physical examination to include, at a minimum, assessments of eyes, mouth, skin, lungs, cardiovascular system, abdomen, and extremities (including joints). Independent assessors must have a source document (paper record in the study file) where the findings in the clinical exam and laboratory analyses supporting the scoring of S2K are described.
o. To be conducted at select European centers.

Table 8 Open-Label Treatment Phase Procedures: Year 2, Arm C

	Treatment Period – Arm C (a)								
Arm C Treatment Phase Procedures (W=Week)	W60	W64	W72	W80	W88, W96	W104	Unscheduled Visit (e)	Early Withdrawal Visit	Follow-up Visit (8 weeks post last dose)
Assessments: Clinic									
Symptom-driven physical exam, vital signs	X	X	X	X	X	X	X	X	X
Weight						X		X	
Assessments: Independent Assessor									
SLEDAI-2K: Blinded Assessor (i)		X		X		X	X	X	
Assessments: Principal Investigator									
SLEDAI-2K: Investigator	X	X	X	X	X	X	X	X	
C-SSRS Since Last Visit	X	X	X	X	X	X	X	X	X
Neurological assessment	X	X	X	X	X	X	X	X	X
SLE Flare Index (f)	X	X	X	X	X	X	X	X	
SLICC-ACR Damage Index						X		X	
Physician Global Assessment (PGA)	X	X	X	X	X	X	X	X	
Survival assessment (c)						X			
Assessments: Patient Reported Outcomes (PROs)									
Patient Global Assessment (b)		X	X			X		X	
FACIT-Fatigue (b)		X	X			X		X	
Lupus QoL (b)		X	X			X		X	
WPAI: Lupus (b)		X	X			X		X	
Exit Interview (g)						X		X	
Central Laboratory Tests									
Urine pregnancy test (WCBP) (d)	X	X	X	X	X	X	X	X	X
Laboratory assessments (include liver chemistries)	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgA, IgM, IgG)	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Anti-dsDNA/ANA, Complement C3/C4	X	X	X	X	X	X	X	X	X
Extractable nuclear antigens (ENAs)	X			X		X		X	

	Treatment Period – Arm C (a)								
Arm C Treatment Phase Procedures (W=Week)	W60	W64	W72	W80	W88, W96	W104	Unscheduled Visit (e)	Early Withdrawal Visit	Follow-up Visit (8 weeks post last dose)
PT/PTT				X		X	X	X	
Antiphospholipid antibodies (aCL, lupus anticoagulant, ± beta-2-glycoprotein-1)	X			X		X	X	X	
Labs and Biomarkers									
B cells subsets	X			X		X		X	X
Immunogenicity: Belimumab				X		X	X	X	X
Pharmacokinetics: Belimumab				X		X	X	X	X
Exploratory Research									
B cell receptor (h)						X	X	X	
Study Treatment									
Collect Electronic Diary						X		X	
Dispense Belimumab for weekly dosing (SC)	X	X	X	X	X				
Study Visit Review Procedures									
AE/SAE review	X	X	X	X	X	X	X	X	X
Concomitant medication review (including SLE medications)	X	X	X	X	X	X	X	X	X
Review HCRU and Patient Diary	X	X	X	X	X	X	X	X	

	Treatment Period – Arm C (a)								
Arm C Treatment Phase Procedures (W=Week)	W60	W64	W72	W80	W88, W96	W104	Unscheduled Visit (e)	Early Withdrawal Visit	Follow-up Visit (8 weeks post last dose)

a. During this study period including follow-up, a study visit time window ± 7 days is acceptable. Note: Every effort should be made to schedule the visit in this window, however if the COVID-19 pandemic situation affects the ability to achieve this then, for those COVID-19 specific instances, the visit window can be expanded to ±28 days.
b. To be conducted prior to clinical assessments.
c. Survival assessment at Week 104 for participants who withdraw before Week 104.
d. The pregnancy test 16 weeks after the last dose of belimumab may be done at home, with the results reported by telephone call to the clinic.
e. Procedures to be performed at Unscheduled Visits are based on reason for Unscheduled Visit, including adverse event or discontinuation of study agent. Guidance is provided in the Study Reference Manual.
f. Blood samples for a B cell receptor analysis should be obtained in the event of a SLE Flare (refer to footnote h).
g. To be conducted at US sites only.
h. To be conducted only at US study sites. B-cell receptor samples are also collected when subjects experience a SLE Flare.
i. Independent assessor will perform symptom-driven physical examination to include, at a minimum, assessments of eyes, mouth, skin, lungs, cardiovascular system, abdomen, and extremities (including joints). Independent assessors must have a source document (paper record in the study file) where the findings in the clinical exam and laboratory analyses supporting the scoring of S2K are described.
j.

15.3. Appendix 3: Assessment Windows

15.3.1. Definitions of Assessment Windows for Analyses

The data is analyzed as per the planned visit assignment.

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

Analysis Set / Domain	Parameter (if applicable)	Target[1]	Analysis Window		Analysis Timepoint Number[4]	Analysis Timepoint
			Beginning Timepoint	Ending Timepoint		
All	All	NA	NA	NA	10	Screening
Year 1 Treatment Phase visits:						
All	All	1	NA	NA	20	Baseline
		29	2	35	30	Week 4
		43	36	49	40	Week 6
		57	50	70	50	Week 8
		85	71	98	60	Week 12
		113	99	126	70	Week 16
		141	127	154	80	Week 20
		169	155	175	90	Week 24
		183	176	189	100	Week 26
		197	190	210	110	Week 28
		225	211	238	120	Week 32
		253	239	266	130	Week 36
		281	267	294	140	Week 40
		309	295	322	150	Week 44
		337	323	350	160	Week 48
		365	351	392	170	Week 52
		365	na	Na	175	Survival-W52[2]
Year 2 Phase Visits:						
All	All	421	393	434	180	Week 60
		449	435	476	190	Week 64
		505	477	532	200	Week 72
		561	533	588	210	Week 80
		617	589	644	220	Week 88
		673	645	700	230	Week 96
		729	701	742	240	Week 104

Analysis Set / Domain	Parameter (if applicable)	Target[1]	Analysis Window		Analysis Timepoint Number[4]	Analysis Timepoint
			Beginning Timepoint	Ending Timepoint		
		729	na	na	245	Survival-W104[2]
		Na	na	na	250	Follow-Up[3]

NOTES:

[1] Study Day with Baseline/Treatment Start Date as Day 1. Baseline record will be derived in each analysis dataset, analysis visit number will be 15.

[2] Survival visit for subjects who withdraw from the double-blind treatment phase but consent to the Week 52 and Week 104 survival assessments.

[3] The follow-up visit occurs 8 weeks after last dose of belimumab for subjects who discontinue study treatment and withdraw from the study up to (i) Week 52 in Arms A and B or (ii) Week 104 in Arm C.

[4] If there are multiple visits within a visit window, the visit closest to the target date will be used. If there are two visits equidistant from the target date, then the scheduled visit will be given preference, if both are unscheduled then the first assessment will be used.

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

15.4.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before the first exposure date to study treatment
Concomitant	Any medication that is not a prior. 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

15.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date, having been absent pre-treatment, or that worsens relative to the pre-treatment state.

15.5. Appendix 5: Data Display Standards & Handling Conventions

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: gsk1550188
Study location	: gsk1550188\mid205646
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0).	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts.	

15.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) 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 DPs.
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 treatment 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 with the exception of certain summaries by year interval in which unscheduled visits may appear in the "anytime post baseline" category where specified e.g. worst laboratory toxicity grades. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

15.6. Appendix 6: Derived and Transformed Data

15.6.1. General

Multiple Measurements at One Analysis Time Point
• For continuous data, the mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • For continuous data, if there are two values within a time window (as per Section 15.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the scheduled assessment will be used, if both assessments are also unscheduled then the 1st assessment will be taken. • For categorical data, if there are two values within a time window (as per Section 15.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the value prior to the target day will be taken. • 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.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

Study Completion
• A participant is considered to have completed the study if he/she has completed all phases of the study, including the Week 104 Visit, as defined in the Schedule of Activities(SoA) (see Section 2 of the protocol) • A participant is considered to have completed the double-blind treatment phase (Year 1) of the study if he/she has completed all 52 weeks of the double-blind treatment phase, including the Week 52 Visit, as defined in the SoA (see Section 2 of the protocol) • Participants who discontinue study treatment and withdraw from the study up to Week 52 are required to complete an Early Withdrawal Visit and a Follow-up Visit; the Early Withdrawal Visit is scheduled 1 to 4 weeks after the last dose of belimumab and the Follow-up Visit is scheduled 8 weeks after the last dose of belimumab • Participants in Arms A or B who withdraw from the study after Week 52 are required to complete an Early Withdrawal Visit 1-4 weeks after withdrawal from the study. • Participants in Arm C who discontinue study treatment and withdraw from the study after Week 52 are required to complete an Early Withdrawal Visit and a Follow-up Visit; the Early Withdrawal Visit is scheduled 1 to 4 weeks after the last dose of belimumab and the Follow-up Visit is scheduled 8 weeks after the last dose of belimumab
Visit assessments completed late
In the event that a PGA, or SLE flare assessment, which may be only completed once labs have been returned to the site, is recorded later than the visit date, then an imputed date will be used. The imputed PGA / SLE flare assessment date will be the earliest date for a completed SLEDAI-2K (IBA or PI) assessment. This may be different than the earliest visit within that window. If there are no SLEDAI-2K assessment dates available then the visit date is used.

15.6.2. Study Population

Age Derivation
Age on any specified day (e.g. screening, 1st dose etc.) will be derived as: If the specified day is on or after the 30th June then: • Year of specific timepoint – DOB year If the specified day is before the 30th June then: • (Year of specific timepoint – DOB year) -1 (Note this assumes day and month of birth is 30 June - as this information is not collected) Age at baseline will be defined as the latest of randomization date and baseline visit date, and derived as above.

Treatment Compliance – Belimumab
• Percent compliance will be calculated based on the formula: Percent Compliance = 100* (Number of injections prescribed - Number of injections missed) / Number of injections prescribed

Extent of Exposure – Belimumab
• Number of days of exposure to belimumab will be calculated based on the formula: **Duration of Exposure in Days = Last injection date – First injection date + 7** • Only complete dates will be used when calculating duration of exposure. First and last injection dates will be used, regardless of any missed doses. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

Extent of Exposure – Rituximab
• Dose intensity in mg will be calculated as the cumulative actual dose divided by 2. • If the total volume of an infusion is not administered, the actual dose infused for that visit will be calculated as: **Actual Dose infused (mg) = Planned Dose (mg) * Percentage of volume infused**

On Treatment Exposure (Year 1)
• Number of days of On-Treatment exposure will be calculated based on the formula: **Duration of On-Treatment Exposure in Days** **= Year 1 on-treatment end date (see Section 5.12) – First Belimumab injection date + 1** • Only complete dates will be used when calculating duration of study exposure. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

On-Study Exposure (Years 1&2 Combined)
• Number of days of On-Study exposure will be calculated based on the formula:

On-Study Exposure (Years 1&2 Combined)
Duration of On-Study Exposure in Days = Date of study completion or withdrawal – First Belimumab injection date + 1 • Only complete dates will be used when calculating duration of study exposure. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

Disease Duration
When the start day is missing, impute with 01. When the start day and month is missing, impute with 01 January. This will impute the longest possible duration.

15.6.3. SLEDAI-2K Total and Organ System Domain

SLEDAI-2K Total and Organ System Domain Scores
SLEDAI-2K 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'). Organ system domain scores are the sum of the weights of items within the organ domain as defined in Table 9. In this study, proteinuria is evaluated using spot-urine protein [represented as protein-creatinine ratio or PC Ratio in the laboratory dataset]. in lieu of the 24-hour urine collection, as evaluated by the investigator.

Table 9 SLEDAI-2K

Organ System	Descriptor	Weight	Definition
CNS[a]	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.		

	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
Vascular[a]	
Musculoskeletal	
Renal	
Mucocutaneous	
Cardiovascular & Respiratory	
Immunologic	
Constitutional[a]	
Hematologic[a]	

a. In the summaries and analyses of SLEDAI-2K organ systems, CVA will be moved from the CNS to the Vascular organ system and the Constitutional organ system will be eliminated and its one component, fever, will be moved to the hematologic organ system.

Adapted from the original source: [Gladman, 2002]. Used with permission from author (Murray Urowitz).

- Blinded independent assessors will conduct the SLEDAI-2K at key time points. The primary and major secondary efficacy endpoints will be conducted using the blinded independent assessors' SLEDAI-2K data
- For SLEDAI-2K after the Day 1 visit, the window is -10 days to + 7 days from the date of assessment post Day 1 visit, excluding the sample that was used in the previous visit assessment.

The SLEDAI-2K score is the sum of **all 24** individual items from the SLEDAI-2K.

SLEDAI-2K missing values

SLEDAI-2K missing scores for laboratory parameters i.e.

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

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

Will be imputed from the previous assessment if the previous assessment is no more than 35days prior.

When it is not possible to calculate SLEDAI-2K score but it is still possible to ascertain that the SLEDAI-2K score is >0, >2, or >4, then this information will be used in the derivation of disease control, clinical remission, complete remission, and LLDAS.
Similarly, when it is possible to determine that the maximum possible value for the SLEDAI-2K, assuming the highest score for missing values is <=2 or <=4 then this will be used in the derivation of disease control nd LLDAS.

SLEDAI-2K Organ System Improvement and Worsening

In the analysis of SLEDAI-2K organ system improvements and worsening, CVA will be moved from the CNS to the Vascular organ system and the Constitutional organ system will be eliminated and its one component, fever, will be moved to the hematologic organ system

Clinical SLEDAI-2K Score (Excluding Serological Activity)

The clinical SLEDAI-2K score (Excluding Serological Activity assessments) is the sum of **22 of the 24** individual items from the SLEDAI-2K, excluding the following 2 items:

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

The scoring of the 22 questions is weighted in the same manner as the SLEDAI-2K, however the maximum theoretical score is now 101.

Note that the wording in the Protocol was “Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint”. The endpoint has been clarified here by using the names of the two SLEDAI-2K item scores, however, this does not represent a change to the planned endpoint, just a clarification.

Partial but informative SLEDAI-2K score

If after imputation for missing questions the SLEDAI-2K total score is still not derivable due to missing individual questions, then the minimum possible score will be considered (sum of the answered questions).
Similarly a maximum possible score (observed questions + maximum response for missing questions) will be considered.

15.6.4. Disease Control

Endpoint Definition

The disease control endpoint is defined as:

- SLEDAI-2K score ≤2 (IBA*),

- Not a Treatment failure
- Not a Study withdrawal

The same derivation will be applied to the secondary endpoint "Disease control (PI)" using the principal investigators assessment of the SLEDAI-2K.

Imputation of Missing values – IBA assessment

Missing IBA assessments based on laboratory assessments i.e.:
Urinary Casts, Hematuria, Proteinuria, Pyuria, Low Complement, Increased DNA Binding, Thrombocytopenia, and Leukopenia
will be imputed from the PI assessment if the laboratory sample (for the PI assessment) was drawn no more than 35 days prior. An imputed assessment can not be used to impute another assessment.
There will be no imputation of missing IBA assessments based on physical examination

Imputation of Missing values – PI assessment

If an individual question of the SLEDAI-2K assessment or the full assessment is missed the previous assessment may be used as a substitute if it was no more than 35 days prior. An imputed assessment cannot be used to impute another assessment.

Partial but informative SLEDAI-2K score

If after imputation for missing questions the SLEDAI-2K total score is still not derivable due to missing individual questions, then the minimum possible score will be considered. If the minimum possible score is >2 then the subject will be considered as a non-responder.
Similarly a maximum possible score will be considered to determine if the maximum possible score is ≤ 2.

Time to Disease Control Sustained to Week 104

A subject has a sustained disease control at a visit if all of the following criteria are met:

1 In disease control at the visit
2 In disease control at the first visit that is at least 24 study weeks prior, or if disease control cannot be assessed at that visit, then in disease control at the visit prior.
3 In disease control for all assessed visits between (1) and (2). Note assessments can be missing.

Note: 24 weeks refers to the difference in visit 'labels' not calendar weeks between visits.
The first visit of sustained disease control is defined as the 1st visit that the subject is a disease control responder and all subsequent visits up to and including Week 104 the subjects is also a disease control responder. Missing assessments are not considered.

Time to disease control sustained to Week 104 =
1st visit of sustained disease control - treatment start date (Day 1) +1

Duration of Disease Control

The duration of disease control is defined as the longest period between 2 visits that the subject is a disease control responder at all visits. Missing assessments are not considered.
Duration of disease control = longest period where
1st visit of disease control – last visit of disease control + 1

Example Subject	SLEDAI-2K score at Week 52	Study Withdrawal (including Lost to Follow-up, or Death) prior to Week 52	Treatment Failure prior to Week 52	IP Discontinuation prior to Week 52	Main Estimand (Hybrid)	Supportive Estimand (Composite)	(Hybrid On Treatment)	Treatment Policy
1	>2	N	N	N	NR	NR	NR	NR
2	>2	N	N	Y	NR	NR	Excluded	NR
3	>2	N	Y	N	NR	NR	NR	NR
4	>2	N	Y and prior to IP discontinuation	Y	NR	NR	NR	NR
5	>2	N	Y but post IP discontinuation	Y	NR	NR	Excluded	NR
6	<=2	N	N	N	R	R	R	R
7	<=2	N	N	Y	R	NR	Excluded	R
8	<=2	N	Y	N	NR	NR	NR	R
9	<=2	N	Y and prior to IP discontinuation	Y	NR	NR	NR	R
10	<=2	N	Y but post IP discontinuation	Y	NR	NR	Excluded	R
11	Incomplete* or entirely missing	N	N	N	NR	NR	NR	NR
12	Incomplete* or entirely missing but not due to study withdrawal	N	N	Y	NR	NR	Excluded	NR
13	Incomplete* or entirely missing but not due to study withdrawal	N	Y	N	NR	NR	NR	NR
14	Incomplete* or entirely missing but not meaningful	N	Y and prior to IP discontinuation	Y	NR	NR	NR	NR
15	Incomplete* or entirely missing but not due to study withdrawal	N	Y but post IP discontinuation	Y	NR	NR	Excluded	NR
16	Missing - does not exist due to study withdrawal	Y and at the same time as IP discontinuation	N	Y	NR	NR	NR	NR

Example Subject	SLEDAI-2K score at Week 52	Study Withdrawal (including Lost to Follow-up, or Death) prior to Week 52	Treatment Failure prior to Week 52	IP Discontinuation prior to Week 52	Main Estimand (Hybrid)	Supportive Estimand (Composite)	(Hybrid On Treatment)	Treatment Policy
17	Missing - does not exist due to study withdrawal	Y but post IP discontinuation	N	Y	NR	NR	Excluded	NR
18	Missing - does not exist due to study withdrawal	Y and at the same time as IP discontinuation	Y and prior to IP discontinuation	Y	NR	NR	NR	NR
19	Missing - does not exist due to study withdrawal	Y but post IP discontinuation	Y and prior to IP discontinuation	Y	NR	NR	NR	NR
20	Missing - does not exist due to study withdrawal	Y but post IP discontinuation	Y but post IP discontinuation	Y	NR	NR	Excluded	NR

R = Responder; NR = Non-Responder

*Incomplete: does not include partial scores where it is possible to determine that the total score must be >2, or that the maximum possible score (assuming worst case for missing data) is <=2

15.6.5. Clinical Remission

Endpoint Definition
Clinical remission for Arms A & B (secondary endpoint) is defined as: • Clinical SLEDAI-2K score[#] = 0 (IBA*), • Not a Treatment Failure • Did not withdraw from the study • 7-day average corticosteroids at a prednisone equivalent dose of 0mg/day for the assessment (7 day average is the average of current and 6 previous days) [#]See Section 15.6.3 *at baseline the principal investigators assessment will be used The same derivation will be applied to the secondary endpoint "clinical remission (PI)" using the principal investigators assessment of the SLEDAI-2K.
Imputation of Missing values – IBA assessment
Missing IBA assessments based on laboratory assessments i.e.: Urinary Casts, Hematuria, Proteinuria, Pyuria, Thrombocytopenia, and Leukopenia will be imputed from the PI assessment if the laboratory sample (for the PI assessment) was drawn no more than 35 days prior. An imputed assessment can not be used to impute another assessment. There will be no imputation of missing IBA assessments based on physical examination
Imputation of Missing values – PI assessment
If an individual question of the SLEDAI-2K assessment or the full assessment is missed the previous assessment may be used as a substitute if it was no more than 35 days prior. An imputed assessment cannot be used to impute another assessment.
Partial but informative Clinical SLEDAI-2K score
If after imputation for missing questions the Clinical SLEDAI-2K score is still not derivable due to missing individual questions, then the minimum possible score will be considered (sum of the answered questions). If the minimum possible score is >0 then the subject will be considered as an observed non-responder (rather than non-responder due to missing data).
Clinical Remission Sustained For At Least 24 Weeks
Sustained response will be reported for all weeks post Week 52 (Year 2), and at any timepoint (i.e. any subjects who had a sustained response at any time during Year 2). Statistical analysis will only be conducted at Week 104 and at 'any timepoint'. A subject has a sustained remission at a visit if all of the following criteria are met: 1 In clinical remission at the visit 2 In clinical remission at the first visit at least 24 study weeks prior, or if clinical remission cannot be assessed at that visit , then in clinical remission at the visit prior. 3 In clinical remission for all assessed visits between (1) and (2). – Note assessments can be missing. Note: 24 weeks refers to the difference in visit 'labels' not calendar weeks between visits.

Time to Clinical Remission Sustained to Week 104
The first visit of sustained clinical remission is defined as the 1st visit that the subject is a clinical remission responder and all subsequent visits up to and including Week 104 the subjects is also a clinical remission responder. Missing assessments are not considered (the rules for sustained response for at least 24 weeks as defined above are also applied here). Time to clinical remission sustained to Week 104 = 1st visit of sustained clinical remission - treatment start date (Day 1) +1
Duration of Clinical Remission
The duration of clinical remission is defined as the longest period between 2 visits that the subject is a clinical remission responder at all visits. Missing assessments are not considered Duration of clinical remission = longest period where 1st visit of clinical remission – last visit of clinical remission + 1

15.6.6. Complete Remission

Endpoint Definition
Complete remission for Arms A & B (secondary endpoint) is defined as: • SLEDAI-2K score = 0 (IBA*), • Not a Treatment Failure (specific to Arms A&B) • Did not withdraw from the study • 7-day average corticosteroids at a prednisone equivalent dose of 0mg/day for the assessment (7 day average is the average of current and 6 previous days) Complete remission for Arm C (the exploratory endpoint) is defined as: • SLEDAI-2K score = 0 (IBA*), • Not a Treatment Failure (specific to Arm C) • Did not withdraw from the study • 7-day average corticosteroids at a prednisone equivalent dose of 0mg/day for the assessment (7 day average is the average of current and 6 previous days) *at baseline the principal investigators assessment will be used Note some tables will contain the endpoint using these 2 different definitions in the same table.
Imputation of Missing values – IBA assessment
Missing IBA assessments based on laboratory assessments i.e.: Urinary Casts, Hematuria, Proteinuria, Pyuria, Low Complement, Increased DNA Binding, Thrombocytopenia, and Leukopenia will be imputed from the PI assessment if the laboratory sample (for the PI assessment) was drawn no more than 35 days prior. An imputed assessment can not be used to impute another assessment. There will be no imputation of missing IBA assessments based on physical examination

Imputation of Missing values – PI assessment
If an individual question of the SLEDAI-2K assessment or the full assessment is missed the previous assessment may be used as a substitute if it was no more that 35 days prior. An imputed assessment cannot be used to impute another assessment.
Partial but informative SLEDAI-2K score
If after imputation for missing questions the SLEDAI-2K total score is still not derivable due to missing individual questions, then the minimum possible score will be considered (sum of the answered questions). If the minimum possible score is >0 then the subject will be considered as an observed non-responder (rather than non-responder due to missing data).
Complete Remission Sustained For At Least 24 Weeks
Sustained response will be reported for all weeks post Week 52 (Year 2), and at any timepoint (i.e. any subjects who had a sustained response at any time during Year 2). Statistical analysis will only be conducted at Week 104 and at 'any timepoint'. A subject has a sustained remission at a visit if all of the following criteria are met: 1 In complete remission at the visit 2 In complete remission at the first visit at least 24 study weeks prior, or if complete remission cannot be assessed at that visit , then in clinical remission the visit prior. 3 In complete remission for all assessed visits between (1) and (2). – Note assessment can be missing. Note: 24 weeks refers to the difference in visit 'labels' not calendar weeks between visits.

15.6.7. SFI FLARE INDEX

SLEDAI-2K Flare Index
(Adapted from Buyon, 2005; Petri, 2005; Neergard, 2006. Petri, 1999)

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

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

a. The modified SLE Flare index excludes severe flares that are triggered only by an increase is SLEDAI-2K Score to greater than 12.

The following scoring rules are based on the SLEDAI-2K flare index:

- SFI reports the first mild /moderate or severe flare occurrence since the last non-missing assessment.
- The SLEDAI-2K criteria will be assessed programmatically (based on the PI assessment at the visit that the flare was reported) to determine if the SLEDAI-2K 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 SLEDAI-2K score to >12.
    - In this case, if any of the mild/moderate reasons are checked or if the SLEDAI-2K score has a change from the last non-missing assessment of at least 3, then the flare will be considered mild/moderate. Otherwise this not a flare

  The last non-missing assessment is the last previous visit were SLE flare was assessed (and is not entirely missing).

Partial but informative SLEDAI-2K score

If after imputation for missing questions the SLEDAI-2K total score is still not derivable due to missing individual questions, then the minimum possible score will be considered (sum of the answered questions). Similarly a maximum possible score (sum of observed questions + maximum response for missing questions) will be considered. If from these scores it is possible to determine that there has be an increase in score from the previous visit of at least 3 then this will be used as indication of a mild/moderate flare. However if it is not possible to determine whether there has been a change of at least 3 from the previous assessment then no assumption will be made about the presence of a mild/moderate flare.

15.6.8. Physicians Global Assessment (PGA) Scoring

Physicians Global Assessment (PGA) Scoring
PGA is collected on a 10cm visual analogue scale (VAS). However, the standard scoring range for the PGA is 0 to 3, therefore the score will be rescaled for reporting by multiplying the collected score by 3/10.

15.6.9. Lupus Low Disease Activity State (LLDAS)

Endpoint Definition		
Criteria	Source data and derivation	Rationale
SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity;	SLEDAI – 2K score as assessed by the principal investigator Individual stated organ systems must have a score of 0, Note: Cardiopulmonary = Cardiovascular & respiratory organ system Vasculitis = Vascular organ system Fever = Constitutional organ system Data on hemolytic anemia and gastrointestinal activity are not available and is not considered in evaluating this criterion but assumed to be captured in the PGA item.	
no new features of lupus disease activity compared with the previous assessment;	No worsening of any of the item scores of the SLEDAI–2K (principal investigator assessment) score compared to the previous assessment	Compared to previous visit to reflect a stable disease state.
PGA (scale 0-3) ≤1;	PGA as reported (closest assessment to the target date that is within the visit window)	
current prednisolone (or equivalent) dose ≤7.5 mg daily;	7 day average prednisone dose (day of visit and 6 prior days) assessed on the day of the SLEDAI-2k assessment	7 Day average due to the planned tapering, as subjects may be on a dosing regimen that varies by day (e.g. 1mg every other day)
well tolerated standard maintenance doses of	The dose on the **day of** the SLEDAI-2K assessment must not exceed:	The protocol stated 'equivalent'

Endpoint Definition		
immunosuppressive drugs and approved biological agents, excluding investigational drugs	• azathioprine: 300mg/day • methotrexate 25mg/week • leflunomide 40mg/day • Mycophenolate sodium≤2.88g/day • Mycophenolate mofetil≤4g/day • Oral cyclophosphamide≤2.5mg/kg/day • 6-mercaptopurine <= 300mg/day • Cyclosporine<=4mg/kg/day • Tacrolimus<=0.2mg/kg/day • Sirolimus<=2mg/day • Thalidomide<=200mg/day • mizoribine<=150mg/day Not to be taken within 28 days prior to the assessment: • Intravenous Cyclophosphamide • Other investigation agent • Anti-TNF therapy (adalimumab, etanercept, infliximab) • Other biologics (abatacept, anakinra) • IVIG • Plasmapheresis Topical treatments will not be considered	medications to those stated in . [Oon, 2019] supplement On the day of assessment as identified in the publications
Not Study withdrawal (including death and lost to follow-up		Did not withdraw or discontinue for any reason
SLEDAI-2K Component: Imputation of Missing values – PI assessment		
If an individual question of the SLEDAI-2K assessment or the full assessment is missed the previous assessment may be used as a substitute if it was no more than 35 days prior. An imputed assessment can not be used to impute another assessment.		
SLEDAI-2K Component: Partial but informative SLEDAI-2K score		
If after imputation for missing questions the SLEDAI-2K total score is still not derivable due to missing individual questions, then the minimum possible score will be considered (sum of the answered questions). If the minimum possible score is >4 then the subject will be considered as a non-responder.		

SLEDAI-2K Component: Imputation of Missing values – PI assessment
Similarly a maximum possible score (observed questions + maximum response for missing questions) will be considered to determine if the maximum possible score is ≤4.

15.6.10. Lupus QOL Scale

The LupusQoL consists of 34 items in eight domains. The number of items in each domain and the item numbers that refer to that domain are tabulated below:

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

The LupusQoL has a five-point Likert response scale for each item and are scored as:

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

Each domain of the LupusQoL is scored separately as :

Calculate the mean raw domain score by adding up the item response scores for the domain and then divide by the number of items answered in that domain. Mean raw domain scores can only be obtained when at least 50% of the items for the domain are answered. A non-applicable response is treated as unanswered.

Transform the mean raw domain score by dividing by four (the number of Likert responses [five] minus one) and then multiplying by 100, as below:

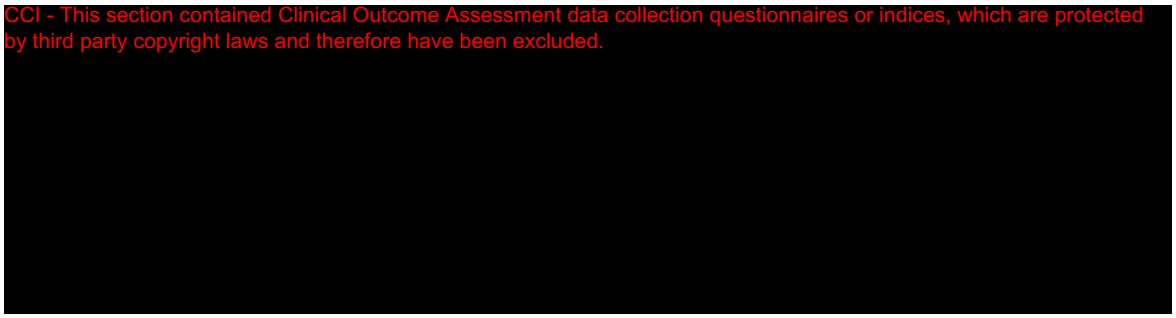
Mean raw domain score x 25 = Transformed score for domain

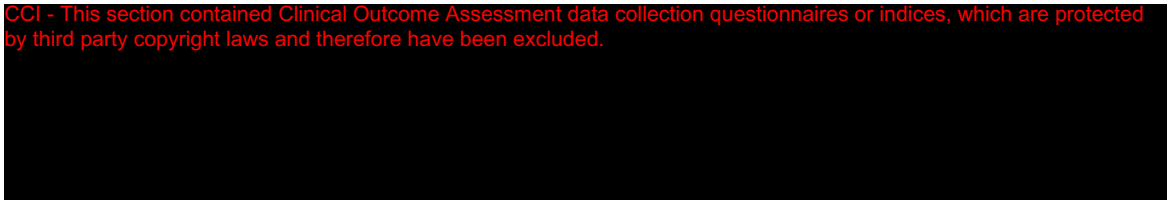
Transformed scores range from 0 (CCI) to 100 (CCI

15.6.11. Work Productivity and Activity Impairment (WPAI)

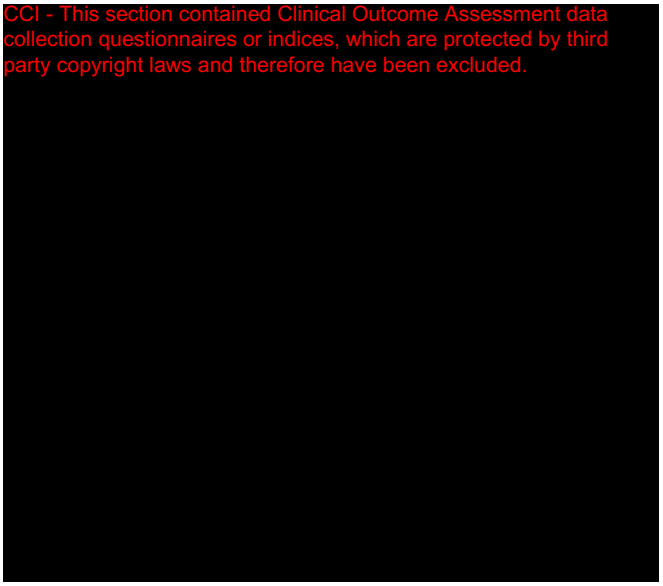
The WPAI consists of 6 questions

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





The following summary measures will be derived:

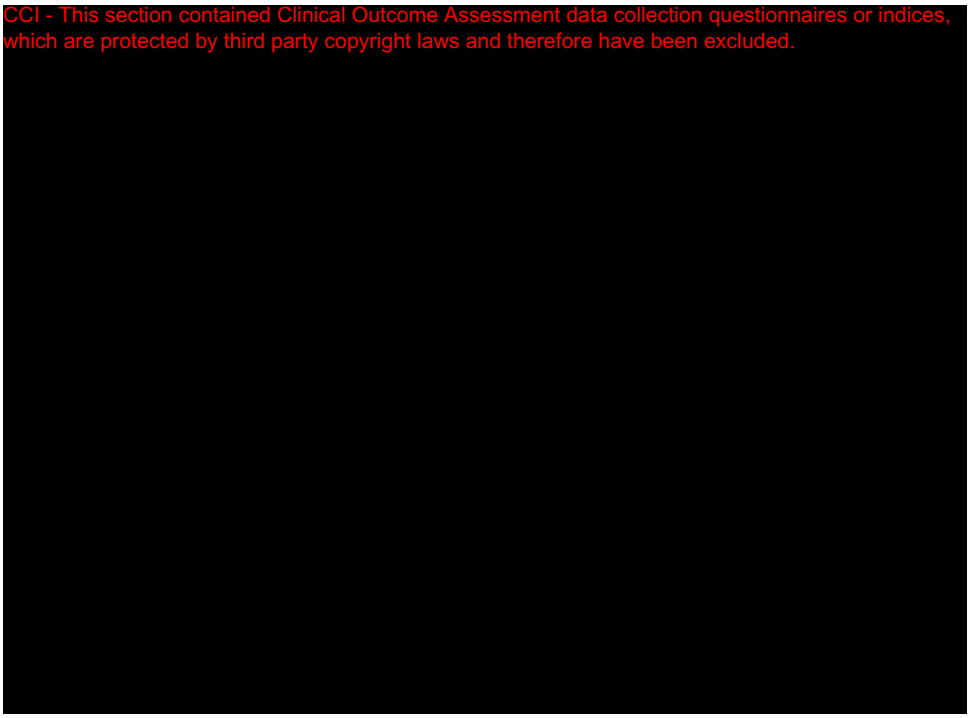


If a question is missing all summary measures that use that question will not be derived.

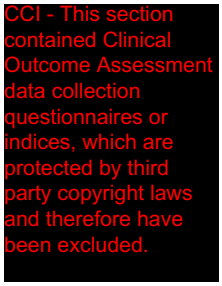
Only the 'Percent overall work impairment due to Lupus' and 'Percent activity impairment due to Lupus' are summarised in the tables.

15.6.12. Functional Assessment of Chronic Illness Therapy (FACIT)

The FACIT – Fatigue scale consists of 13 questions:



Each Question is answered on a Likert response scale and scored as numbered:



The total score is the sum of the responses (inverted for reversed items) multiplied by 13, then divided by the number of questions answered i.e.

$$\frac{\{(4-\mathrm{HI7})+(4-\mathrm{HI12})+(4-\mathrm{An1})+(4-\mathrm{An2})+(4-\mathrm{An3})+(4-\mathrm{An4})+\mathrm{An5}+\ \mathrm{An7}\\ +(4-\mathrm{An8})+(4-\mathrm{An12})+(4-\mathrm{An14})+(4-\mathrm{An15})+(4-\mathrm{An16})\}*13}{Number\ of\ questions\ answered}$$

The total score will only be derived if at least 11 questions (80%) of the scale is completed.

15.6.13. Disease Control Without Current Immunosuppressant and with Current Corticosteroids ≤ 5mg/day

Disease Control
Disease control for Arms A & B (the primary endpoint) is defined as: • SLEDAI-2K score ≤2 (IBA*), • Without immunosuppressants on the day of the assessment and 55 days prior to the assessment, • 7-day average corticosteroids at a prednisone equivalent dose of ≤5mg/day for the assessment (7 day average is the average of current and 6 previous days) • Without study withdrawal Disease control for Arms C (the exploratory endpoint) is defined as: • SLEDAI-2K score ≤2 (IBA*), • Without any new immunosuppressants, and not greater than the maximum of baseline (Day 1) day and Week 12 visit dose on the day of the assessment and 55 days prior to the assessment, • 7-day average corticosteroids at a prednisone equivalent dose of ≤5mg/day for the assessment (7 day average is the average of current and 6 previous days) • Without study withdrawal *at baseline the principal investigators assessment will be used Note some tables will contain the endpoint using these 2 different definitions in the same table. The same derivation will be applied to the secondary endpoint "disease control (PI)" using the principal investigators assessment of the SLEDAI-2K.

15.6.14. 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 has been set to 0.
- The following routes are considered to provide systemic exposure: oral, buccal, parenteral subcutaneous, intramuscular, intradermal, and intravenous. Although not systemic, intra-articular steroids are also identified for treatment failure rules. Topical routes of administration are excluded (e.g., topical, conjunctival, intranasal).
- At data base release, 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 below.

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

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

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`
CORTISONE	0.2
CORTISONE ACETATE	0.2
CRONOLEVEL	8.3333`
DEFLAZACORT	0.8333`
DEXAMETHASONE	6.6666`
DEXAMETHASONE ACETATE	6.6666`
DEXAMETHASONE SODIUM PHOSPHATE	6.6666`
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

Prednisone Conversion Factors (mg)	
Preferred term	**Conversion factor for converting to a prednisone-equivalent dose**
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
HS	1
OAM	1/30
Once	1
PRN	Null
Q2H	12
Q2W	1/14
Q3H	8
Q3MO	1/84
Q3w	1/21
Q4H	6
Q4W	1/28
Q6H	4
Q8H	3
QAM	1
QD	1
QH	24
QHS	1
QID	4
QOD	½
QPM	1

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

15.6.15. Treatment Failure Rules During Study Conduct

A treatment failure is defined as any subject who receives a protocol-prohibited medication or a dose of allowable (but protocol restricted) medication that results in treatment failure designation prior to the analysis visit of interest (e.g. Week 52, Week 64, Week 104).

The treatment failure rules are detailed in the protocol Section 7.7.

15.6.15.1. Summary

Occurrence	Post Study Start Treatments	TX Failure: Arms A/B	TX Failure: Arm C
After Day 1	• NEW anti-malarial medication for SLE (other than for anti-malarial prophylaxis) • NEW immunosuppressant medication • Prohibited Medications and Non-Drug therapies	**Yes**	**Yes**
After Week 4	• Immunosuppressant medication	**Yes**	**No**
After Week 12	• Immunosuppressant medication dose increased over baseline (Day 1) or Week 12 visit dose, whichever is higher	**Not Applicable**	**Yes**
Week 27 onwards	• Corticosteroid (Prednisone equivalent) dose >5mg/day (Average day of assessment and 6 prior days)	**Yes**	**Yes**

Occurrence	Post Study Start Treatments	TX Failure: Arms A/B	TX Failure: Arm C
After Week 26	• High Dose CS for Non-SLE use (Maximum use 7 days, taper [≤5 mg/day]. 21 days)	**Yes**	**Yes**
After Week 44	• Aspirin doses >1000 mg days if never received such doses between Day 1 and Week 44 (Note: It does Not apply if given <7 days)	**Yes**	**Yes**
Weeks 44 to 52*	• NSAIDs (dose above Day 1 or the visit day starting the 8 weeks interval for ≥7 days) • Intraarticular CS injections • High Dose CS for Non-SLE use	**Yes**	**Yes**
After Week 52	• IP – Belimumab SC	**Yes**	**No**
Weeks 56 to 64*	• NSAIDs (dose above Day 1 or the visit day starting the 8 weeks interval for ≥7 days) • Intraarticular CS injection • High Dose CS for Non-SLE use	**Yes**	**Yes**
Weeks 96 to 104*	• NSAIDs (dose above Day 1 or the visit day starting the 8 weeks interval for ≥7 days) • Intraarticular CS injections • High Dose CS for Non-SLE use	**Yes**	**Yes**

*8 weeks prior to major efficacy assessments (Primary endpoint [Week 52] and major secondary endpoints [Weeks 64, 104]).

15.6.15.2. SLE Medication Categories

Medication Category	Rule
Anti-malarials	Set to "ANTIMALARIALS" if the preferred term begins with "QUINACRINE", "QUININE", "HYDROXYCHLOROQUINE", "MEPACRINE", or "CHLOROQUINE" AND the route of administration is not 'TOPICAL', 'VAGINAL', 'CONJUNCTIVAL', 'INTRANASAL', 'INHALATION', 'INTRA-OCULAR', 'INTRATRACHEAL', 'EPIDURAL', 'INTRA-ARTICULAR', or 'OTHER'.
Steroids	Set to 'STEROIDS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'H02' AND Route of administration is "INTRADERMAL", "INTRAMUSCULAR", "BUCCAL", "PARENTERAL" "INTRAVENOUS", "ORAL", "SUBCUTANEOUS", or "INTRA-ARTICULAR".

Medication Category	Rule
Immunosuppressants	Set to 'IMMUNOSUPPRESSANTS' if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04A' or the preferred term begins with "CYCLOPHOSPHAMIDE" (oral and parenteral routes) or "MERCAPTOPURINE" (oral route) AND route of administration is not "TOPICAL" or "OPHTHAMLIC"AND not classified above as "ANTIMALARIALS".
NSAIDs	Set to NSAIDs if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'M01A'.Glucosamine and Chondroitin not considered NSAIDs
Aspirin	Set to "ASPIRIN" if CMDECOD contains "ACETYLSALICYLIC ACID" or "ACETYLSALICYLATE LYSINE".
Prohibited	Set to "PROHIBITED" if at least one associated ATC code (ATCCD1 – ATCCD6) begins with 'L04AB' or 'V98' or if any of the following conditions are met, if CMDECOD equals ," BELIMUMAB", "ADALIMUMAB", "ETANERCEPT", "INFLIXIMAB", "CERTOLIZUMAB", "TOCILIZUMAB", "GOLIMUMAB", "RITUXIMAB", "ABATACEPT", "ANAKINRA", "CANAKINUMAB", "USTEKINUMAB", "BRODALUMAB", "SECUKINUMAB", "IXEKIZUMAB", "EPRATUZUMAB", "TABALUMAB", "ATACICEPT", "IMMUNOGLOBULIN" (IV route), "CYCLOPHOSPHAMIDE" (IV route), or "PLASMAPHERESIS"

15.6.15.3. General Conventions

- Assessment of dose is based on analysis dose. Analysis dose is daily dose adjusted for dosing frequency, and in the case of steroid is converted to prednisone equivalents. Exception is intra-articular dose where analysis dose is not populated.
- In the event there are multiple visit dates within a visit window, the date for determining treatment failure, will be the earliest date at which efficacy data (from SLEDAI-2K (IBA), SLEDAI-2K (PI), PGA, and SLE Flare) is recorded. This may be different than the earliest visit within that window.
- If a critical visit (Week 52, 64 , and 104], is missing from efficacy data (from SLEDAI-2K (IBA and PI), PGA, SLE Flare, LLDAS) then the date is imputed as the target day for that visit.
- Actual visit date, not target visit date, is used to assess treatment failures.
    - If the subject's Day 169 (Week 24) study visit occurs on Day 171, the date for Day 171 is used when applying the treatment failure rules.
- Prohibited medications/dosages started on the date of early withdrawal are considered a TF (see clarification below for steroids). If the prohibited medication/dose starts after the date of withdrawal it will not be part of the TF assessment.

- All potential TF rule violation are output programmatically and all adjudicated.
- Clinical may amend the date of TF during adjudication if, for instance, a subject did not meet the criterion on the date identified by the program but did meet it later.

15.6.15.4. Steroids

- SLE-related steroids are steroids where medication type is marked as 'Systemic Lupus Erythematosus (SLE)' (CMTYPCD=156), regardless of reason for medication (CMREAS).
- Total steroids include steroids for SLE and non-SLE reasons.
- Baseline dose is the 7-day average based on the 7 days **prior** to, but not including, treatment start date.
- The average steroid dose on any post baseline day is the sum of the steroids on that day and the prior 6 days divided by 7, so long as all days are post the baseline visit.
- The first day that the TF rule
    - Received a prednisone equivalent corticosteroid 7-day average dose of >5 mg/day after Week 26 visit

  is applied will be when all values used in the average steroid dose are after Week 26 visit (not including the week 26 visit day) i.e. 7 days after Week 26 visit
- The final week interval for subjects who complete Week 104 will be 7 days prior to the exit visit date; [exit visit -7 days]. to [exit visit -1 day]. The day of Week 104 visit will not be included.
- The final interval for subjects who withdraw early will be the 7 days up to and including the exit visit date; [exit visit/early withdrawal date -6]. to [exit visit/ early withdrawal date]. The day of withdrawal will be included.
- The above rules may miss a subject who starts/increases a steroid close to the day of withdrawal. In this situation it is possible that the subject may have withdrawn prior to the end of the interval for computing their 7-day average exceeding the TF threshold. Hence all subjects whose dose of steroid increased within 7 days (including day of withdrawal) of withdrawal, and have not already crossed the dose threshold for TF based on the 7-day average rule, will be output for clinical adjudication. If clinical adjudication determines these to be treatment failures the date of treatment failure will be set to the date of withdrawal.
- A subject who is receiving 0mg of steroid at baseline will be allowed to take ≤5mg of steroid post baseline without being considered a treatment failure.
- Intra-articular steroids are not included in average steroid dose calculations.
- Subjects with more than one dosing regimen that involves alternate day dosing will be reviewed to ensure the daily dose is calculated correctly.
- The 7 day average steroid >5mg/day rule will include SLE and non-SLE steroids in the identification of potential treatment failures. Treatment failure review will

exclude cases where the 7 day average steroids is >5mg/day due non-SLE steroids on a by subject review basis.

Intra-articular (IA) injections

- Participants may receive intraarticular injections during the study with the exception of within 8 weeks prior to the key efficacy endpoints (i.e. Week 52, 64, and 104). A participant who receives any intraarticular injection(s) within 8 weeks before to the Weeks 52, 64, and/or 104 visits will be defined as a treatment failure.

Corticosteroids for Reasons Other Than SLE Disease Activity

Corticosteroids for non-SLE reasons (e.g., asthma, contact dermatitis, etc) may be given short-term at higher doses than <=5 mg/day according to the following guidelines:

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

  and/or

- Up to 60 mg/day (prednisone) for 2-3 days ,

  and/or

- Up to 40 mg/day (prednisone) for 4-7 days.

After Week 26, the duration of high dose corticosteroids use for reasons other than SLE must not exceed 7 days, after which time, tapering should begin. The total corticosteroid dose must be tapered to <=5 mg/day within 21 days of the 1st dose of a course of high dose corticosteroids given for non-SLE reasons. In addition, no new high dose corticosteroids for reasons other than SLE are allowed that result in an average corticosteroid dose of >5 mg/day during the intervals starting 8 weeks before the key efficacy visits at Weeks 52, 64, and 104. During the intervals of 8 weeks before these efficacy endpoints, any new high dose corticosteroid use will declare the participant as a treatment failure. The day of the Week 44, 56, and 96 visits will count as the start of these 3 intervals (imputed visit date will be used for Week 56).

NOTE: Inhaled and topical corticosteroids are allowed throughout the course of the study

15.6.15.5. Anti-malarials

Dose of anti-malarial at baseline is the dose the subject received on the treatment start date (Day 1). If a patient is receiving an anti-malarial at baseline it will be assumed that the dose is stable and not a loading dose.

Anti-malarial therapies may be continued, or dose adjusted during the study.

For non-SLE reasons (e.g., for the experimental treatment of COVID-19) an anti-malarial may be initiated for a subject not previously on an anti-malarial, or dose increased above

the common allowable maximum doses (defined below) according to the following guidelines, for short-term treatment:

- < 21 days treatment duration
- Not during the intervals within 8 weeks before the key efficacy visits (actual visit date) at Weeks 52, 64, and 104.

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

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

The common allowable maximum doses of anti-malarial drugs are:

- Hydroxychloroquine – 400 mg/day
- Chloroquine – 500 mg/day
- Quinacrine – 100 mg/day

For compounded anti-malarials, no individual component may exceed the maximum dose above.
NOTE: The use of anti-malarials for anti-malarial prophylaxis is permitted.

15.6.15.6. Other Immunosuppressant Agents

Arms A, B, and C

- Starting any new immunosuppressant agent after Day 1 for increased lupus disease activity will cause the participant to be declared a treatment failure. An immunosuppressant agent may however be replaced with one of the agents listed below due to documented toxicity or lack of availability. Replacement to be determined by clinical review
- New topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed after Day 1.

Arms A and B

- Participants can maintain their baseline stable immunosuppressant regimen or adjust their dose as clinically required, up to the Week 4.
- At or prior to the Week 4 visit, immunosuppressants will be discontinued.
- All immunosuppressant medications post Week 4 (day after the visit 4 visit date) will be clinically reviewed to determine if they are a treatment failure.

Arms C

- Participants may continue their baseline immunosuppressant agents throughout the study.
- Dosage of existing immunosuppressant agents may be increased as clinically necessary until Week 12. From the day after the Week 12 visit, any increase in dose over the baseline (Day 1) or Week 12 visit dose, whichever is higher, will cause the participant to be declared a treatment failure.

The common allowable maximum doses for immunosuppressant agents at baseline (Day 1) and during the study (pre Week 4 for Arms and B) are listed below:

- Azathioprine – 300 mg/day
- 6-mercaptopurine – 300 mg/day
- Mycophenolate mofetil (PO)/ mycophenolate mofetil hydrochloride (IV) – 4 g/day
- Mycophenolate sodium (PO) – 2.88 g/day
- Methotrexate – 25 mg/week
- Oral cyclophosphamide – 2.5 mg/kg/day
- Cyclosporine – 4 mg/kg/day*
- Tacrolimus – 0.2 mg/kg/day*
- Sirolimus – 2 mg/day*
- Thalidomide – 200 mg/day
- Leflunomide – 40 mg/day*
- Mizoribine – 150 mg/day
- Other immunosuppressant agents not listed above, the investigator must contact the Medical Monitor for approval

*Clinical loading dose is permitted when replacing immunosuppressant agents.

15.6.15.7. Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Aspirin, and Acetominophen

NSAIDs and aspirin should be initiated and stabilized prior to entry into the trial.

Baseline is defined as the NSAID/Aspirin received on the treatment start date (Day 1)

NSAIDs may be continued and dose adjusted as clinically indicated until 8 weeks before efficacy visits, i.e., Weeks 52, 64, and 104. During the intervals of 8 weeks before these efficacy endpoints, any increase in the NSAID dose above the dose at Day 1 or the visit day starting the interval of 8 weeks prior to these key efficacy visits, whichever is higher, will declare the participant as a treatment failure unless the NSAID is given for <7 days. The day of the Week 44, 56, and 96 visits will count as the start of these 3 intervals.

An NSAID may be replaced with another NSAID due to documented toxicity or lack of availability. Replacement due to toxicity/ lack of availability will be assessed during clinical adjudication.

New NSAIDs may not be added after Day 1 unless given for <7 days. Initiation of an NSAID after Day 1 that is given >=7 days will declare the participant as a treatment failure.

NSAIDS with an administration route of ‘TOPICAL’ or ‘CONJUNCTIVAL’’ will not be considered as TF’s.

Aspirin will not be considered in the NSAID TF rules.

Daily doses of aspirin up to 1000 mg/day are allowed at any time during the study. Daily doses of aspirin above 1000 mg/day may be initiated at any time up to the Week 44 visit and may continue through the end of the study. For participants who never received an aspirin regimen at a dose >1000 mg/day between the Day 1 and Week 44 visit, starting a new aspirin regimen at a dose >1000 mg/day after the Week 44 visit will declare the participant a treatment failure unless the aspirin is given for <7 days.

Daily doses of aspirin above 1000 mg/day may not be initiated in the 8 weeks before Week 64 and 104. The same rules as at Week 44 will be applied at Weeks 56 and 96

ACETYLSALICYLATE LYSINE (in mg) will be converted to standardised dose by multiplying by 0.556.

Acetaminophen (paracetamol) is primarily an analgesic and lacks the anti-inflammatory properties of other NSAIDs. The use of acetaminophen is recommended when possible to treat non-SLE related conditions, in the absence of a pre-existing hepatic function deficiency.

PRN use of NSAIDs or Aspirin will be identified as a potential TF and reviewed on a by subject review basis.

15.6.15.8. Prohibited Medications

Medications prohibited by the protocol specified rule of:

- 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.
- Co-enrollment into another study of a different investigational agent or that may interfere with the conduct of this protocol.

cannot be assessed by the data recorded on the CRF, but would be identified through CRA monitoring. Should such events occur they will be addressed through the TF review process.

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

15.6.15.9. Belimumab in Year 2

This use of PI prescribed belimumab in Year 2 is a treatment failure for subjects in Arms A and B. Incorrectly taking Year 1 belimumab in Year 2 is not a treatment failure. For subjects in Arms A and B all belimumab taken in Year 2 will be adjudicated to determine if it is an incorrect late dose or a prescribed re-start medication.

Receiving belimumab is not a treatment failure for Arm C subjects.

15.6.16. Coronavirus Disease 2019 (COVID-19) Environment Onset Date

A COVID-19 environment onset date has been defined by GlaxoSmithKline for each Country as:

Country	COVID-19) Environment Onset Date
Argentina	10/FEB/2020
Brazil	10/FEB/2020
Canada	10/MAR/2020
France	25/FEB/2020
Germany	10 FEB/2020
Korea, Repubic of	10/FEB/2020
Mexico	10/FEB/2020
Netherlands	10/FEB/2020
Russia Federation	13/MAR/2020
Spain	10/FEB/2020
United States	10/FEB/2020

This represents the best estimate of the outbreak of COVID-19 within each Country at this time.

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completing all phases of the study, including the Week 104 visit. • Withdrawn subjects will not be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3 or will be summarized as withdrawal visits.

15.7.2. Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should not be displayed as missing.
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.

15.7.2.1. Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	Missing concomitant medication start date (CMSTDT) is imputed as treatment start date (TRTSDT) unless: ○ concomitant medication end date (CMENDT) is prior to treatment start date (TRTSDT), whether CMENDT is complete (DD/MM/YY) or partial (some combination of CMENDT day, month or year imputed) OR ○ The month or month and year of the partial CMSTDT are different from the month and/or year of TRTSDT OR

Element	Reporting Detail
	○ "Taken prior to study?" is checked. If any of the above conditions are met then CMSTDT is imputed with JAN for missing month and 01 for missing day, whatever is applicable. The recorded partial date will be displayed in listings.

15.8. Appendix 8: Laboratory Parameters and Toxicity Grades

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count RDW Hemoglobin Hematocrit Activated partial thromoplastin time Prothrombin Time	RBC Indices: MCV MCH MPV MCHC %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose – Nonfasting	Calcium (corrected)	Alkaline phosphatase	eGRF
Routine Urinalysis	• Standard Urinalysis Macro and Urinalysis Micro (microscopic examination if blood or protein is abnormal) • Specific gravity • pH, Glucose, Protein, Blood, Ketones, Occult Blood, Bilirubin, Nitrite, Leukocyte Esterase by dipstick • Spot Urine (protein:creatinine ratio)			
Immunoglobulins	• Serum isotypes: IgG, IgM, IgA			
Autoantibodies	• ANA titer • Anti-dsDNA • aCL • Beta-2-glycoprotein • Lupus anticoagulant • Extractable nuclear antigens (ENAs)			

Laboratory Assessments	Parameters
Serum Complement	• Complement C3 • Complement C4
Urine Drug Screen	• Amphetamines, Barbiturates, Benzodiazepines, Cocaine Metabolites, Marijuana Metabolites, Methadone, Opiates, Phencyclidine, Propoxyphene, Ethanol
Genetics	• Blood sample collection
Belimumab PK	• Blood sample collection
Rituximab PK	• Blood sample collection
RNA Interferon Signature	• Blood sample collection
PBMC	• Blood sample collection
Immunogenicity	• Blood sample collection
B Cell Subset	• Blood sample collection
B-Cell Receptor	• Blood sample collection
BLyS Protein	• Blood sample collection
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) •

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are stated in the protocol. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Laboratory parameters may need to have units converted for reporting. Equivalent units are:

$1x10^9/L = 1,000,000,000cells/L = 1,000cells/\mu L = 1,000cells/mm^3$

1g/L = 100mg/dL = 100mg/100mL = 1mg/mL

15.8.1. Adverse Event and Laboratory Value Severity Grade Tables

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

(continued)

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

Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

(continued)

1. Modified from (DMID) Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium				
Hyponatremia	130-135 meq/L	123-129 meq/L	116-122 meq/L	< 116 meq/L
Hypernatremia	146-150 meq/L	151-157 meq/L	158-165 meq/L	> 165 meq/L
Potassium				
Hypokalemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalemia	5.6-6.0 meq/L	6.1-6.5 meq/L	6.6-7.0 meq/L	> 7.0 meq/L
Phosphate				
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL	1.0-1.4 mg/dL	< 1.0 mg/dL
Calcium- (Corrected For Albumin)				
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2-1.4 meq/L	0.9-1.1 meq/L	0.6-0.8 meq/L	< 0.6 meq/L
Albumin				
Hypoalbuminemia	3.00-3.49 g/dL	2.50-2.99 g/dL	2.00-2.49 g/dL	< 2.00 g/dL
Bilirubin (Total)				
Hyperbilirubinemia (Total)	> 1.0-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5-5 x ULN	> 5 x ULN
Glucose				
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycemia (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
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)

Modified from (DMID) Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

Modified from (DMID) Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

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

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

RBC = red blood cell; hpf = high power field.
Modified from (DMID) Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

Modified from (DMID) Adult Toxicity Tables, 2001

Adverse Event and Laboratory Value Severity Grade Tables (continued)

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood		None	Severe mood changes requires medical intervention	Acute psychosis requiring Hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia

Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lymphopenia	>0.8 (GI/L)	<=0.8 - >.5(GI/L)	<=0.5->0.2(GI/L)	<=0.2(GI/L)

Source: CTCAE 4.03

15.9. Appendix 9: Biomarkers

	SI BIOMARKER DATASET				SDTM LB DATASET	
Name	BICATCD	BICAT	BITESTCD	BIORRESU	LBTESTCD	LBSTRESU
	GSK_TestCode	GSK_TestName		GSK_Unit	SDTM TESTCD	SDTM UNIT
Anti-dsDNA	ANDSAB	Anti-dsDNA antibody	CONC	IU/ML	ADSDNAAB	IU/mL
C3	C3	Complement component 3	CONC	G/L	C3	g/L
C4	C4	Complement component 4	CONC	G/L	C4	g/L
CD19+ Total B cells	CD19	CD19+	CONC	CELLS/ML	CD19	10^3/L
B cells CD20+	CDX111	CD19+ CD20+	CONC	CELLS/ML	CDX111_C	10^3/L
B cells CD20+	CDX111	CD19+ CD20+	PCTBCELL	%	CDX111_P	%
Naive B cells IgD+	CDX203	CD19+ CD27- IgD+	CONC	CELLS/ML	CDX203	10^3/L
Naive B cells IgD+	CDX203	CD19+ CD27- IgD+	PCTBCELL	%	CDX203	%
Naive CD20+ CD27-	CDX731	CD19+CD20+CD27-	CONC	CELLS/ML	CDX731_C	10^3/L
Naive CD20+ CD27-	CDX731	CD19+CD20+CD27-	PCTBCELL	%	CDX731_P	%
Activated Total B cells CD95+	CDX742	CD19+CD95b+	CONC	CELLS/ML	CDX742_C	10^3/L
Activated Total B cells CD95+	CDX742	CD19+CD95b+	PCTBCELL	%	CDX742_P	%
Memory CD20+ CD27+	CDX732	CD19+CD20+CD27+	CONC	CELLS/ML	CDX732_C	10^3/L
Memory CD20+ CD27+	CDX732	CD19+CD20+CD27+	PCTBCELL	%	CDX732_P	%
Non-switched memory CD27+ IgD+	CDX84	CD19+ CD27+ IgD+	CONC	CELLS/ML	CDX84	10^3/L

	SI BIOMARKER DATASET				SDTM LB DATASET	
Name	BICATCD	BICAT	BITESTCD	BIORRESU	LBTESTCD	LBSTRESU
	GSK_TestCode	GSK_TestName		GSK_Unit	SDTM TESTCD	SDTM UNIT
Non-switched memory CD27+ IgD+	CDX84	CD19+ CD27+ IgD+	PCTBCELL	%	CDX84_PC	%
Switched memory CD27+ IgD-	CDX86	CD19+ CD27+ IgD-	CONC	CELLS/ML	CDX86	10^3/L
Switched memory CD27+ IgD-	CDX86	CD19+ CD27+ IgD-	PCTBCELL	%	CDX86_PC	%
Plasmablasts CD27b CD38b	CDX734	CD19+CD27b+ CD38b+	CONC	CELLS/ML	CDX734_C	10^3/L
Plasmablasts CD27b CD38b	CDX734	CD19+CD27b+ CD38b+	PCTBCELL	%	CDX734_P	%
Plasmablasts CD20+ CD27b CD38b	CDX735	CD19+CD20+CD27b+CD38b+	CONC	CELLS/ML	CDX735_C	10^3/L
Plasmablasts CD20+ CD27b CD38b	CDX735	CD19+CD20+CD27b+CD38b+	PCTBCELL	%	CDX735_P	%
Plasmablasts CD20- CD27b CD38b	CDX736	CD19+CD20-CD27b+CD38b+	CONC	CELLS/ML	CDX736_C	10^3/L
Plasmablasts CD20- CD27b CD38b	CDX736	CD19+CD20-CD27b+CD38b+	PCTBCELL	%	CDX736_P	%
Transitional CD24b CD27-CD38b	CDX199	CD19+ CD24b+ CD38b+ CD27-	CONC	CELLS/ML	CDX199	10^3/L
Transitional CD24b CD27-CD38b	CDX199	CD19+ CD24b+ CD38b+ CD27-	PCTBCELL	%	CDX199_P	%
Transitional CD10+ CD24b CD27- CD38b	CDX738	CD19+CD10+CD24b+CD27-CD38b+	CONC	CELLS/ML	CDX738_C	10^3/L
Transitional CD10+ CD24b CD27- CD38b	CDX738	CD19+CD10+CD24b+CD27-CD38b+	PCTBCELL	%	CDX738_P	%
CD3+ Total T cells	CD3	CD3+	CONC	GI/L	CD3	10^9/L
CD4+ T cells	CDX03	CD3+ CD4+	CONC	GI/L	CDX03	10^9/L
CD8+ T cells	CDX02	CD3+ CD8+	CONC	GI/L	CDX02	10^9/L

15.10. Appendix 10: Abbreviations & Trade Marks

15.10.1. Abbreviations

Abbreviation	Description
aCL	Anti-cardiolipin
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Anti-nuclear Antibody
ANCOVA	Analysis of Covariance
anti-dsDNA	Anti-double-stranded DNA
BLyS	B-Lymphocyte Stimulator
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMQ	Customized MedDRA Query
CNS	Central Nervous System
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue Scale
FACS	Florescence Activated Cell Sorting
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HZ	Herpes Zoster
IBA	Independent Blinded Assessor
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
Ig	Immunoglobulin
IP	Investigational Product
ITT	Intent-To-Treat
IV	Intravenous
LLDAS	Lupus Low Disease Activity State
LLN	Lower Limit of Normal
LOQ	Limit of Quantification
MAR	Missing At Random
MCID	Minimal Clinically Important Difference

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat
NSAID	Nonsteroidal Anti-inflammatory Drug
OI	Opportunistic Infections
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PGA	Physician Global Assessment
PI	Principal Investigator
PISR	Post-Injection Systemic Reactions
PK	Pharmacokinetic
PopPK	Population Pharmacokinetic
PP	Per Protocol
PROs	Patient Reported Outcomes
PSAP	Program Safety Analysis Plan
PT	Preferred Term
PtGA	Patient Global Assessment
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous
SDTM	Study Data Tabulation Model
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
TB	Tuberculosis
ULN	Upper Limit of Normal
WPAI	Work Productivity and Activity Impairment Questionnaire

15.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
BENLYSTA (belimumab)

Trademarks not owned by the GlaxoSmithKline Group of Companies
Rituxan
SAS

15.11. Appendix 11: List of Data Displays

15.11.1. Data Display Numbering

RAP generated displays follow the Format A XY.ZZ, where:

A refers to the reporting effort i.e.

- T = Table
- L = Listing
- F = Figure

X refers to the reporting effort i.e.

- 1 = After all subjects have completed Week 52 i.e. Year 1 data
- 2 = After all subjects have completed Week 104 i.e.Year 2 & Year 1&2

Y refers to the Section i.e.

- 1 = Study population
- 2 = Efficacy
- 3 = Safety
- 4 = Health outcomes
- 5 = Biomarkers
- 6 = Pharmacokinetic

ZZ is an incremental count with a new number for every output.

15.11.2. Mock Example Shell Referencing

Example mock-up displays are provided in documents

205646 Study Pop Shells
205646 Efficacy Shells
205646 Safety Shells
205646 Health Outcomes Shells
205646 Biomarker Shells
205646 PK Shells

15.11.3. Deliverables

Delivery	Description
DB SAC	Double Blind Statistical Analysis Complete – Primary SAC for Year 1
EOS SAC	End of Study Statistical Analysis Complete – EoS SAC for Year 2 and Years 1&2 Combined

16. ATTACHMENTS

16.1. Attachment 1: AESI Preferred Term Definitions

The AESI definitions under the current version of MedDRA at the time of reporting will be found via the following IMMS pathname:

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