TITLE PAGE

Protocol Title: 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)

Protocol Number: 205646 Amendment 04 (Global)

Short Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE) – BLISS-BELIEVE

Compound Number: GSK1550188

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

PPD

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Global)	*30-Apr-2020*
Amendment 3 (Global)	*15-Aug-2019*
Amendment 2 / KOR-1	*02-Feb-2019*
Amendment 2 / ARG-1	*11-Dec-2018*
Amendment 2 / DEU-2	*28-Nov-2018*
Amendment 2 (Global)	*17-Nov-2018*
Amendment 1 /ARG-1	*02-Jul-2018*
Amendment 1/DEU-2	*27-Nov-2017*
Amendment 1/DEU-1	*23-Oct-2017*
Amendment 1/KOR-1	*22-Jun-2017*
Amendment 1 (Global)	*17-Apr-2017*
Original Protocol	*16-Jan-2017*

Amendment 04 (Global): 30-APR-2020

Rationale for the Amendment: In response to the COVID-19 pandemic, changes are being made in order to protect patient safety and data integrity. 1) Visit windows are being conditionally extended for all subject visits for the study. 2) Clarification that the independent blinded assessor can be called upon to perform the S2K efficacy assessment at an unscheduled visit. 3) In the event that subjects are unable to visit the site, it is acceptable for sites to supply investigational product (belimumab) to subjects by shipment to the subject. 4) Clarification regarding acceptable use and dosage of anti-malarial treatments (e.g. hydroxychloroquine). 5) Change to the language describing the timing of the primary analysis. 6) Recommendations for safety contact with subjects in the event they cannot attend clinic visits. 7) Guidance for study treatment discontinuation if a subject has suspected or confirmed COVID-19 infection.

In addition, several corrections and clarifications have been made which are unrelated to the COVID-19 pandemic.

Section # and Name	**Description of Change**	**Brief Rationale**
1. Synopsis, Table of endpoints	Secondary endpoint “Time to clinical remission sustained to Week 64, defined as Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day.” changed to	Correction of error and alignment of the protocol with the reporting and analysis plan.

Section # and Name	Description of Change	Brief Rationale
	"Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day."	
2: Schedule of Activities (SoA) Table 1,Table 2, Table 3 and Table 4	Visit windows. Footnote a – if the COVID-19 pandemic is restricting the ability of sites to schedule subject visits within the protocol defined windows (±7 days), then it is permissible to use an expanded visit window (±28 days). Unscheduled visit. The column for this visit in Table 1-Table 4 has been changed to insert a cross in the box for the S2K blinded assessor. The footnote in Table 1-Table 4 corresponding to the unscheduled visit has also been amended to refer the reader to the relevant section of the protocol for more information. Post-treatment and exit interview. The footnote in Table 1-Table 4 corresponding to this interview has been amended to remove the requirement for the interview to be done prior to clinical assessments.	In light of the COVID-19 pandemic, this allows increased flexibility for sites to schedule visits and collect key efficacy and safety data. Provides greater flexibility to sites for obtaining the blinded assessor's S2K assessment if subjects are unable to attend protocol defined visits. Correction. It is not essential for the interviews to be conducted prior to clinical assessments.
4: Objectives and Endpoints	Secondary endpoint "Time to clinical remission sustained to Week 64, defined as Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day."	Correction of error and alignment of protocol with reporting and analysis plan.

Section # and Name	Description of Change	Brief Rationale
	changed to "Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day."	
7.3 Method of Treatment Assignment	Language added to clarify arrangements for direct supply of belimumab autoinjectors to subjects in the event subjects are unable to visit the site to collect them.	Allow subjects to continue treatment with belimumab if unable to visit the site, for example, as a consequence of the COVID-19 pandemic.
7.7.1 Allowable medications	Subsection 7.7.1.1 (Anti-malarials) has been amended to include provision for subjects to have short term treatment with hydroxychloroquine for reasons other than lupus, for example, experimental treatment of COVID-19.	Response to potential change in use of anti-malarials as a consequence of the COVID-19 pandemic.
8.2 Discontinuation of study treatment	Language added to provide guidance for investigators regarding treatment with investigational product should a subject have a suspected or confirmed COVID-19 infection.	Provision of guidance to assist investigators in response to the COVID-19 pandemic.
9.4 Assessments at Unscheduled Visits	Language added to help provide guidance to investigators for safety monitoring of subjects via telephone or video call if subjects are unable to attend protocol defined visits at the site,	Maintain investigator contact with and safety monitoring of subjects in response to the COVID-19 pandemic.
10. Statistical Considerations	Language has been added to sub-Section 10.1.1 and Section 10.4 to clarify that the timing of w52 reporting and the planned estimands for the statistical analyses may be reviewed based upon the evolving impact of COVID-19.	Clarification that COVID-19 may impact upon the timing and the estimands of the statistical analysis.

Section # and Name	Description of Change	Brief Rationale
	A correction has been made in Section 10.4.1 to clarify that the MITT population (and not the ITT population) will be used to conduct the analysis of the primary and key secondary endpoints.	Correction and alignment of protocol with the reporting and analysis plan.
Appendix 9. Clinical Laboratory Tests	Language added to clarify that local laboratory tests are recommended if disruption as a consequence of COVID-19 prevents or delays central laboratory tests.	Support continued safety and efficacy assessment in response to COVID-19.
Appendix 13. Protocol Amendment History	Has been fully updated with details of all global and country specific amendments.	Provide complete history of amendments.
Throughout protocol	Minor editorial revisions	Corrections of typographical errors and minor revisions for clarity.

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1. SYNOPSIS

Protocol Title: 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)

Short Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE) - BLISS-BELIEVE

Rationale:

SLE is characterized by autoantibodies, including antibodies to double-stranded DNA (dsDNA), and by abnormal B cell activation and differentiation, indicating that therapies which deplete or modulate B cells could be beneficial in treating SLE. Belimumab and rituximab are monoclonal antibodies that achieve their expected pharmacology through different but complementary mechanisms; therefore, based on their mechanisms of action, synergistic effects when used in combination in the treatment of SLE are possible compared to either treatment alone. Belimumab treatment increases peripheral memory B cells potentially by mobilization from tissues this may include the autoreactive B cell compartment. This mobilization would expose these cells to more efficient depletion by rituximab. Continuing belimumab after a single course of rituximab would then suppress the B-lymphocyte stimulator (BLyS) elevation observed after rituximab monotherapy, thus suppressing the signal which leads to rapid repopulation of B cells, including autoreactive B cells. This study will assess whether co-administration of belimumab and a single cycle of rituximab may optimize treatment with belimumab, resulting in improvements in clinical status with a favorable safety profile.

Objectives and Endpoints:

The key evaluations are based on comparing belimumab with or without a single cycle of rituximab (the combination arm vs. the control arm). There are limited analyses planned to compare the combination of belimumab with a single cycle of rituximab (combination arm) to belimumab with standard therapy (reference arm). Details of the analyses to be conducted will be described in the Reporting and Analysis Plan (RAP), including analysis of the combination arm vs. the control arm and the combination arm vs. the reference arm.

Objectives	Endpoints
Primary: Efficacy • 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 score ≤2, achieved without immunosuppressants and with

Objectives	Endpoints
	corticosteroids at a prednisone equivalent dose of ≤5 mg/day at Week 52.
Secondary: Efficacy (Major)	• Proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day at Week 104.
Secondary: Efficacy (Other)	• Proportion of participants with a state of disease control, defined as a SLEDAI-2K score ≤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 =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of complete remission, defined as SLEDAI-2K score=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 =0, achieved without

Objectives	Endpoints
	immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of complete remission, defined as a SLEDAI-2K score =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 $\leq$2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of $\leq$5 mg/day. • Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. (Serological activity, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Duration of disease control, defined as SLEDAI-2K score $\leq$2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of $\leq$5 mg/day • Duration of clinical remission, defined as Clinical SLEDAI-2K score =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. (Serological activity, i.e., anti-dsDNA positivity and/or

Objectives	Endpoints
	hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Change from baseline in SLEDAI-2K score by visit • Proportion of participants with SLEDAI-2K organ improvement by visit • Proportion of participants with SLEDAI-2K 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 $\leq$4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; (2) no new features of lupus disease activity compared with the previous assessment; (3) PGA (scale 0-3) $\leq$1; (4) current prednisolone (or equivalent) dose $\leq$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 $\leq$2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of $\leq$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 =0, achieved without

Objectives	Endpoints
	immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit; using the Principal Investigators assessment of SLEDAI-2K. (Serological activity score, i.e. anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.)
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) • 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, $\geq$4) by visit
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

Objectives	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

Overall Design:

This is a Phase 3, 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 SLE. Participants will be randomly assigned to 1 of 3 treatment arms; belimumab plus rituximab-placebo (Arm A, control), belimumab plus rituximab (Arm B, combination), or open-label belimumab plus standard therapy (Arm C, reference). Blinded independent assessors will conduct the SLEDAI-2K at key time points. An Independent Data Monitoring Committee (IDMC) will review the safety data on a regular basis.

Number of Participants:

A total of approximately 560 participants are expected to be screened, with a goal of randomizing at least 280 participants (50% screen failure rate).

The sample size may be increased up to a maximum of 320 participants if the dropout rate, missing data or number of major protocol deviations suggests further participants are necessary to ensure robust conclusions can be drawn. The decision to increase the sample size will be made without unblinding the trial.

Treatment Groups and Duration:

Overview

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 51 weeks. Arm C (reference) is an open-label arm with belimumab subcutaneous (SC) 200 mg/week and standard therapy for 104 weeks. Arm C (reference) will provide a qualitative reference to assess the relative performance of Arm A (control) and Arm B (combination) vs. currently available standard SLE therapy (Arm C). The concomitant medication rules and definitions of treatment failure are the same for the

double-blind control and combination arms, Arms A and B, but differ from those for the open-label reference arm, Arm C.

Randomization and the first dose of belimumab should be completed within 35 days of initiation of screening procedures. Participants will be receiving stable standard therapy at entry. 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). Belimumab will be administered SC on Day 1 and then weekly (i.e., every 7 days ±1 day) through Week 51 for Arms A and B, and through Week 103 for Arm C. SC injections will be administered at alternating injection sites between the left or right thighs and the abdomen. Rituximab-placebo or rituximab will be administered by intravenous (IV) infusions at Weeks 4 and 6 for Arms A and B. Participants in Arms A and B will be administered a pre-medication regimen 30 minutes before each rituximab-placebo or rituximab infusion on Weeks 4 and 6, including methylprednisolone 100 mg IV or equivalent, an antihistamine, and acetaminophen or equivalent.

Participants in any arm who are deemed treatment failures for efficacy endpoints at any time during the study will be encouraged to remain in the study and continue to have all efficacy and safety assessments.

Participants randomized to Arms A or B who enter the study on immunosuppressants will discontinue immunosuppressants prior to or on the day of the Week 4 visit. Continuing the stable immunosuppressant dose until Week 4 allows participants to receive 3 weeks of belimumab SC prior to discontinuing their immunosuppressants. Corticosteroids may be adjusted as necessary during this transition period. If participants in Arms A and B receive immunosuppressants after the Week 4 visit they will be deemed treatment failures. Participants in Arm C will continue their stable immunosuppressants throughout the study at the discretion of the investigator. If participants in Arm C require an increased dose of their stable immunosuppressant after Week 12 or addition of a new immunosuppressant they will be considered a treatment failure.

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 ≤5mg/day by Week 26. If the investigator believes the participant would benefit from continued steroid taper and, if tolerated, a prolonged corticosteroid taper should continue after Week 26 with the goal of corticosteroid discontinuation. Participants who are able to tolerate the final taper will be withdrawn from corticosteroids. If a participant is unable to tolerate the final stage of the corticosteroid taper, the investigator may reinitiate corticosteroids at a prednisone equivalent dose of up to and including 5 mg/day. If a 7-day average prednisone equivalent dose of >5 mg/day is required at any time after Week 26 visit (i.e., beginning first day of Week 27), the participant will be considered a treatment failure for the efficacy endpoints.

Anti-malarial therapies for SLE may not be initiated during the study, but may be continued or dose-adjusted during the study, and will be allowed within the definitions of

the efficacy endpoints. Switching of anti-malarial due to toxicity or lack of availability is permitted

Non-Steroidal Anti-Inflammatory drugs (NSAIDs) (for ≥7 days) may not be initiated during the study, but may be continued and dose adjusted as clinically indicated until the Week 44 visit. After the Week 44 visit any increase in the NSAID dose above the baseline (Day 1) or Week 44 dose, whichever is higher, will declare the participant as a treatment failure unless the NSAID is given for <7 days.

During the 52-week double-blind portion of the study, participants in Arms A and B who cannot tolerate discontinuation of immunosuppressants or taper of corticosteroids or, in the opinion of the investigator, require added therapy, will be considered treatment failures for the efficacy endpoints. Blinding to the treatment assignments in Arms A and B will be maintained. At the investigator's discretion, these participants may continue treatment with belimumab, and/or be treated with additional SLE therapies as necessary, including corticosteroids and/or immunosuppressants. Participants in Arm C who are unable to tolerate the corticosteroid taper or, in the opinion of the investigator, require increased doses of their baseline immunosuppressants or addition of a new immunosuppressant will be considered treatment failures for the efficacy endpoints.

Participants in Arms A and B will enter into the 52-week treatment-free, observational phase of the study after completing Week 52 (Weeks 53 through 104). “Treatment-free” refers to no active treatment with study treatment (i.e., belimumab and/or rituximab). Participants in Arm C will continue to receive belimumab SC and their stable immunosuppressants during Weeks 53 through 104. For participants in all three treatment arms, treatment with anti-malarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day will be allowed in Weeks 53 to 104.

During Weeks 53 to 104, additional treatment may be given if the investigator believes the participant would benefit because he/she: a) responded to study treatment but did not meet the primary efficacy endpoint, or b) responded to study treatment but subsequently experienced increasing disease activity which requires additional therapy. Additional treatment may include open-label belimumab, corticosteroids (>5 mg/day), and/or immunosuppressants, and will be administered at the discretion of the investigator. Treatment with open-label rituximab is allowed within the protocol, but is not encouraged. Belimumab will be provided by the sponsor for those participants who reinitiate treatment with belimumab, but additional treatment with rituximab and/or other medications will not be provided by the sponsor. NOTE: These participants will be considered treatment failures for the Week 64 efficacy analyses if the additional treatment (see above) occurs before the Week 64 visit, and for the Week 104 efficacy analyses if the additional treatment occurs before the Week 104 visit. Participants who are deemed treatment failures will continue to be followed in the study and have all efficacy and safety assessments performed.

In the event that a participant discontinues the study or withdraws consent early, an Early Withdrawal visit 1-4 weeks after last dose of study treatment and a Follow Up visit 8 weeks after the last dose of study treatment should be scheduled. Additionally, an attempt

will be made to ascertain survival status at approximately 52 and 104 weeks after the first dose of study treatment.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 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	
RNA for Interferon Signature		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														
Further Research																
Blood Leukocyte Analysis (PBMC) (p)		X											X		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 Section 9 for pregnancy test requirements.
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. Please refer to Section 9.4 and to the guidance 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 at US sites 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 select European sites

Table 2 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
Further Research									
Blood Leukocyte Analysis (PBMC) (k)				X		X		X	
B cell receptor (l)						X	X	X	
B cell subsets (n)	X			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 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. Please refer to Section

9.4 and to the 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 suspected 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 rescue therapy.
j. Follow up visit is required only for subjects who receive belimumab rescue 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 at US sites experience a suspected 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 3 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														
Further Research																
B cell subsets (o)		X	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 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 discontinue 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 WOCBP 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 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. Please refer to Section 9.4 and to the guidance 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 suspected SLE Flare (refer to footnote l).
k. To be conducted at US sites only.
l. To be conducted only at US study sites as part of further research. B-cell receptor samples are also collected at US sites when subjects experience a suspected 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 4 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

	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)
Extractable nuclear antigens (ENAs)	X			X		X		X	
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
Further 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	

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. .(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. Please refer to Section 9.4 and to the guidance provided in the Study Reference Manual.
f. Blood samples for a B cell receptor analysis should be obtained in the event of a suspected 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 at US sites only when subjects experience a suspected 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.

3. INTRODUCTION

3.1. Study Rationale

Systemic Lupus Erythematosus (SLE) is characterized by autoantibodies, including antibodies to double-stranded DNA (dsDNA), and by abnormal B cell activation and differentiation [Davidson, 2001], indicating that therapies which deplete or modulate B cells could be beneficial in treating SLE. Belimumab and rituximab are monoclonal antibodies that achieve their expected pharmacology through different but complementary mechanisms; therefore, based on their mechanisms of action, synergistic effects in the treatment of SLE are possible. Belimumab treatment increases peripheral memory B cells potentially by mobilization from tissues this may include the autoreactive B cell compartment. This study will assess whether co-administration of belimumab and a single cycle of rituximab may optimize treatment with belimumab, resulting in improvements in clinical status with a favorable safety profile, by comparing participants randomized to belimumab plus rituximab vs. belimumab plus rituximab-placebo. An open-label arm is included to provide a qualitative reference to standard therapy.

3.2. Background

Belimumab is an important treatment option for patients with SLE, but significant numbers of patients do not achieve a state of low disease activity, and are still left with moderate level of residual disease activity. There is a large unmet medical need for additional effective treatment which could meaningfully reduce disease-related morbidity and mortality and limit the toxicity associated with traditional treatment regimens such as corticosteroids and immunosuppressants.

Rituximab treatment results in nearly complete depletion of CD20+ B cells in the peripheral blood within hours of treatment. In contrast, relatively high numbers of CD20+ B cells persist in the bone marrow following initial treatment with rituximab [Boumans, 2011]. Belimumab treatment increases peripheral memory B cells potentially by mobilization from tissues this may include the autoreactive B cell compartment from tissues into the periphery. This mobilization would expose these cells to more efficient depletion by rituximab. Continuing belimumab after a single course of rituximab would suppress the B-lymphocyte stimulator (BLyS) elevation observed after rituximab monotherapy, thus suppressing the signal which leads to potential repopulation of autoreactive B cells.

A treatment regimen which could reliably and effectively achieve and maintain low disease activity or remission, including patients with earlier and potentially more reversible disease prior to the development of permanent disability or end-organ damage, would change the paradigm by which SLE is treated today. This patient population has a large unmet medical need as 50% of SLE patients develop end-organ damage within the first 5 years of diagnosis [Urowitz, 2012]. Recent scientific research suggests that a combination treatment with anti-BLyS and anti-CD20 may potentially address this need. Anti-BLyS and anti-CD20 therapeutics operate through different but complementary mechanisms and the addition of a single cycle of rituximab treatment may optimize the effect of belimumab treatment in SLE.

Synergy may emerge through the following mechanisms:

- Belimumab may cause redistribution of memory and germinal center B cells from lymphoid tissue into blood, where they are exposed to higher rituximab concentrations in the absence of local tissue factors that protect the B cells in their niches, which is likely to increase B cell depletion.
- Neutralization of serum BLyS level increases seen after rituximab monotherapy, preventing rapid B cell repopulation which is associated with SLE disease flares.
- Increased stringency of B cell reconstitution in the presence of anti-BLyS therapy with belimumab, resulting in fewer auto-reactive cells being formed after B cell depletion with rituximab.

Preclinical data supporting the hypothesis that a combination of belimumab and rituximab may provide additional efficacy over either agent alone were generated in a human-CD20 expressing mouse model. Experiments using this model demonstrated relative resistance of the marginal zone (MZ) B cell compartment to anti-CD20 antibody monotherapy. Approximately 50% of these cells remained following anti-CD20 mAb as compared to complete depletion of circulating mature B cells. MZ B cells were rendered sensitive to anti-CD20 mAb depletion when they were effectively mobilized from tissues into the vasculature with anti-αL and anti-α4 integrand mAbs. Thus, the tissue B cells were not inherently resistant to anti-CD20 mAb treatment: treatment response was enhanced by prior mobilization of the MZ B cells into the vasculature [Gong, 2005]. Additionally, when mouse BLyS receptor (BR3)-Fc and anti-hCD20 were combined in this model, there was more effective tissue B cell depletion of MZ B cells and follicular (FO) B cells than with either agent alone. Similar observations were made in murine SLE models [Lin, 2015] in which dual targeting resulted in greater efficacy with increased tissue B cell depletion, greater reduction in a range of auto-antibody levels, and significant decreases in total IgG1, IgG2b, IgG3, IgM, and IgA when compared to BLyS inhibition and CD20 B cell depletion alone.

There have been 4 recent case reports of patients with SLE and Sjogren's Syndrome demonstrating the ability of the combination to induce remission or states of disease control for prolonged periods [Kraaij, 2014; De Vita, 2014; Simonetta, 2016]. In one case a 32-year-old woman with a 3 year history of lupus nephritis who previously failed 2 induction regimens was treated with rituximab which led to a partial response. When there was still B cell depletion but as B cells began to repopulate, the patient was started on belimumab at which point the patient entered remission on no steroids or immunosuppressants. Remission persisted after 18 months. The second case involved a 42-year-old man with lupus nephritis who likewise had failed standard therapy and induction regimens. Initiation of rituximab led to only partial response and a full relapse occurred while the patient was still B cell depleted but B cells began to repopulate, at which point belimumab was started. The patient entered a prolonged (>12 months) state of disease control on no steroids or immunosuppressants but on belimumab. The third case involved a 23-year-old woman with refractory lupus nephritis who failed standard therapy and the addition of belimumab only resulted in transient partial reduction of proteinuria. Belimumab was stopped and the patient received one cycle of rituximab with no significant or sustained effects on disease activity, and a rebound increase in serum B-

cell activating factor of the TNF ligand family (BAFF) levels was detected. Belimumab was reintroduced and the patient experienced "rapid and dramatic" improvements in clinical and biological parameters including proteinuria. After more than 18 months no disease flares or proteinuria relapses were observed. In the fourth case, a patient with severe, refractory (including to prior courses of rituximab) Sjogren's Syndrome with associated Mucosa associated lymphoid tissue (MALT) lymphoma and cryglobulinemic vasculitis was treated with belimumab. The patient did not respond and so, as a last resort, rituximab was tried again, while there was still ongoing exposure to belimumab. This was followed by complete and persistent regression of the lymphoma, skin ulcers and vasculitis. Cryoglobulins and rheumatoid factor became persistently negative and the patient is in remission after three and a half years.

A detailed description of the chemistry, pharmacology, efficacy and safety of belimumab is provided in the most recent version of the Belimumab Investigator's Brochure. Refer to the local rituximab approved product label for description of the chemistry, pharmacology, efficacy, and safety of rituximab.

3.3. Benefit/Risk Assessment

More detailed information about the established benefits and risks of belimumab and rituximab, including expected adverse events (AEs), may be found in the Belimumab Investigator's Brochure and local rituximab approved product label, respectively.

There are no published clinical trial data for the co-administration of belimumab with rituximab; however, the following data were reviewed and no new safety risks beyond what would be expected for either agent alone is suggested from the limited data available from patients who may have had overlapping exposures to belimumab and rituximab:

- The GSK Safety Database of AEs from clinical trials and post-marketing experience
- An insurance claims database (Safety Works)
- In-stream, blinded data from an ongoing GSK study of belimumab in subjects with vasculitis who were induced with high dose corticosteroids and either rituximab or cyclophosphamide
- In stream, blinded data from an ongoing GSK study of belimumab co-administered with rituximab in the treatment of primary Sjögren's syndrome

Given that the experience of co-administration of anti-CD20 and anti-BLyS therapies to date is very limited, robust safety monitoring and stopping rules are being implemented to safeguard subject safety. The key risk assessment and mitigation strategy for this protocol is outlined below and in Section 8.2.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
Infections:		
Prolonged B cell suppression and more complete B cell depletion expected; potential for more profound hypogammaglobulinemia with increased risk for serious infections including opportunistic infections (OIs), Progressive multifocal leukoencephalopathy (PML), and Hepatitis B virus (HBV) reactivation.	*Rituximab:* The rate of serious infections with rituximab in the rheumatoid arthritis (RA) population is 4% per year. Reactivation of hepatitis B has also been very rarely reported in RA patients receiving rituximab. Late onset neutropenia occurs rarely in patients treated with rituximab. *Belimumab:* The rate of serious infections for SLE is 5% of subjects receiving either belimumab or placebo. *Belimumab and Rituximab Coadministration:* Infections are expected events for both belimumab and rituximab. Cases of PML have been very rarely reported, including fatal events, for both rituximab and belimumab in autoimmune diseases. There is preclinical evidence for prolonged B cell suppression and more complete B cell depletion as well as effect on IgG1+ plasma cells in the long-lived bone marrow niche thought to be less	Exclusions based on significant infection history, serologic evidence of past or present HBV or Hepatitis C virus (HCV) infection; IgG <250 mg/dL (note: <400mg/dL for Germany), IgA deficiency (IgA level <10 mg/dL), neutrophils $<1.5X10^9$/L. A PML management plan including neurologic questionnaire, patient alert card, and stopping criteria will be utilized. An independent PML Panel is also available for consultations. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be reported to the Medical Monitor within 24 hrs. The

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
	sensitive to immunotherapy [Lin, 2015] with dual B cell immunotherapy. Assessment of the translatability of the IgG reductions to humans is difficult to make due to species differences in B cell biology and different treatments; however, the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with coadministration treatment. Neutropenia: SLE disease related neutropenia and Rituximab induced neutropenia may result in further reduction in circulating neutrophils and/or influence timing of this neutropenia onset as compared to when Rituximab is administered alone.	appropriateness of continuing study agent, while the case is being assessed, should be discussed. Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately. Neutropenia: Individual subject's treatment with belimumab and rituximab/rituximab-placebo will be discontinued for (a) life threatening infection; (b) IgG <400 mg/dL if associated with a serious infection. Subjects should be monitored for neutropenia throughout the study. Neutropenia should be managed appropriately according to local practice and clinical judgement should be applied with regard to the appropriateness of continuing study treatment in these subjects. • Study treatment with rituximab/rituximab-placebo (infusions Week 4 and/or Week 6) must be temporarily withheld and the GSK medical monitor consulted about

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
		continued dosing if a subject experiences a neutrophil count <1x10^9/L. • Study treatment with belimumab (Arms A/B and C) must be temporarily withheld and the GSK medical monitor consulted about continued dosing if a subject experiences a neutrophil count <0.5x10^9/L.
Systemic Infusion / Injection-Related Reactions, Hypersensitivity Reactions and Immunogenicity:		
Serum Sickness: Serum sickness has been associated with rituximab in autoimmune indications [Meijer, 2010]. There is a potential risk for increased immunogenicity due to cross reactivity which could lead to increased frequency of hypersensitivity reactions, particularly of the delayed type.	*Rituximab:* The incidence of serum sickness associated with rituximab in pSS studies has ranged from 6-38% [Carubbi, 2014]. Administration of belimumab and rituximab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Delay in the onset of serious hypersensitivity reactions can occur. Both rituximab and belimumab have been associated with delayed type non-acute Hypersensitivity reaction (HSR)/serum sickness, although no relationship to Anti-drug Antibody (ADA) has been established. *Belimumab and Rituximab Coadministration*: Incidences of hypersensitivity and infusion reactions have been noted to be higher with co-administration vs. mono-biologic therapy but no	Immunogenicity will be evaluated with periodic assessment over the course of the study. A pre-medication regimen will be given before each rituximab/rituximab placebo infusion: methylprednisolone 100 mg IV, an antihistamine and acetaminophen or equivalent. Subjects should remain under clinical supervision for 3 hours after completion of the first belimumab injection and the rituximab/placebo infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. If subjects are to receive belimumab after 4 consecutive weeks of not receiving belimumab, the first belimumab dose must be administered in the clinic and subject

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
	association with ADA has been established [Weinblatt, 2006].	should remain under clinical supervision for 3 hours after the completion of the dose. Patients will be given an alert card for HSR and delayed HSR/serum sickness.
Malignancy:		
There is an increased risk of malignancy, including Non-Hodgkin's lymphoma, in SLE. There is a theoretical increased risk of malignancy with combination immunosuppressive mechanisms.	*Belimumab and Rituximab:* Immunomodulatory drugs like rituximab and belimumab may increase the risk of malignancy. To date, no causal relationship between belimumab or rituximab and malignancy, including B cell lymphoma, has been detected, both of which have been administered long term and in combination with other immunosuppressants of various mechanisms.	Subjects with a history of malignancy in the 5 yrs prior to randomization, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ of the uterine cervix, will be excluded. Monitor patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.
Interaction with Vaccinations:		
There is a risk of reduced antibody titers with mono and dual B cell immunotherapy. The potential synergistic effect of rituximab and belimumab may result in a prolonged B cell depletion that could have a similar inhibitory impact on vaccine responses as administering repeated doses of rituximab.	*Rituximab:* As described in the label [Rituxan package insert, 2016], the response to pneumococcal vaccination (a T cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with rituximab plus methotrexate (MTX) as compared to patients treated with MTX alone (19% vs. 61%). Additionally, a lower proportion of patients in the rituximab plus MTX	Immunization with live vaccines is prohibited from 30 days prior to Day 1 and during belimumab use. Subjects' vaccination status should be assessed and current immunization guidelines followed; all necessary vaccinations should be administered if possible no later than 30 days prior to Day 1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
	group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%). In a combination study, median antibody titers (tetanus, diphtheria, pneumococcus) at Week 32 were reduced from baseline in atacicept (recombinant fusion protein which inhibits BLyS and APRIL) but not placebo-treated patients who had been previously treated with rituximab. However, these values recovered close to baseline by Week 16 of the follow-up, there were few shifts to below protective titers, and no between group differences with respect to the frequency of shifts. *Belimumab:* The efficacy of concurrent vaccination in patients receiving belimumab is not known; however, in the belimumab vaccination trial, evaluation of the impact of belimumab treatment on response to on-treatment vaccination with 23-valent pneumococcal vaccine revealed that immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
Psychiatric Events:		
There is an identified risk of psychiatric events with belimumab and rituximab.	*Rituximab:* Depression and anxiety were common AEs in rituximab RA trials. *Belimumab:* There have been reports of depression and suicidality in patients receiving belimumab.	Subjects who, in the investigator's opinion, pose a significant suicide risk will be excluded. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be completed at each visit Subjects will be monitored closely for signs and symptoms of psychiatric illness including depression and suicidal ideation. Subjects displaying such signs and symptoms will be treated appropriately and referred as necessary to specialty psychiatric care.
Cardiac Disorders:		
	Rituximab: Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. There is no data on the safety of rituximab in patients with moderate to severe heart failure or severe, uncontrolled Cardiovascular (CV) disease. *Belimumab and Rituximab:* Hypotension may accompany infusion/postinjection systemic reactions with both rituximab and belimumab.	Exclude subjects with severe heart failure (New York Heart Association, Class IV) or other severe, uncontrolled cardiac disease. Closely monitor any patients with cardiac history or those who have experienced prior cardiopulmonary adverse reactions during administration of rituximab/rituximab placebo. Consider withholding antihypertensive medications 12 hours prior to rituximab/rituximab placebo infusion.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Belimumab (GSK1550188), Rituximab, and Belimumab and Rituximab Coadministration		
Severe Skin reactions:		
	Rituximab: Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; some with fatal outcome, have been reported with rituximab.	Permanently discontinue treatment in the case of such an event with suspected relationship to treatment.
Posterior Reversible Encephalopathy Syndrome (PRES):		
	Rituximab: Cases of Posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.	Medical monitor will be notified of any new neurologic symptoms. Medical monitor and investigator will consider the possibility of PRES in differential diagnosis.

3.3.2. Benefit Assessment

The primary data supporting efficacy of intravenous (IV) belimumab were the Phase 3 trials (C1056 and C1057) in which 1684 subjects were treated for up to 52 weeks (C1057) or 76 weeks (C1056) (Belimumab Investigator's Brochure, Section 5.3.1.2). Belimumab produced significant improvements in the SLE Responder Index as well as in the individual component Safety of Estrogen in Lupus National Assessment Trial (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score in both studies. Pooled analyses demonstrated steroid sparing and decreased risk of severe flares over 52 weeks. Clinical trial data for belimumab since approval continue to show efficacy in the treatment of SLE through decreased SLE flares and decreased disease activity across multiple organ systems (Belimumab Investigator's Brochure, Section 5.3.1.3). Similar results were observed in the pivotal Phase 3 trial of belimumab SC 200 mg/week (BEL112341), with significant improvements in the SLE Responder Index and time to first severe flare endpoints. The inclusion of rituximab provides an opportunity for subjects with active SLE despite standard lupus therapy to benefit from potentially disease modifying regimen that may include induction of disease control or clinical remission and a reduction in or complete discontinuation of corticosteroids and immunosuppressant therapy.

3.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures that will be implemented to minimize risk to subjects participating in this study, the potential risks associated with co-administration of belimumab and rituximab are justified by the anticipated benefits that may be afforded to patients with SLE who choose to participate in this trial.

4. OBJECTIVES AND ENDPOINTS

The key evaluations are based on comparing belimumab with or without a single cycle of rituximab (the combination arm vs. the control arm). There are limited analyses planned to compare the combination of belimumab with a single cycle of rituximab (combination arm) to belimumab with standard therapy (reference arm). Details of the analyses to be conducted will be described in the Reporting and Analysis Plan (RAP), including analysis of the combination arm vs. the control arm and the combination arm vs. the reference arm.

Objectives	Endpoints
Primary: Efficacy • 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 SLEDAI- 2K score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 52. (Serological activity, i.e., anti-dsDNA positivity and/or

Objectives	Endpoints
	hypocomplementemia, is scored in the SLEDAI-2K endpoint.)
Secondary: Efficacy (Major)	• Proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5 mg/day at Week 104.
• Secondary: Efficacy (Other)	• Proportion of participants with a state of disease control, defined as a SLEDAI-2K score ≤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 =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of complete remission, defined as SLEDAI-2K=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 at Week 104, defined as

Objectives	Endpoints
	Clinical SLEDAI-2K score=0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, sustained for at least 24 weeks. (Serological activity score, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Proportion of participants with a state of complete remission, defined as a SLEDAI-2K score =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 $\leq$2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of $\leq$5 mg/day • Time to clinical remission sustained to Week 104, defined as Clinical SLEDAI-2K score =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. (Serological activity, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Duration of disease control, defined as SLEDAI-2K score $\leq$2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of $\leq$5 mg/day • Duration of clinical remission, defined as Clinical SLEDAI-2K score =0, achieved

Objectives	Endpoints
	without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day. (Serological activity, i.e., anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.) • Change from baseline in SLEDAI-2K score by visit • Proportion of participants with SLEDAI-2K organ improvement by visit • Proportion of participants with SLEDAI-2K 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 $\leq$4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; (2) no new features of lupus disease activity compared with the previous assessment; (3) PGA (scale 0-3), $\leq$1; (4) current prednisolone (or equivalent) dose $\leq$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 $\leq$2, achieved without immunosuppressants and with

Objectives	Endpoints
	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 =0, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day, by visit; using the Principal Investigators assessment of SLEDAI-2K. (Serological activity score, i.e. anti-dsDNA positivity and/or hypocomplementemia, is excluded from the Clinical SLEDAI-2K endpoint.)
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)

Objectives	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 subjects with improvement in FACIT-Fatigue score exceeding the Minimal Clinically Important Difference (MCID, ≥4) by visit
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 • 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 score by visit • Change from baseline in WPAI: Lupus percent activity impairment score by visit

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 3, 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 SLE. Participants will be randomly assigned to 1 of 3 treatment arms; belimumab plus rituximab-placebo (Arm A, control), belimumab plus rituximab (Arm B, combination), or belimumab plus standard therapy (Arm C, reference). Arms A and B are double-blind; Arm C is open-label. In order to minimize bias given that Arm C is open-label, blinded independent assessors will conduct SLEDAI-2K evaluations at key time points, including the primary and key secondary efficacy endpoints. An Independent Data Monitoring Committee (IDMC) will review the safety data periodically to ensure external medical and statistical review of safety issues (Section 10.4.4).

Randomization and the first dose of belimumab should be completed within 35 days of initiation of screening procedures. Participants will be receiving stable standard therapy at entry. 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). Belimumab will be administered subcutaneously (SC) on Day 1 and then weekly (i.e., every 7 days ±1 day) through Week 51 for Arms A and B, and through Week 103 for Arm C. SC injections will be administered at alternating injection sites between the left or right thighs and the abdomen. Rituximab-placebo or rituximab will be administered by IV infusions at Weeks 4 and 6 for Arms A and B. Participants in Arms A and B will be administered a pre-medication regimen 30 minutes before each rituximab-placebo or rituximab infusion on Weeks 4 and 6, including methylprednisolone 100 mg IV or equivalent, an antihistamine, and acetaminophen or equivalent. The primary efficacy endpoint will be measured at Week 52.

Participants from any arm who are deemed treatment failures at any time during the study will be encouraged to remain in the study and continue to have all efficacy and safety assessments.

Participants randomized to Arms A and B who enter the study on immunosuppressants will discontinue immunosuppressants at or prior to the Week 4 visit. Continuing the stable immunosuppressant dose until Week 4 allows participants to receive 3 weeks of belimumab SC prior to discontinuing their immunosuppressants. Corticosteroids may be adjusted as necessary during this transition period. If participants in Arms A and B receive immunosuppressants after the Week 4 visit they will be deemed treatment failures for the efficacy endpoints. Participants in Arm C who enter the study on stable immunosuppressants may continue their stable immunosuppressants throughout the study at the discretion of the investigator. If participants in Arm C require an addition of a new immunosuppressant after Week 12 they will be considered a treatment failure. See Section 7.7.1.4 for additional details on management of immunosuppressants.

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. If the investigator believes the participant would benefit from continued steroid taper and, if tolerated, a prolonged corticosteroid taper should continue after Week 26 with the goal of corticosteroid discontinuation. Participants who are able to tolerate the final taper will be withdrawn from corticosteroids. If a participant is unable to tolerate the final stage of the corticosteroid taper, the investigator may reinitiate corticosteroids at a prednisone equivalent dose of up to and including 5 mg/day. If a 7-day average prednisone equivalent dose of >5 mg/day is required at any time after Week 26, the participant will be considered a treatment failure for the efficacy endpoints. The recommended corticosteroid taper scheme is described in Appendix 2.

Anti-malarial therapies for SLE may not be initiated during the study, but may be continued or dose-adjusted during the study, and will be allowed within the definitions of the efficacy endpoints.

During the 52-week double-blind phase, participants in Arms A and B who cannot tolerate discontinuation of immunosuppressants or taper of corticosteroids or, in the opinion of the investigator, require added therapy, will be considered treatment failures for the efficacy endpoints. Blinding to the treatment assignments in Arms A and B will be maintained. At the investigator's discretion, these participants may continue treatment with belimumab, and/or be treated with additional SLE therapies as necessary, including corticosteroids and/or immunosuppressants. Participants in Arm C who are unable to tolerate the corticosteroid taper or, in the opinion of the investigator, require increased doses of their baseline immunosuppressants or addition of a new immunosuppressant will be considered treatment failures for the efficacy endpoints.

Participants in Arms A and B will enter into the 52-week treatment-free, observational phase of the study after completing Week 52 (Weeks 53 through 104). “Treatment-free” refers to no active treatment with study treatment (i.e., belimumab and/or rituximab). Participants in Arm C will continue to receive belimumab SC and their stable immunosuppressants during Weeks 53 through 104. Treatment with anti-malarials, NSAIDs, and/or corticosteroids with a prednisone equivalent dose of ≤5 mg/day will be allowed in Weeks 53 through 104 in all three arms.

During Weeks 53 to 104, additional treatment may be given if the investigator believes the participant would benefit because he/she: a) responded to study treatment but did not meet the primary efficacy endpoint; or b) responded to study treatment but subsequently experienced increasing disease activity which requires additional therapy. Additional treatment may include open-label belimumab, corticosteroids (>5 mg/day), and/or immunosuppressants, and will be administered at the discretion of the investigator. Additional treatment with rituximab is allowed, but not encouraged. Belimumab will be provided by the sponsor to those participants who reinitiate treatment with belimumab, but additional treatment with rituximab and/or other SLE medications will not be provided by the study. These participants will be considered treatment failures for the Week 104 efficacy analyses. Participants who are deemed treatment failures will be encouraged to continue in the study and to have all efficacy and safety assessments.

Additional information on management of participants who receive open-label belimumab and/or rituximab, including the schedule for obtaining immunogenicity samples, is provided in the Study Reference Manual (SRM).

Participants who discontinue study therapy but remain in the study will follow the study visit schedule.

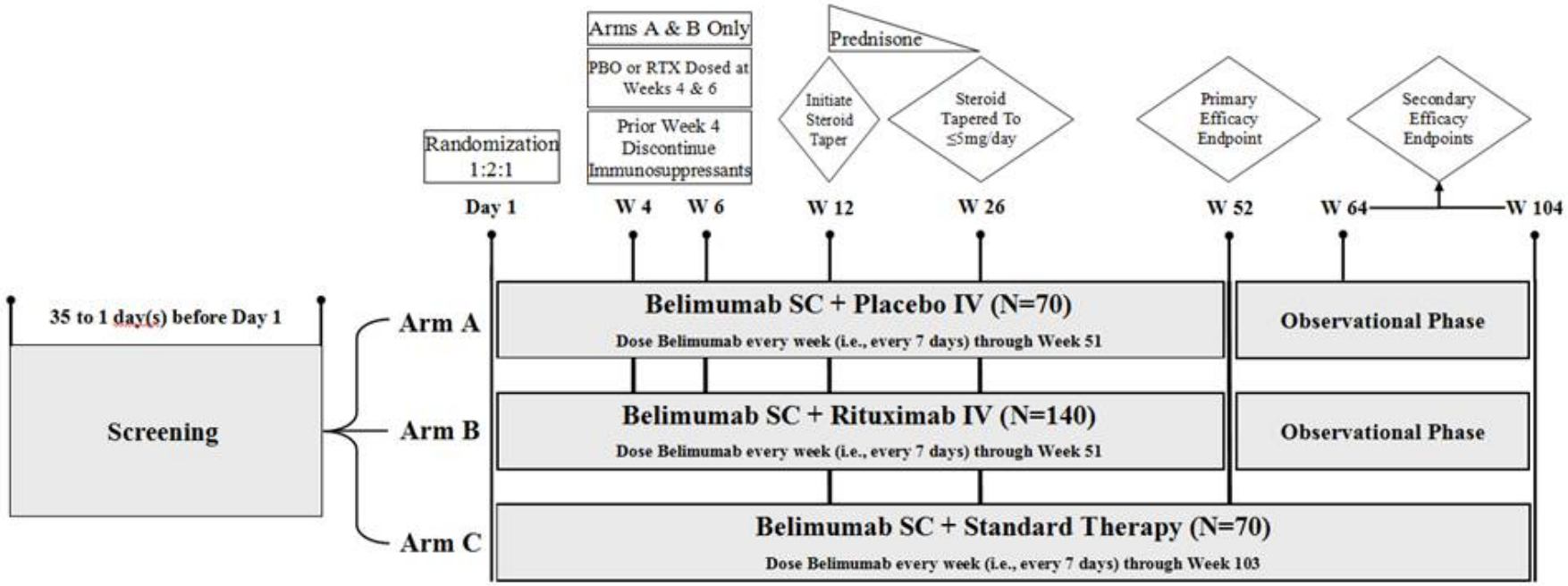
Participants who discontinue study treatment and withdraw from the study up to Week 52 are required to complete an Early Withdrawal Visit and a Follow-up Visit; the Early Withdrawal Visit is scheduled 1 to 4 weeks after the last dose of belimumab and the Follow-up Visit is scheduled 8 weeks after the 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.

Female participants of child bearing potential will have a urine pregnancy test 16 weeks after the last dose of belimumab and/or or monthly for 1 year after the last dose of rituximab or rituximab-placebo, whichever is later.

In the event that a participant withdraws from the study or withdraws consent, an attempt will be made to ascertain survival status at approximately 52 weeks and 104 weeks after the first dose of study treatment.

A study schematic is provided in Figure 1.

Figure 1 Study Schematic



5.2. Number of Participants

A total of approximately 560 participants are expected to be screened, with a goal of randomizing at least 280 participants (50% screen failure rate).

The sample size may be increased up to a maximum of 320 participants if the dropout rate, missing data or number of major protocol deviations suggests further participants are necessary to ensure robust conclusions can be drawn. The decision to increase the sample size will be made without unblinding the trial.

See Section 10.2, Sample size determination.

5.3. Participant and 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 SoA (Section 2).

Participants who discontinue study therapy but remain in the study will follow the study visit schedule.

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.

Women of child bearing potential are required to have a urine pregnancy test 16 weeks after the last dose of belimumab and/or monthly until 12 months after the last dose of rituximab or rituximab-placebo, whichever is later.

Participants who are deemed to meet treatment failure criteria at any time in the study will be encouraged to remain in the study and continue to have all efficacy and safety assessments.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

5.4.1. Selection of Controls

The belimumab plus rituximab-placebo arm (Arm A) will be used as the study control arm because belimumab has demonstrated efficacy in 4 large, controlled, Phase 3 controlled clinical trials, HGS1006-C1056 (referred to hereafter as C1056), HGS1006-

C1057 (C1057), BEL113750, and BEL112341, and remains the only biologic approved for the treatment of SLE. An open-label reference arm of belimumab plus standard therapy, including immunosuppressants (Arm C) is included to provide a qualitative reference to assess the relative performance of Arm A (control) and Arm B (combination) vs. belimumab plus standard SLE therapy in current practice (Arm C, reference).

Belimumab SC 200 mg weekly will be dosed for 51 weeks for Arms A and B since this was the dose and duration of therapy for the primary endpoint in the positive Phase 3 study of SC belimumab (BEL112341). The SC 200 mg weekly dose was selected for study BEL112341 because it provides steady-state average belimumab concentrations similar to those in the 10 mg/kg every 4 weeks dose groups, which were positive for the primary endpoint in the pivotal Phase 3 studies of IV belimumab (C1056 and C1057). Arm B will explore the combination of rituximab (2 doses of 1000 mg IV at Weeks 4 and 6) and 51 weeks of belimumab SC dosing. 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 antihistamine, and an acetaminophen or equivalent.

As rituximab is not approved for the treatment of patients with SLE, no standard dosing regimen is established. In this study, rituximab dosing will follow 1 cycle of the approved dosing recommendation for rheumatoid arthritis (RA) which is 2 IV doses of 1000 mg given in a 2-week interval. This rituximab regimen demonstrated rapid B cell depletion of CD19-positive cells (<5 cells/μL) in approximately 90% of subjects by 2 weeks after the infusions in a large Phase 3 SLE trial [Merrill, 2010].

Rituximab or rituximab-placebo will be dosed at Weeks 4 and 6, after initiation of belimumab and discontinuation of baseline immunosuppressants. Participants who enter the study on immunosuppressants will have these medications discontinued at or prior to the Week 4 visit. The justification for dosing at Week 4 and Week 6 includes: 1) separation of start times for belimumab and rituximab, thereby allowing for observation of safety events which may be attributable to starting treatment with the individual agents, and b) evidence that belimumab may mobilize B cells into the periphery making them available targets for anti-CD20 treatment, thus starting belimumab prior to rituximab may allow more efficient peripheral B cell depletion by rituximab [Stohl, 2012].

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

Participants who:

2. Have a clinical diagnosis of SLE based on 4 or more of the 11 American College of Rheumatology (ACR) criteria (see Appendix 11).

3. Have a screening SLEDAI-2K score ≥6 (This refers to the total score. Serological activity, i.e., anti-double stranded deoxyribonucleic acid [dsDNA]) positivity and/or hypocomplementemia is not required to be present in SLEDAI-2K assessment, but are scored if present).

4. Have unequivocally positive autoantibody test results defined as an anti-nuclear (ANA) titer ≥1:80 and/or a positive anti-dsDNA (≥30 IU/mL) serum antibody test from 2 independent time points as follows:

   - Positive test results from 2 independent time points within the study screening period. Screening results must be based on the study's central laboratory results

   OR

   - One positive historical test result and 1 positive test result during the screening period.

   NOTE: Historical documentation of a positive test of ANA (e.g., ANA by HEp-2 titer) and anti-dsDNA (e.g., anti-dsDNA by Farr assay) that must include the date and type of the test, the name of the testing laboratory, and numerical reference range, whenever available. Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.

Concomitant Medications

5. Are on a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 1 (i.e., day of first dose of study treatment) with the exception that switching one agent for another of the same class for tolerability or availability reasons, which will be allowed within 30 days of Day 1.

   - Corticosteroids (prednisone or prednisone equivalent)
   - For those subjects on alternating daily doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.
   - Any immunosuppressant or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (e.g. tacrolimus, cyclosporine), sirolimus, cyclophosphamide, 6-mercaptopurine, mizoribine, or thalidomide. (Note: oral cyclophosphamide use is exclusionary in Germany)
   - Anti-malarials (e.g., hydroxychloroquine, chloroquine, quinacrine).
   - Non-steroidal anti-inflammatory drugs (NSAIDs).

NOTES:

- Corticosteroids may be added as a new medication or their doses adjusted up to 30 days prior to Day 1.
- New SLE therapy other than corticosteroids must not be added within 60 days prior to Day 1.

6. Male and/or female

   A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 16 weeks after the last dose of belimumab, or at least 12 months after the last dose of rituximab or rituximab-placebo, whichever is later.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 4 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Symptomatic herpes zoster within 3 months prior to screening.
2. Evidence of active or latent tuberculosis (TB). Documentation may include medical history and examination, chest X-rays (posterior, anterior, and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration ≥5 mm at 48 to 72 hours, regardless of Baccillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON-TB Gold Plus test.

   NOTE: The choice to perform a TST or a QuantiFERON-TB Gold Plus test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.

3. Significant allergies to humanized monoclonal antibodies.
4. History of hypersensitivity to belimumab and/or rituximab or known to have titers of human anti-mouse antibody or history of hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. Alanine transferase (ALT) >2x upper limit of normal (ULN).
7. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. IgA deficiency (IgA level < 10 mg/dL).
9. IgG < 250 mg/dL. (Note: <400 mg/dL for Germany only)
10. Neutrophils < 1.5 x $10^{9.}$
11. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.
12. Severe heart failure (New York Heart Association Class IV) or other severe, uncontrolled cardiac disease.
13. QTc >450 msec or QTc >480 msec in participants with bundle branch block.

NOTES:

- The QTc is the QT interval corrected for heart rate according to Bazette's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually overread.

14. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
15. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, psychiatric, malignancy, or infectious diseases) which, in the opinion of the principal investigator, could confound the results of the study or put the subject at undue risk.
16. Have an acute or chronic infection requiring management as follows:

    - Currently on any suppressive therapy for a chronic infection such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria.
    - Hospitalization for treatment of infection within 60 days of Day 1.
    - Have had infection requiring treatment with parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 1. Prophylactic anti-infective treatment is allowed.

17. Have severe lupus kidney disease (defined by proteinuria >6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine >2.5 mg/dL), or have severe active nephritis requiring induction therapy not permitted by protocol (e.g., IV cyclophosphamide), or have required hemodialysis or high dose prednisone or equivalent (>100 mg/day) within 90 days of Day 1.

18. Have severe active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis, or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 1.
19. Have a planned surgical procedure, laboratory abnormality, or condition (e.g., poor venous access) that, in the opinion of the principal investigator, makes the subject unsuitable for the study.
20. Have evidence of serious suicide risk, including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 2 months or who, in the investigator's opinion, pose a significant suicide risk.
21. Have a history of an anaphylaxis reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies.

Prior/Concomitant Therapy

22. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the screening period or during the study.
23. Have received any of the following within 364 days of Day 1:
    - Belimumab.
    - Rituximab.
    - Abatacept.
    - Any B cell targeted therapy (anti-CD20 agents other than rituximab, anti CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI Fc, anti-BAFF (LY2127399), anti-Interferon alpha agents or anti-BLyS other than belimumab).
    - A biologic investigational agent other than B cell targeted therapy (e.g., abetimus sodium, anti CD40L antibody [BG9588/ IDEC 1311]). (Investigational agent applies to any drug not approved for sale in the country in which it is being used.)
24. Have required 3 or more courses of systemic corticosteroids (e.g., IV pulse therapy or high dose oral treatment) within 364 days of Day 1. (Topical or inhaled steroids are permitted.)
25. Have received any of the following within 90 days of Day 1:
    - Anti-TNF therapy (e.g., adalimumab, etanercept, infliximab)
    - Interleukin-1 receptor antagonist (anakinra)
    - Intravenous immunoglobulin (IVIG)
    - High dose prednisone or equivalent (>100 mg/day)
    - Plasmapheresis.
26. Have received any of the following within 60 days of Day 1:
    - A non-biologic investigational agent (Investigational agent applies to any drug not approved for sale in the country in which it is being used.)

- Intravenous (IV) cyclophosphamide and, for Germany only, oral cyclophosphamide
- Any steroid injection (e.g., intramuscular [IM], intraarticular, or IV).

NOTE: New inhaled and topical steroids and new topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed. Any NSAID use for <1 week is allowed.

Diagnostic assessments

27. Positive immunodeficiency virus (HIV) antibody test.
28. Positive serology for Hepatitis B, defined as (i) HB surface antigen positive (HBsAg+) OR (ii) HB core antibody positive (HBcAb+).
29. Positive Hepatitis C (HCV) antibody test.

Other Exclusions

30. Have current drug or alcohol dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 1.
31. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicates participation in the study.
32. Unable to administer study treatment (belimumab) by SC injection and has no other reliable resource to administer the injection.

6.3. Lifestyle Restrictions

No restrictions are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria. SAEs are collected during screening if they are related to study participation.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time; all screening procedures must be repeated.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	**Belimumab (GSK1550188)**	**Rituximab**	**Rituximab-placebo**
Dosage formulation:	Sterile, liquid product.	Sterile, liquid concentrate.	
Unit dose strength(s)/Dosage level(s):	200 mg/mL; 1mL (deliverable)	500 mg/50 mL (single-use vial)	
Route of Administration	SC injection	IV infusion	IV infusion
Dosing instructions:	Once weekly SC injection via autoinjector in thigh or abdomen	1000 mg IV infusion at Week 4 and Week 6	IV infusion at Week 4 and Week 6
Packaging and Labeling:	Belimumab will be provided in cartons (5 auto-injectors/carton). Each carton will be labeled as required per country requirement.	Rituximab will be provided as a single 50 mL vial in its original carton. Each carton will be labeled as required per country requirement.	Placebo is saline in 250 mL bags, sourced locally

Study Treatment Name:	**Belimumab (GSK1550188)**	**Rituximab**	**Rituximab-placebo**
Manufacturer:	**Prefilled syringe:** Prefilled syringe components are procured from Becton Dickinson. Prefilled syringe is filled with drug product and assembled at GSK, Barnard Castle, UK. **Autoinjector:** The autoinjector components are manufactured by Scandinavian Health Limited (SHL) and assembled with the prefilled syringe at GSK, Barnard Castle, UK.	**Single-Use Vial:** Refer to local rituximab approved label.	
Device:	Single-use autoinjector	Not applicable	Not applicable

7.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices: a prefilled syringe contained within an autoinjector device.
- Instructions for medical device use are provided to the participant upon enrollment.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study. (See Section 9.7).

7.2. Dose Modification

No dose modifications of belimumab or rituximab/rituximab-placebo are allowed.

7.3. Method of Treatment Assignment

All participants will be assigned to study treatment in accordance with the randomization schedule and randomization must occur before any investigational product is administered. Participants will be centrally randomized using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. A participant will be assigned a subject number at the time the informed consent is signed. Once a subject number has been assigned to a participant, it cannot be re-assigned to another participant.

A randomization schedule will be generated with the following treatment assignments:

Arm	Treatment Description
A	Belimumab SC for 52 weeks + Rituximab IV Placebo at Weeks 4 and 6
B	Belimumab SC for 52 weeks + Rituximab IV 1000 mg at Weeks 4 and 6
C	Belimumab SC plus standard therapy for 104 weeks

Study treatment will be dispensed at the study visits summarized in the SoA (Section 2). Returned study treatment should not be re-dispensed to the participants. In the event that a subject is unable to attend their planned study visit (see Section 2) to receive their carton of belimumab autoinjectors, if allowable under local regulations and approved by the sponsor, the investigator may with the agreement of the subject arrange to have the autoinjectors dispensed and shipped directly to the subject.

At least 280 participants will be randomized in a 1:2:1 ratio to 1 of 3 treatment groups: belimumab plus rituximab-placebo (Arm A, target N=70), belimumab plus rituximab (Arm B, target N=140), or belimumab plus standard therapy (Arm C, target N=70). Randomization of participants will be stratified by screening SLEDAI-2K score (≤9 vs. ≥10), immunosuppressant use at screening (immunosuppressant use vs. no use), and screening corticosteroid dose (prednisone equivalent ≤10 mg/day vs. >10 mg/day).

7.4. Blinding

The study is double-blind with regard to whether participants are randomized to Arm A (belimumab plus rituximab-placebo) or Arm B (belimumab plus rituximab). Randomization to Arm C will not be blinded. In order to minimize bias given that Arm C is open-label, independent assessors blinded to treatment group (A, B, or C) will conduct the SLEDAI-2K assessments at selected visits, including those that are components of the primary and major secondary endpoints, on the schedule provided in the SoA (Section 2).

Investigators and the Sponsor/Study Team will remain blinded to the results of the B cells subsets because those data could potentially unblind whether or not the participant received rituximab.

An unblinded pharmacist will be used at each study site to prepare rituximab and its placebo for IV administration. Unblinded monitors will be assigned to review all pharmacy records, storage, and procedures.

The IWRS will be programmed with blind-breaking instructions. In case of emergency, the investigator has the sole responsibility for determining if unblinding a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic Case Report Form (eCRF), as applicable.

An unblinded pharmacist at each site will be assigned to use the IWRS randomization software, to order and to receive all drug shipments and notifications.

A participant may continue in the study if that participant's treatment assignment is unblinded by the investigator or treating physician. The event or condition which led to the unblinding will be recorded in the eCRF.

An Independent Data and Monitoring Committee (IDMC) will conduct periodic reviews of unblinded data to ensure external objective and/or statistical review of safety issues (see Section 10.4.4). The composition, remit, and procedures of the IDMC are provided in the IDMC Charter.

Review and adjudication of treatment failures, AEs of special interest and protocol deviations will be performed by blinded individuals in preparation for the Week 52 and end of study data base locks (DBLs). Subject level data will not be shared with site personnel until after the end of study reporting is complete.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with a Serious Adverse Event (SAE) for purposes of regulatory reporting. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or

automated) area in accordance with the labeled storage conditions with access limited to authorized unblinded site staff, e.g., unblinded pharmacist.

3. The investigator, institution, the head of the medical institution or delegate (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- The first dose of belimumab will be administered by the participant at the clinical site under medical supervision. (Participants may be assisted in administration of their SC dose of belimumab at this first dose and with subsequent doses.) Participants will remain in the clinic for at least 3 hours for observation. The date and time of the dose administered in the clinic will be recorded in the Patient Diary.

  NOTE-1: If a participant misses a dose of belimumab on the scheduled day of administration, instruct the participant to self-administer the missed dose as soon as possible during that dosing week. If subject did not self-administer the dose by end of the weekly dosing period, SKIP that dose. The participant should not administer two doses on the same day and two doses should not be administered to make up for a dose missed for a full 7 day dosing window. Thereafter, the subject can resume self-administering belimumab weekly on their usual day of administration.

  NOTE-2: If a participant has administered a partial dose or was unable to completely self-administer a dose of belimumab due to malfunction of the autoinjector or user error, instruct the subject to SKIP additional attempts and not re-inject for that week's belimumab dose. Thereafter, the subject should resume self-administering belimumab weekly on their usual day of administration during the following weekly dosing period. The participant should not self-administer 2 doses on the same day, even if they believe that they did not receive any medication from the first administration attempt. (See Section 9.7.8 - Device Malfunction).

  NOTE 3: Participants who miss 4 or more consecutive doses of belimumab must receive the next dose of belimumab in the clinic and remain in the clinic for at least 3 hours for observation as with the initial belimumab dose.
  The site should contact the Medical Monitor if participants miss 8 or more consecutive doses of belimumab to evaluate continuation in the study.

- When participants self-administer study treatment at home, compliance with belimumab will be assessed through review of the self-injection patient diary with each participant during site visits and documented in the source. A record of the number of belimumab autoinjectors dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays will also be recorded in the eCRF.
- Rituximab or rituximab-placebo will be administered IV to participants at the site or infusion center, following administration of the premedication regimen. Administration of the premedication regimen and the rituximab or rituximab-placebo will be documented in the source documents and reported in the eCRF, including whether the full infusion was administered and over what period of time. Study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

7.7. Concomitant Therapy

This section reviews the medications and the doses allowed and prohibited during the course of the study.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from the start of treatment until the follow-up visit at the time points specified in the SoA must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Allowable Medications

Participants must be on a stable SLE treatment regimen for at least 30 days prior to Day 1 (see Section 6.1). These medications may include corticosteroids, anti-malarial agents, immunosuppressant agents and nonsteroidal anti-inflammatory agents (NSAIDs).

New SLE therapy other than corticosteroids must not be added within 60 days of Day 1.

Once a participant is randomized and receives the 1st dose of study agent on Day 1, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the participant being defined as a treatment failure. Rules regarding declaring a participant as a treatment failure may vary according to timing and are handled differently in Arms A and B vs. Arm C. Participants declared treatment

failures are encouraged to remain in the study and receive all efficacy and safety assessments through Week 104.

7.7.1.1. Anti-malarials

Anti-malarial therapies for SLE may be continued or dose adjusted during the study, and will be allowed within the definitions of the efficacy endpoints. A new anti-malarial (e.g., hydroxychloroquine, chloroquine, quinacrine) may not be started during the course of the study for SLE. Starting any new anti-malarial treatment for SLE after Day 1 will declare the participant a treatment failure.

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.

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.

Clinical loading dose is permitted for initiation or replacement.

NOTE: The use of anti-malarials for anti-malarial prophylaxis is permitted.

7.7.1.2. Corticosteroids

Received dose for all systemic corticosteroids will be converted to prednisone equivalent dose. As such, when “prednisone” is used throughout this protocol, it refers to prednisone dose or equivalent.

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

At baseline, the average daily dose of corticosteroids is the sum of corticosteroid dose over 7 consecutive days up to, but not including Day 1, divided by 7. While on study

treatment, the average daily dose of corticosteroids is the sum of all corticosteroid doses over 7 consecutive days up to and including the day of interest, divided by 7, unless otherwise specified.

Participants may enter the study on any prescribed dose of corticosteroids. If a participant is not receiving corticosteroid therapy on study Day 1, once the subject is randomized and receives the 1st dose of study agent on Day 1, the investigator may add corticosteroid medication as clinically required (for example, in order to manage the transition period for discontinuing immunosuppressants by Week 4). Dosage of corticosteroids may be adjusted as clinically necessary until Week 12. After the initial 12 weeks of the study, a protocol specified corticosteroid taper is recommended to begin and should be initiated and conducted under the direction of the investigator. The taper will proceed with a target of reaching a prednisone equivalent dose of ≤5 mg/day by Week 26. The recommended corticosteroid taper scheme is described in Appendix 2. Corticosteroids may be adjusted as clinically necessary through Week 26, participants will not be declared treatment failures unless they are not able to successfully taper to a 7-day average prednisone equivalent dose of ≤5 mg/day after Week 26. For purposes of defining treatment failure, after Week 26, the average daily dose of corticosteroids is the sum of corticosteroid dose on the 7 days immediately following the Week 26 visit, divided by 7 (the corticosteroid dose on the day of the Week 26 visit is not included in the calculation). After Week 26, if a participant's average daily dose of corticosteroid exceeds a prednisone equivalent dose of 5 mg/day at any time the participant will be declared a treatment failure. (The date of treatment failure will be the end of the 7-day interval which meets the treatment failure rule.)

If the investigator believes the participant would benefit from continued corticosteroid taper after Week 26, and if it is tolerated, a prolonged corticosteroid taper should continue with the goal of discontinuing corticosteroids. Recommendations for the schedule of this taper are included in Appendix 2. Participants who are able to tolerate the final taper will be withdrawn from corticosteroids. If a participant is unable to tolerate the final stage of the corticosteroid taper, the investigator may reinitiate corticosteroids at a prednisone equivalent dose of up to and including 5 mg/day. If a 7-day average prednisone equivalent dose of >5 mg/day is required at any time after Week 26, the participant will be considered a treatment failure for the efficacy endpoints. Participants who are declared treatment failures are encouraged to remain in the study through Week 104 and receive all safety and efficacy assessments.

For purposes of assessing the major secondary endpoint at Week 64 (the proportion of participants with a state of clinical remission, defined as a Clinical SLEDAI-2K score = 0), achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64), participants must be on a dose of 0 mg/day on the 7 days immediately following the Week 64 visit (the corticosteroid dose on the day of the Week 64 visit is not included in the calculation).

Intraarticular Injections:

- Participants may receive intraarticular injections during the study with the exception of within 8 weeks prior to the key efficacy endpoints (i.e., Weeks 52, 64, and 104). A

participant who receives any intraarticular injection(s) within 8 weeks before the Week 52, 64, and/or 104 visits will be defined as a treatment failure.

7.7.1.3. 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.

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

7.7.1.4. Other Immunosuppressant Agents

Belimumab SC 200 mg/week will be initiated in all treatment arms on Day 1 of the study. Participants who enter the study on immunosuppressant therapy in Arms A and B will continue their stable immunosuppressant regimen until up to Week 4. At or prior to the Week 4 visit, immunosuppressants will be discontinued. Corticosteroids may be adjusted as necessary during this transition period. Participants in Arm C may continue their immunosuppressant agents throughout the study.

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.

For participants in Arms A and B, the dose of existing immunosuppressant agents may be adjusted, as clinically required, up to the Week 4 visit. Any existing immunosuppressant agents will be discontinued at or prior to the Week 4 visit for Arms A and B.

Participants in Arm C may continue their existing immunosuppressant agents throughout the course of the study. Dosage of existing immunosuppressant agents may be increased as clinically necessary until Week 12. 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 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 (Note: use not permitted in Germany)
- Cyclosporine – 4 mg/kg/day*
- Tacrolimus – 0.2 mg/kg/day*
- Sirolimus – 2 mg/kg/day*
- Thalidomide – 200 mg/day
- Leflunomide – 40 mg/day*
- Mizoribine – 150 mg/day

*Clinical loading dose is permitted when replacing immunosuppressant agents. Monitor blood levels as clinically indicated.

An immunosuppressant agent may be replaced with one of the agents above due to documented toxicity or lack of availability. For other immunosuppressant agents not listed above, the investigator must contact the Medical Monitor for approval.

New topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed after Day 1.

7.7.1.5. Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Aspirin, and Acetaminophen

Since NSAIDs and aspirin may affect efficacy parameters (e.g., arthritis) and may affect renal function (NSAID nephropathy), the use of these agents should be initiated and stabilized prior to entry into the trial.

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.

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.

An NSAID may be replaced with another NSAID due to documented toxicity or lack of availability.

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.

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.

7.7.2. Prohibited Medications and Non-Drug Therapies

Participants who start prohibited medications or therapies at any time during the study will be considered treatment failures for analysis (i.e., non-responders). The Medical Monitor must be contacted to discuss the appropriateness of continuing study treatment. The following medications and therapies are prohibited at any time during the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used.
- Co-enrollment into another study of a different investigational agent or that may interfere with the conduct of this protocol.
- Anti-TNF therapy (e.g., adalimumab, etanercept, infliximab).
- Other biologics with effects on the immune system (e.g., abatacept, interleukin-1 receptor antagonist [anakinra]).
- IVIG.
- IV cyclophosphamide and for Germany only, oral cyclophosphamide
- Plasmapheresis.

7.7.3. Live Vaccines

Live vaccines are not permitted in the study. Participants who require a live vaccine during the study should have study agent discontinued prior to receiving the live vaccine.

7.7.4. Additional SLE Therapy

In the 52-week, double-blind treatment phase, participants in Arms A or B who fail to adequately respond to study treatment or in the medical judgment of the investigator

cannot meet the corticosteroid taper rules, tolerate immunosuppressant withdrawal at Week 4, or who will require additional therapy will be considered treatment failures. Participants who are treatment failures will be encouraged to remain in the study and receive all safety and efficacy assessments through Week 104. At the discretion of the investigator, the participant may continue to receive belimumab SC 200 mg/week. If additional medical treatment is necessary it will also be at the discretion of the investigator and may include corticosteroids and/or immunosuppressants.

In the 52-week observational phase (Weeks 53 to 104), participants in Arms A and B may continue or reinitiate open-label belimumab SC 200 mg weekly treatment if (a) they responded clinically in the 52-week treatment phase of the study but did not meet the primary efficacy endpoint, or (b) responded clinically but subsequently experienced an increase in disease activity requiring treatment. If a participant requires rescue therapy in addition to the re-initiation of treatment with belimumab, corticosteroids >5 mg/day of a prednisone equivalent and/or immunosuppressants may be given at the discretion of the investigator. Reason for rescue therapy and medication dosing requirements should be documented in source records. Treatment with open-label rituximab is allowed, but not encouraged. Belimumab will be provided by the study, but other SLE treatments, including rituximab, will not be provided by the sponsor. In these situations the participants in Arms A or B would be considered treatment failures for the efficacy endpoints. Participants who are declared treatment failures will be encouraged to remain in the study and continue to receive all safety and efficacy assessments. Additional information on management of participants who receive open-label belimumab and/or rituximab, including the schedule for obtaining immunogenicity samples, is provided in the SRM.

Participants in Arm C will continue to receive belimumab during Weeks 53 to 104. Participants in Arm C who, in the opinion of the investigator, require additional treatment, may receive rescue therapy including corticosteroids >5 mg/day of a prednisone equivalent and/or new, additional or increased immunosuppressants at the investigator's discretion. Treatment with open-label rituximab is allowed, but not encouraged. Other SLE treatments, including rituximab, will not be provided by the study. In these situations, the participants in Arm C would be considered treatment failures for the efficacy endpoints. Participants who are declared treatment failures will be encouraged to remain in the study and continue to receive all safety and efficacy assessments.

Management of additional SLE therapy, including required laboratory tests and other procedures, is described in the SRM.

7.8. Treatment after the End of the Study

At the end of the study, participants who wish to continue treatment with belimumab may do so by being prescribed commercially available belimumab.

8. DISCONTINUATION CRITERIA

8.1. Withdrawal from the Study

Participants are free to withdraw from the study at any time, for any reason. Participants may withdraw consent, including use and disclosure of research-related health information at any time, for any reason. Participants may be withdrawn/removed, if necessary, by the investigator or the sponsor for safety, behavioral, administrative, or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

In addition, for participants who are WOCBP who receive rituximab or rituximab-placebo at the Week 4 visit, or at both the Weeks 4 and 6 visits, but who discontinue the study prior to the Week 60 visit, maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until 12 months after the last dose of rituximab or rituximab-placebo was administered.

8.2. Discontinuation of Study Treatment

Participants who discontinue study treatment should be encouraged to continue to participate in study visits in accordance with the SoA (Section 2), especially all remaining safety evaluations.

If a participant experiences a clinically significant AE that the investigator believes may be definitely, possibly, or probably related to study treatment and could potentially be exacerbated by the next dose, the investigator may delay study treatment dosing by up to one week or withhold one dose. If a similar concern is present at the time of the next scheduled dose, the investigator should contact the Medical Monitor to determine whether treatment with belimumab or rituximab (or rituximab-placebo) should be postponed further or discontinued.

Participants may be withdrawn from study treatment for any of the following reasons:

- Prohibited concurrent medication or therapy or prohibited dose of concurrent medication or therapy (see Section 7.7.2).
- Unacceptable toxicity.
- Pregnancy will require withdrawal from study treatment, belimumab and/or rituximab when the pregnancy is recognized. Maintenance of contraception and monthly telephone calls for urine pregnancy test results will be required until 12 months after the last dose of rituximab or rituximab-placebo was administered. Participants who become pregnant during the study will be encouraged to remain in the study to be followed for all efficacy and safety assessments including the course and outcome of the pregnancy. If the outcome of the pregnancy occurs after a subject completes or leaves the study, attempts

will be made to obtain follow up information, including the outcome of the pregnancy.

NOTE: (Germany only): Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.

All participants should be monitored closely for infection. Participants who develop IgG <250 mg/dL confirmed by repeat test 1 week (>2 days) after the initial result, will have study treatment withheld, and the investigator must contact the Medical Monitor to determine if study treatment should be continued. In addition, increased vigilance for infection is recommended in participants who develop IgG <550 mg/dL. Those with a decrease in IgG below 400 mg/dL that is associated with a serious infection (i.e., an infection reported as an SAE) will be withdrawn from study treatment. In addition, if any participant develops a life-threatening infection regardless of IgG status, the investigator must contact the Medical Monitor to determine whether study treatment should be continued.

Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported with the use of rituximab. In case of such an event, treatment should be permanently discontinued.

A participant will be withdrawn from study treatment if he or she meets liver stopping criteria (defined in Section 8.2.1), presents with suicidal ideation of type 4 or 5 on the C-SSRS, or in the investigator's judgment, the participant is at risk for a suicide attempt. Participants who are withdrawn from study treatment will remain in the study for observation and continue to have all safety and efficacy assessments.

For any study participants exhibiting symptoms consistent with COVID-19, please consider holding dosing of investigational product (IP) and consult with the Medical Monitor. If a participant tests positive for COVID-19, or if no testing is available, hold dosing of IP until symptoms resolve and contact the Medical Monitor. If a positive COVID-19 test result is reported, please consult with the Medical Monitor on whether resolution of symptoms alone, without retesting, is enough to resume dosing of the investigational product.

8.2.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

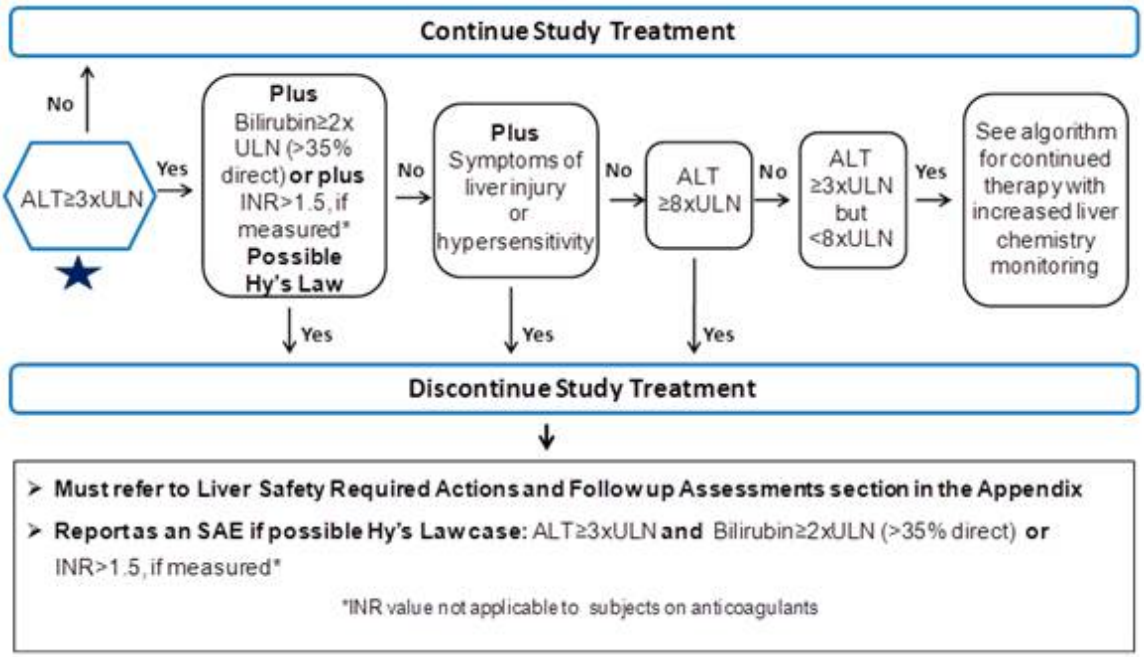
Discontinuation of study treatment is required when:

- a participant meets one of the conditions outlined in **Algorithm A** or **Algorithm B**

OR

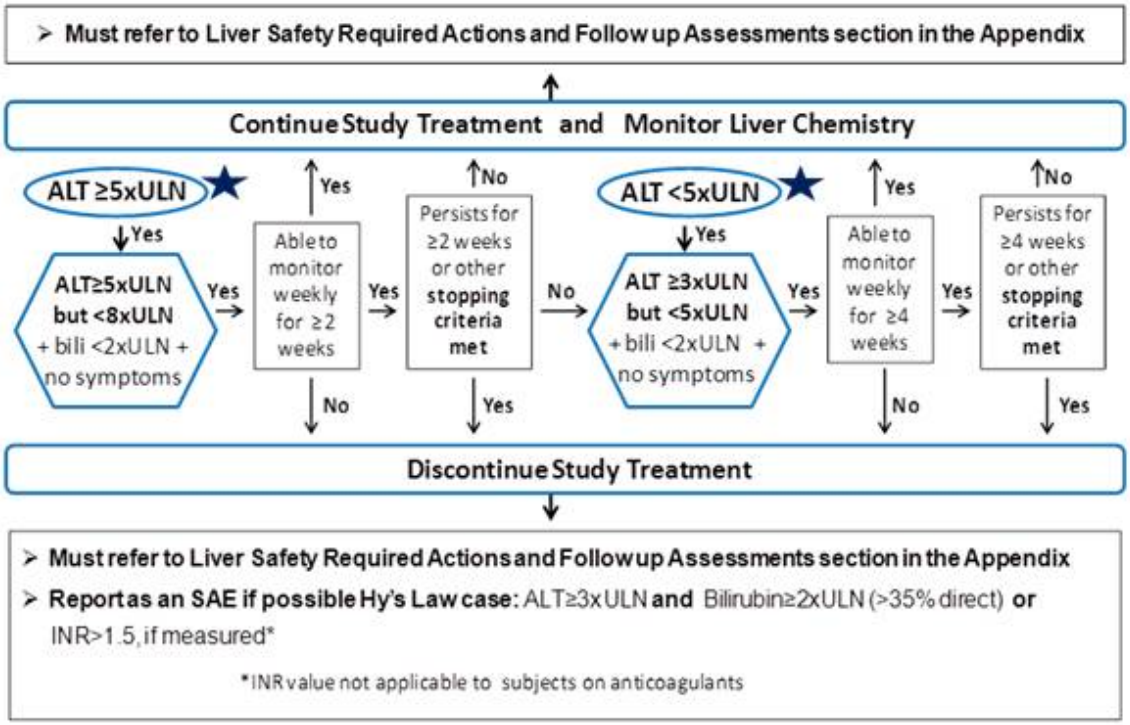
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation it is in the best interest of the participant.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



See Appendix 5 for liver safety required actions and follow-up assessments.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



See Appendix 5 for liver safety required actions and follow-up assessments.

8.2.2. Study Treatment Restart

If participant meets liver chemistry stopping criteria do not restart participant with study treatment unless:

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant

Refer to Appendix 6 for full guidance.

8.3. Temporary Discontinuation and Re-Start of Belimumab

Study treatment with belimumab (Arms A/B and C) must be temporarily withheld and the GSK medical monitor consulted about continued dosing if a subject experiences a neutrophil count $<0.5x10^9$/L.

Withdrawal of study treatment does not require withdrawal from the study; participants who discontinue study treatment should be encouraged to continue the study with all safety and efficacy assessments. Participants who miss 4 consecutive doses of belimumab must have the next dose of belimumab in the clinic and stay for observation for 3 hours.

8.4. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, compliance, administrative or other reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.5. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
    - The maximum amount of blood collected from each participant over the two year duration of the study for study related assessments, including any extra assessments that may be required, will not exceed 1100 mL, with the exception of additional blood required for the Blood Leukocyte analysis as specified below.
        - Additional blood (2 samples of 40 mL each in Year 1 and 2 samples of 40 mL each in Year 2) for the Blood Leukocyte analysis will be collected from participants from US study sites. If a participant in the Blood Leukocyte analysis withdraws from the study and completes an Early Withdrawal Visit, a 40 mL sample will be collected at the Early Withdrawal Visit.
        - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Screening Assessments

Information collected during the screening phase assessments represent key data that identify and define participant baseline status. This information is critical for the evaluation and comparison of subsequent safety and efficacy assessments.

Informed Consent

Informed consent will be obtained from the participant prior to the initiation of any study procedures or study-specific data collection.

Participants who give written consent will enter a screening period of up to 35 days. A participant may be randomized when all screening procedures have been completed and eligibility criteria confirmed.

Screening Assessments

During the screening period the following assessments will be performed:

Demographic parameters will be captured: year of birth, sex, race, and ethnicity.

Medical history/medication will be assessed as related to the exclusion criteria listed in Section 6.2. A complete medical history will be taken at the Screening Visit. Information from the medical history is important to establish the baseline condition of the participant, and will impact the safety monitoring assessments during the study. Any significant medical conditions affecting the participant in the past 5 years should be

recorded on the Medical conditions page of the eCRF. The history should include the following:

- Past or current conditions
- Prior surgical procedures
- Pharmacotherapy and chronic or current use of any medication or herbal preparation
- Prior use of belimumab and/or rituximab
- Allergies and significant allergic reactions
- Significant infections, or history of recurrent infection, including urinary and respiratory tract infections
- Smoking history (current or previous smoker, number of cigarettes smoked per day)
- Cardiovascular medical history/risk factors (as detailed in the eCRF).

Pregnancy Test

A serum pregnancy test will be performed for women of child-bearing potential at the Screening Visit and a urine pregnancy test will be performed during each subsequent clinic visit. Refer to the pregnancy section (Section 9.7.6). (Argentina only: Additional urine pregnancy tests will be performed at specified study weeks (i.e., non visit weeks) during study year 2 (see SoA in Section 2).

Full physical examination

The full physical examination will include complete assessment of all organ systems including assessments of the head and neck (including eyes, ears, nose, throat, and thyroid gland), skin, musculoskeletal (including evaluation of both small and large joints), neurological, respiratory, and cardiovascular systems, gastrointestinal system, and abdomen (including liver and spleen), lymph nodes and extremities.

Electrocardiogram

A single 12-lead ECG will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Laboratory tests

The following laboratory tests will be performed at screening, as related to the eligibility criteria described in Section 6.2.

- Autoantibodies and complement
- HIV, hepatitis B and Hepatitis C screen
- Immunoglobulin (IgG, IgA, IgM)

- Urinalysis
- Hematology and blood chemistry
- Drug and alcohol screen
- PT/PTT

Repeat samples may be taken for retesting for technical issues with the samples. If the investigator decides to repeat a laboratory test of an abnormal (exclusionary) value, it is recommended that the investigator contact the study team for additional consultation. Sharing the relevant medical history and current findings with the GSK Medical Monitor would help to determine if re-testing is warranted.

SLEDAI-2K

The SLEDAI-2K is a clinical index for measuring SLE disease activity in the previous 10 days.

9.2. Assessments at Baseline

Procedures at the Baseline Visit are listed in the SoA (Section 2). They include clinical and efficacy assessments, patient reported outcome (PRO) assessments, laboratory tests, pharmacokinetics, pharmacogenetics, biomarkers and blood samples for immunogenicity. The interim medical history, including SLE medications, should be reviewed to assure that the participant's eligibility for the study has not changed. Additional information about these procedures are provided in Section 9.6 (clinical and efficacy), Section 9.6.1 (patient reported outcome assessments), Section 9.9.4 (laboratory tests), Section 9.10 (pharmacokinetics), Section 9.11 (pharmacodynamics), Section 9.12 (genetics), Section 9.13 (biomarkers) and blood samples for immunogenicity (Section 9.13.1) and in the SRM.

9.3. Assessments at Scheduled Visits

Procedures at the Scheduled Visits are listed in the SoA (Section 2). They include clinical and efficacy assessments, patient reported outcome assessments, laboratory tests, pharmacokinetics, biomarkers, and blood samples for immunogenicity. Time windows are provided for each study visit to allow flexibility in site and participant scheduling. All study visits should occur within the visit window of the scheduled study visit. Additional information about these procedures are provided in Section 9.6 (clinical and efficacy), Section 9.6.1 (patient reported outcome assessments), Section 9.9.4 (laboratory tests), Section 9.10 (pharmacokinetics), Section 9.11 (pharmacodynamics), Section 9.13 (biomarkers) and blood samples for immunogenicity (Section 9.13.1) and in the SRM. Participants who are deemed treatment failure and/or discontinue study treatment, but remain in the study, will follow the study visit schedule.

9.4. Assessments at Unscheduled Visits

Unscheduled visits may be performed for a variety of reasons, including safety. The specific procedures to be performed at an Unscheduled Visit depend on the reason for the

Unscheduled Visit. Additional information on the procedures to be performed at an Unscheduled Visit is provided in the SRM.

Note: if a subject is unable to attend their scheduled visit, for example as a consequence of restrictions related to the COVID-19 pandemic, for continued safety monitoring, the investigator should contact the subject by telephone or video call to review adverse events (including suicidal ideation/behavior and neurological symptoms), concomitant medications and ongoing SLE treatments including belimumab. These reviews will be documented in the source records and the eCRF. Such telephone/video contacts may be recorded as unscheduled visits. No attempt should be made to perform efficacy assessments at these telephone/video contacts.

9.5. Assessments at Early Withdrawal Visits and Follow-up Visits

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. Procedures at the Early Withdrawal Visits and Follow-up Visits are listed in the SoA (Section 2).

9.6. Efficacy Assessments

Overview

Planned time points for all efficacy assessments are listed in the SoA (Section 2). At selected time points, the SLEDAI-2K is performed by independent assessors who are blinded with regard to the treatment group assignment. Time windows are provided for each study visit to allow flexibility in site and participant scheduling. All study visits should occur within the visit window of the scheduled study visit. Details regarding the conduct of the efficacy assessments described below are provided in the SRM. In addition, information from the SLEDAI-2K, PGA, laboratory tests, use and doses of SLE medications, and clinical evaluations will be used to calculate the Lupus Low Disease Activity State (LLDAS) [Franklyn, 2016].

SLEDAI-2K

The SLEDAI-2K is a clinical index for measuring SLE disease activity in the previous 10 days.

Physician's Global Assessment

The Physician's Global Assessment (PGA) is a physician-reported visual analogue scale that provides an overall measure of the participant's current disease activity.

SLICC-ACR Damage Index

The Systemic Lupus International Collaborating clinics (SLICC) -American College of Rheumatology (ACR) Damage Index measures irreversible changes occurring since the diagnosis of SLE.

SLE Flare Index

The SLE Flare Index identifies whether a participant has experienced a mild/moderate or severe flare.

Lupus Low Disease Activity State

The Lupus Low Disease Activity State (LLDAS) incorporates multiple measures of disease activity, specifically:

- 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
- Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs.

9.6.1. Patient-Reported Outcomes Assessments

Patient-Reported Outcome (PRO) questionnaires will be completed by participants at clinic visits on the schedule outlined in the SoA (Section 2). PRO questionnaires should be completed by participants, whenever possible before the investigator's safety evaluation and efficacy assessment (e.g., SLEDAI-2K) at a clinic visit, in the order specified in the SRM. Patient interviews (post-treatment and exit interviews) will be conducted in a subgroup of participants, as described below.

Patient Global Assessment

The Patient Global Assessment (PtGA) asks participants to rate the severity of their SLE between 0 (CCI [redacted]) and 10 (CCI [redacted]) that best represents their current level of disease activity. ("Considering all of the ways your systemic lupus erythematosus (lupus) affects you, how do you feel your lupus is today?")

FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy - Fatigue Scale (FACIT-Fatigue) version 4.0 includes 13 fatigue-related items that ask patients to rate fatigue during the previous 7 days, yielding an overall score from 0 to 52, with lower scores representing worse fatigue (www.facit.org). The use of the FACIT-fatigue scale in SLE patients has been validated by Lai et al [Lai, 2011] and together with results from other studies including Cella and colleagues [Cella, 2005], an MCID of ≥4 was concluded [Lai, 2011].

LupusQoL

The LupusQoL is a valid SLE-specific health related qualify of life (HRQOL) instrument with 34 questions across 8 domains. Questions are related to the patient experience in the prior 4 weeks, and a 5-point Likert response format is used, ranging from 0 (CCI CCI to 4 (CCI). A LupusQoL summary score for each domain is reported on a 0 to 100 scale, with greater values indicating better HRQOL [McElhone, 2007].

WPAI: Lupus

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a measure of overall work impairment that discerns time missed from work and impairment of work and regular activities due to a specific disease or health problem. WPAI outcomes include work time missed, impairment while working, overall work productivity impairment and activity impairment expressed as impairment percentages with higher percentages implying greater impairment and less productivity [Reilly, 1993]. The WPAI: Lupus reflects the impairments due to lupus.

Patient Interviews

Patient interviews will provide a qualitative summary of participants' experience of treatment benefits, treatment satisfaction, and experience as a study participant. Adverse events will not be solicited during the interview however, if an SAE is described by the participant, it will be collected and processed according to GSK required timelines and procedures. These interviews will be conducted in a subgroup of participants in the US at the Week 52 and Week 104 study visits (or upon early withdrawal after Week 12). Interview questions designed to fully assess a participant's experience with a study medication will be administered in a semi-structured format by a trained interviewer. Participant feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis. The interview technique and questions will be described in the SRM.

9.7. Adverse Events

The definitions of an AE or SAE can be found in Appendix 7.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

9.7.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in study participants after completion of their participation in the study. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 7.

9.7.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.7.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious and serious AEs of special interest (AESI) (i.e., infections, malignancies, and depression/suicidality/self-injury) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.5). Further information on follow-up procedures is given in Appendix 7.

9.7.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of

participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.7.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 7 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.7.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 16 weeks after the last dose of belimumab or 12 months (i.e., Week 58) after the last dose of rituximab/rituximab-placebo, whichever is later.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.7.7. Medical Device Incidents

Medical devices (i.e., belimumab autoinjector) are provided for use in this study for the purposes of self-administration of study treatment. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and

documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.7.1 and Appendix 7 of the protocol.

Also see Section 7.6 regarding instructions to subjects in the event of a device malfunction.

9.7.7.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 8.

9.7.7.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE or SAE will be followed and reported in the same manner as other AEs (see Section 9.7.1). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.7.7.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor by via the SAE- coordinator. Regulatory Reporting Requirements for Medical Device Incidents.
- The Device Malfunction/Failure Reporting Form will be sent to the sponsor along with the Medical Device Incident Form (see Section 9.7.8).
- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal

responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.7.8. Device Malfunction

Medical devices (Belimumab Autoinjector) that are provided for use in this study for the purposes of self-administration of study treatment may malfunction during use (e.g., parts missing, device leaking, needle bent). The information provided in this section applies to occurrence and reporting of device malfunctions that are NOT associated with an AE/SAE.

If when using an autoinjector, the subject experiences a device malfunction, the participant should stop using the device and SKIP additional attempts and not re-inject for that week's belimumab dose. (See NOTE-1 in Section 7.6 for additional instruction regarding administration of study treatment following a device malfunction).

The subject should record the malfunction in the Smartphone and contact the site the same day or as soon as possible to report the device malfunction. The study site should record the malfunction on the Device Malfunction/Failure Reporting Form (see form in the SRM) and forward the information to GSK as described on the form by the next business day. The subject should return that malfunctioned device to the study site at the next scheduled visit for shipment back to GSK for evaluation.

9.8. Treatment of Overdose

For this study, any dose of belimumab greater than 200 mg per week will be considered an overdose.

There is limited experience with overdosage of belimumab. Adverse reactions reported in association with cases of overdose have been consistent with those expected for belimumab.

Two doses up to 20 mg/kg administered 21 days apart by IV infusion have been given to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

GSK does not recommend specific treatment for an overdose of belimumab.

For this study, any dose of rituximab in excess of 1000 mg IV within a 24 hour period will be considered an overdose. There has been no experience of overdosage with rituximab. GSK does not recommend specific treatment for an overdose of rituximab.

In the event of a belimumab and/or rituximab overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AEs/SAEs
3. Document the quantity of the excess dose as well as the duration of the overdosing.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.9. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.9.1. Physical Examinations

- The full physical examination at screening will include complete assessment of all organ systems including assessments of the head and neck (including eyes, ears, nose, throat, and thyroid gland), skin, musculoskeletal (including evaluation of both small and large joints), neurological, respiratory, and cardiovascular systems, gastrointestinal system, and abdomen (including liver and spleen), lymph nodes and extremities.
- A symptom-driven physical examination at the scheduled and unscheduled clinic visits will include, at a minimum, assessments of eyes, mouth, skin, lungs, cardiovascular system, abdomen and extremities (including joints).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.9.2. Vital Signs

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

9.9.3. Electrocardiograms

- A single 12-lead ECG will be obtained during screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

9.9.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 9 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 9, must be conducted in accordance with the laboratory manual and the SoA.

9.9.5. Neurological Assessment

A questionnaire-based neurological examination to detect any signs or symptoms consistent with the diagnosis of Progressive Multifocal Leukoencephalopathy (PML) will be conducted by the investigator or designated site staff at each visit. If a question is answered 'yes' and the reason for the symptom is unknown (i.e., is not definitively explained by other known cause), the participant will be referred to a neurologist for evaluation and the medical monitor contacted within 24 hours. An MRI with gadolinium enhancement (pending renal function evaluation) and/or cerebrospinal fluid (CSF) JCV PCR is recommended to be performed to confirm the diagnosis of PML, if suspected.

9.9.6. Suicidal Risk Monitoring

There have been some reports of suicidal ideation or behavior symptoms, as reported in the product label in some patients being treated with belimumab for SLE. GSK considers it important to monitor for such events before and during clinical studies with compounds such as this.

Participants being treated with belimumab should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing belimumab in participants who experience signs of suicidal ideation or behavior.

Families and caregivers (where appropriate and at the discretion of the participant) of participants being treated with belimumab should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior AND treatment emergent suicidal ideation and behavior will be assessed during Study 205646 using C-SSRS. It is

recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior. The Medical Monitor should be notified when these events occur. In addition, a "yes" to any suicidal behavior or ideation question on the C-SSRS prompts the completion of the Possible Suicidality Related Questionnaire (PSRQ). Details of the C-SSRS and PSRQ questionnaires will be provided in the SRM.

9.10. Pharmacokinetics

- Blood samples of approximately 2 mL each will be collected for measurement of serum concentrations of belimumab or rituximab, respectively, as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the pharmacokinetics (PK) of belimumab or rituximab. For each belimumab and rituximab PK sample collection the following is required: collect 2 mL whole blood into a 2 mL serum blood collection tube. Specimen will be allowed to clot and the tube then centrifuged at approximately 1600 g for 15 minutes at room temperature to separate the clot from the serum. The resultant serum will be transferred to appropriately labeled 1.8 mL polypropylene tubes.
- Samples collected for analyses of belimumab or rituximab serum concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these serum samples.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.11. Pharmacodynamics

Blood Leukocyte Analysis

Blood samples for B cell analysis will be collected as indicated in the SoA (Section 2). B cell flow cytometry panels will be used to measure changes over the course of therapy in blood cells, B cells and B cell subsets including but not limited to: the transitional, naive, memory, activated and plasma B cell compartments. For subsets of interest, absolute numbers of cells and proportions relative to all B cells will be determined.

Further Research

Further research samples are optional and will be reported separate from the Clinical Study Report (CSR) including but not limited to:

Additional blood samples for further B cell research will be collected from subjects at select European study sites as indicated in the SoA (Section 2).

Peripheral blood mononuclear cells (PBMCs) may be collected only at US study sites to allow for examination of additional selected leukocyte populations to support further evaluation of the mechanisms of action of study treatment.

9.12. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 10 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.13. Biomarkers

Biomarker analyses are specified in the following sections.

Biomarker assessments designated as “further research” require an additional further research consent and will be reported separate from the CSR.

Remaining aliquots of any biomarker samples collected as part of this protocol may be utilized for future analyses as permitted by consent and local regulations.

9.13.1. Immunogenicity Assessments

Serum samples will be collected for belimumab (Arms A, B, and C) and rituximab (Arms A and B) immunogenicity assessments as indicated in the SoA (Section 2).

9.13.2. RNA

Blood samples will be drawn before dosing on Day 1 (Baseline) for analysis of interferon signature.

9.13.3. B Cell Receptors

Blood samples for further research B cell receptor analysis will be drawn as indicated in the SoA (Section 2). Blood samples for B cell receptor analysis will also be drawn if the participant experiences a suspected SLE Flare, as defined by the SLE Flare Index.

9.13.4. BLyS Protein

Blood samples will be collected for quantification of BLyS protein levels as indicated in the SoA (Section 2).

9.14. Medical Resource Utilization and Health Economics

Health care resource utilization (HCRU) data will be collected for all participants throughout the study. Participants will be asked to record medical encounters each week (see SoA, Section 2). Protocol-mandated medical resource utilization is excluded. The investigator and clinical site staff will review the reported HCRU at each visit. The data will be used to conduct exploratory economic analyses and will include:

- 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.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

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 assessment of the relative performance of Arm A (control) and Arm B (combination) vs. standard SLE therapy (Arm C) will also be conducted.

The primary efficacy endpoint is defined as: the proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤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 will be evaluated first and then the two major secondary endpoints (i.e., Clinical SLEDAI 2K score =0 at Week 64 next and then SLEDAI-2K score ≤2 at Week 104) for statistical significance based on the pre-specified sequence for interpretation. 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.

10.1.1. Analysis for Marketing Application

Primary Analysis

A statistical analysis will be completed once all participants have completed 52 weeks of the study, if feasible. If the Week 52 database freeze is delayed due to COVID-19 pandemic, the timing of the Week 52 reporting may be reviewed and changes will be documented in the RAP.

End of Study Analysis

After the initial 52 week double-blind phase, participants in Arms A and B will enter into the 52-week double blind treatment-free, observational phase of the study (Weeks 53 through 104). Participants in Arm C will continue to receive belimumab SC and standard therapy, which may include their stable immunosuppressants, during Weeks 53 through 104. A final analysis will be conducted following the completion of Week 104.

10.2. Sample Size Determination

In order to ensure adequate exposure for evaluation of safety, the study is designed with a target of 140 participants to be randomized into the combination arm. At least 280 participants will be randomised in this study, with a target of 70 participants in Arm A, 140 participants in Arm B and 70 participants in Arm C. This sample size provides at least 98% power (for the comparison of Arm B to Arm A at Week 52) at the 5% level of significance assuming the underlying response in the control arm is 10% and the true population effect is ≥25% with treatment Arm B (combination assumed response rate of 35%). The primary endpoint will be based on assuming study dropouts = treatment failures, and so the assumed responder rates for treatment Arms A and B already account for participant dropout rates. However, the sample size may be increased up to a maximum of 320 participants if the dropout rate, missing data or number of major protocol deviations suggests further participants are necessary to ensure robust conclusions can be drawn. Sample size was calculated using PASS 12 and is based in the Likelihood ratio test. No inferential tests are planned between Arm C and Arm A or Arm B; therefore no adjustment for multiplicity is required.

There are limited clinical data with therapies including both belimumab and rituximab. Based on elicitation of opinion from external experts, as well as the rarity of remission or disease control seen in published external studies and internal GSK review of previous belimumab data, a rate of 35% achieving a state of disease control (i.e., Arm B) is considered to be highly significant in SLE care. The assumed 10% responder rate in Arm A (control) at 52 weeks was estimated based on exploration of historical data from three comparable belimumab Phase 3 trials (IV: C1056 [BLISS-76] and C1057 [BLISS-52] and SC: BEL112341) in patients with SLE, albeit with some significant differences from this study in protocol inclusion criteria, control of background therapy for SLE, SLEDAI-2K derivation and treatment failure rules. The estimated Arm A

(control) response rates based on data from previous belimumab Phase 3 studies ranged from 3.3% (C1056), 7.3% (C1057), and 8.3% (BEL112341). It is appreciated that these rates are derived from studies that did not include a forced steroid or immunosuppressant taper. Due to the limitations of the historical data and therefore the likely imprecision of the estimated responder rates, a more conservative estimate of the assumed belimumab monotherapy arm of 10% is being used for sample size calculations.

Assuming a 10% control responder rate and 70 participants in Arm A and 140 participants in Arm B, the minimum detectable effect (MDE) at p-value <0.05 is a 11% improvement (i.e., an observed improvement with the combination of 11% or more would give a p-value <0.05).

Sample Size Sensitivity

A sample size sensitivity analysis was conducted on the primary endpoint, to investigate the impact on power if the assumed underlying control response rate deviates from 10% or the treatment difference deviates from 25%. The results of these analyses are displayed in Table 5.

Table 5 Power if the Underlying Response Rates Vary from 10% (Control) and 35% (Combination)[a]

Control Rate (Arm A)	Combination Rate (Arm B)	Power
5%	30%	99%
15%	40%	97%
10%	25%	75%
10%	30%	93%
10%	40%	99%

a. All calculations assume a 5% level of significance, N=70 (control), N=140 (combination).

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who are randomized. This population will be comprised of participants according to the treatment that a participant was randomized to receive, regardless of the actual treatment received.
Intent-To-Treat (ITT)	All randomized participants who received at least one dose of study treatment. This population will be comprised of participants according to the treatment that a participant was randomized to receive, regardless of the actual treatment received.
Modified Intent-	Arm A&B: All randomized participants who received at least one dose of study

Population	Description
To- Treat (MITT)	treatment will be included. Arm C: All randomized participants who received at least one dose of study treatment and for whom their independent blinded assessor was not potentially unblinded (i.e., enrolled after 07SEPT 2018) will be included. This population will be comprised of participants according to the treatment that a participant was randomized to receive, regardless of the actual treatment received.
Per-Protocol (PP)	All randomized participants who receive at least one dose of study treatment excluding participants with major protocol deviations with potential to impact efficacy assessments.

All further populations to be used for the assessment of health outcomes, biomarkers and pharmacokinetics data will be defined in the RAP.

10.4. Statistical Analyses

Following an assessment of the impact of COVID-19 on the planned estimands, it may be necessary to update existing estimands or add new estimands. Where required, details of these analyses will be included in the RAP.

10.4.1. Efficacy Analyses

Unless otherwise stated, the primary and key secondary efficacy endpoints will be conducted using the:

- MITT population
- Blinded independent assessors SLEDAI-2K data

Endpoint	Statistical Analysis Methods
Primary	**Endpoint:** The proportion of participants with a state of disease control defined as a SLEDAI 2K-score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 52. (Arm B: combination vs Arm A control) **Analysis:** The proportion of subjects achieving a treatment response (as defined for the primary endpoint) at Week 52 will be compared between Arm B (combination) vs Arm A (control) using a logistic regression model. The independent variables in the model will include treatment group, baseline SLEDAI-2K score (≤9 vs. ≥10 mg/day), immunosuppressant use at baseline (immunosuppressant use vs. no use), and baseline corticosteroid dose

Endpoint	Statistical Analysis Methods

	(prednisone equivalent ≤10 mg/day vs. ≥10 mg/day). 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.
	
	Missing data for the primary endpoint will be handled as follows:
	
	• The study is designed to continue to collect data for participants who prematurely discontinue from their randomized treatment. All data on the primary endpoint collected for these participants will be included in the primary analysis, irrespective of whether they are classified as 'on-treatment ' or not. 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, therefore no missing data will be assumed as all participants will be classed as either a non-responder or responder. The basic premise of the DO/TF=NR analysis is that a participant meeting any of treatment failure criteria defined below (prior to Week 52), will be considered a treatment failure and thus counted as a non-responder in the statistical analysis:
	
	  • Received protocol prohibited medication, including non-study rituximab, prior to Week 52;
	  • Received immunosuppressants after Week 4;
	  • Received a prednisone equivalent corticosteroid dose of >5 mg/day after Week 26;
	  • Withdrew from the study prior to Week 52.
	
	Sensitivity Analysis: Sensitivity analyses will be defined in the RAP and will explore the impact of missing data and treatment failure imputation.

Secondary (First Major)	**Endpoint:** The proportion of participants with a state of clinical remission defined as a Clinical SLEDAI-2K score =0, achieved without immunosuppressants and corticosteroids at a prednisone equivalent dose of 0 mg/day at Week 64. (Arm B: combination vs Arm A control) Note: For purposes of the Major Secondary Endpoint, Clinical SLEDAI-2K is scored similar to the SLEDAI-2K but excludes serological activity scores, i.e., anti-dsDNA positivity and/or hypocomplementemia. **Analysis:** The proposed statistical analyses planned for the primary endpoint will be repeated for the first major secondary endpoint. The following treatment failure criteria (prior to Week 64) will be used: 1. Received protocol prohibited medication, including non-study rituximab, prior to Week 64; 2. Received immunosuppressants after Week 4;

Endpoint	Statistical Analysis Methods
	3. Received a prednisone equivalent corticosteroid dose of >5 mg/day after Week 26; 4. Received open-label belimumab in the Week 52 to Week 64 period; 5. Withdrew from the study prior to Week 64.
Secondary (Second Major)	**Endpoint:** The proportion of participants with a state of disease control defined as a SLEDAI-2K score ≤2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of ≤5mg/day at Week 104. **Analysis:** The proposed statistical analyses planned for the primary endpoint will be repeated. The following treatment failure criteria will be used: 1. Received protocol prohibited medication, including non-study rituximab, prior to Week 104; 2. Received immunosuppressants after Week 4; 3. Received a prednisone equivalent corticosteroid dose of >5 mg/day after Week 26; 4. Received open-label belimumab after Week 52; 5. Withdrew from the study prior to Week 104;
Exploratory	An exploratory assessment, using descriptive statistics, of the relative performance of Arm A (control) vs standard SLE therapy (Arm C) and Arm B (combination) vs. standard SLE therapy (Arm C) will also be conducted using the primary and key secondary endpoints. Details, including treatment failure rules for Arm C, will be described in the RAP.

10.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Secondary	Descriptive statistics will be used to summarize AEs, SAEs, AEs of special interest (AESI), changes in laboratory parameters, and immunogenicity (both anti-belimumab and anti-rituximab antibodies will be assessed). The frequency of laboratory abnormalities will be tabulated by treatment group. The frequency of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term and compared between treatment arms.

10.4.3. Other Analyses

Secondary Efficacy (Other), PK, pharmacodynamic, biomarker, and PRO exploratory analyses will be described in the RAP.

10.4.4. 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 will occur after approximately 60 participants have been randomized (approximately 15 in each of Arms A and C and approximately 30 in Arm B) and completed 12 weeks of study treatment OR approximately 6 months after the treatment of the 1st participant, whichever is earlier. After the initial review, the IDMC will review the data approximately every 6 months. For coordination with other ongoing IDMC activities, the initial meeting may be scheduled prior this milestone, and then will resume the above described schedule (approximately every 6 months). 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 nonserious), 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. Investigators and IRBs/IECs will be notified of the outcome of each IDMC meeting. 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.

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12. APPENDICES

12.1. Appendix 1:Abbreviations and Trademarks

ACR	American College Of Rheumatology
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Anti-Nuclear Antibody
APRIL	A Proliferation-Inducing Ligand
BAFF	B-cell Activating Factor Of The TNF Ligand Family
BLyS	B-Lymphocyte Stimulator
BR3	BLyS Receptor 3
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DBL	Data Base Lock
DMC	Data Monitoring Committee
dsDNA	Double Stranded Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
FDA	US Food and Drug Administration
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBC	Hepatitis C Virus
HBV	Hepatitis B Virus
HCRU	Health care resource utilization
HGS	Human Genome Sciences
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramascular
IP	Investigational Product
IRB	Institutional Review Boards
ITT	Intent-to-Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
mAb	Monoclonal Antibody
MALT	Mucosa Associated Lymphoid Tissue
MDE	Minimum detectable effect

MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
MTX	Methotrexate
MZ	Marginal Zone
NSAID	Non-Steroid Anti-Inflammatory Drug
OI	Opportunistic Infection
PBMC	Peripheral Blood Mononuclear Cell
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PP	Per-Protocol
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient Reported Outcomes
pSS	Primary Sjögren's Syndrome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RA	Rheumatoid Arthritis
RAP	Reporting And Analysis Plan
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SC	Subcutaneous(ly)
SELENA	Safety of Estrogen in Lupus National Assessment Trial
SHL	Scandinavian Health Limited
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
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNF	Tumor Necrosis Factor
US	United States
WOCBP	Woman of Childbearing Potential

Trademark Information

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Rituxan

12.2. Appendix 2:Recommended Corticosteroid Taper Schedule

A two-phase corticosteroid taper will be employed in the study.

Taper Phase 1 will occur under the direction of the investigator between study Weeks 12 and 26 with a target prednisone equivalent corticosteroid dose of ≤5 mg/day by study Week 26. Participants who cannot tolerate prednisone equivalent corticosteroid dose of ≤5 mg/day after Week 26 will be considered treatment failures. Participants who are deemed treatment failures will be encouraged to remain in the study and continue to have all efficacy and safety assessments. The recommended corticosteroid taper schedule for Phase 1 is outlined in Table 6. Common corticosteroid doses and prednisone equivalents are presented in Table 7. Adjustments may be made for tolerability at the investigator's discretion.

Table 6 Recommended Oral Corticosteroid Taper (Prednisone equivalent dosing)

Study Week	Prednisone equivalent dose (mg/day)
12	60
13	55
14	50
15	45
16	40
17	35
18	30
19	25
20	20
21	17.5
22	15
23	12.5
24	10
25	7.5
26	5

Taper Phase 2 will occur starting at Week 26 after subjects have been successfully tapered to prednisone equivalent corticosteroid dose of ≤5 mg/day. In order to attempt to discontinue participants' corticosteroids a prolonged prespecified taper will be employed. A decrease of 1 mg/day on one day per week is recommended until a participant is decreased to 0 mg/day. For example, the first week of this taper a participant who was receiving a prednisone equivalent corticosteroid dose of 5 mg/day will receive 4 mg on Monday and 5 mg/day from Tuesday through Sunday. In the second week of the taper the participant will receive 4 mg on Monday and Tuesday and then 5 mg/day from Wednesday through Sunday, etc until the participant is on 0 mg/day. Thus, the discontinuation of 5 mg/day would take 35 weeks to accomplish.

Table 7 Common Corticosteroid Equivalent Approximate Dose (mg) and Prednisone- Equivalent Multiplier Factor

Corticosteroids	Equivalent Dose (mg)	Prednisone-Equivalent Multiplier Factor
Prednisone	5	NA
Prednisolone	5	1
Triamcinolone	4	1.25
Cortisone	25	0.2
Hydrocortisone	20	0.25
Methylprednisolone	4	1.25
Betamethasone	0.6 - 0.75	8.3 – 6.7
Dexamethasone	0.75	6.7

References:
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Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977;63;200-7.

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12.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the standard of care medications, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 16 weeks after the last dose of belimumab and/or monthly until 12 months after the last dose of rituximab or placebo, whichever is later. If stricter female or male contraception requirements are specified in the country-specific label for induction and/or maintenance standard of care medications, they must be followed.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

- Additional pregnancy testing during the treatment period per the SoA and at 16 weeks after the last dose of belimumab and/or monthly until 12 months after the last dose of rituximab or placebo, whichever is later, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing using a serum sample, with a sensitivity of 5 mIU/mL will be performed and assayed in the central laboratory at the Screening Visit. Urine pregnancy test kits provided by the central laboratory will be used for all other scheduled pregnancy tests and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study. Participants who discontinue study treatment should be encouraged to continue to participate in study visits in accordance with the SoA (Section 2), especially all remaining safety evaluations.

Breast-feeding (Germany only): Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.

12.4. Appendix 4:Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

An Independent Data Monitoring Committee (IDMC) will conduct periodic reviews of unblinded data to ensure external objective and/or statistical review of safety issues. The composition, remit, and procedures of the IDMC are provided in the IDMC Charter (see Section 10.4.4).

An Independent Adjudication Team, including representatives from Clinical, Biostatistics, and Data Management, will be established before the Week 52 data are unblinded. This team will participate in the review and adjudication of treatment failures, AEs of special interest, and protocol deviations in preparation for the Week 52 and end of study data base locks (DBLs). After unblinding, only members of the Independent Adjudication Team will continue to participate in the review and adjudication of treatment failures, AEs of special interest, and protocol deviations in preparation for the end of study DBL (unblinded team members will no longer participate in adjudication). Members of the Independent Adjudication Team remain blinded until the End of Study Data Base Freeze (DBF).

Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate. GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.5. Appendix 5:Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 6) • If restart is **not granted**, permanently discontinue study treatment and continue	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5]. • Belimumab and rituximab pharmacokinetic (PK) within 8 weeks after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total

participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** 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)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009;37:1779-84.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43(5):2363–69.

12.6. Appendix 6:Liver Safety Study Treatment Restart Guidelines

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcoholic hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has a confirmed genetic marker associated with liver injury, the presence of the marker should be excluded.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart has been obtained.

If restart of study treatment is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart of study treatment. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK
- Participants approved by GSK for restart of study treatment must return to the clinic twice a week for liver function tests until stable liver function tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the participant meets protocol-defined liver function stopping criteria after study treatment restart, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the IRB/IEC, must be informed of the outcome for the participant following study treatment restart.
- GSK must be notified of any adverse events, as per Appendix 7.

12.7. Appendix 7:Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are

requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the SAE coordinator by telephone.

SAE Reporting to GSK via Paper CRF
• If the electronic system is unavailable for more than 24 hours, then facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

12.8. Appendix 8:Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1.1 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 7. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.9. Appendix 9:Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
- Local laboratory results are required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation and for those patients at select sites participating in the further research B-cell analyses. In addition, local laboratory results are recommended if central laboratory results cannot be obtained (perhaps as a consequence of disruption associated with the COVID-19 pandemic).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count RDW Hemoglobin Hematocrit	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,			

Laboratory Assessments	Parameters
	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)
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)

Laboratory Assessments	Parameters
	• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • PT/PPT

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.2 and Appendix 5. 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).

Lab data that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

12.10. Appendix 10:Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples may be used for research related to belimumab, rituximab, or any concomitant medicines, or systemic lupus erythematosus (SLE) and related diseases. They may also be used to develop tests/assays including diagnostic tests related to belimumab, rituximab, or any concomitant medicines, and SLE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples may be analyzed if it is hypothesized that this may help further understand the clinical data or the disease under study.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belimumab, rituximab, or study treatments of these drug classes. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belimumab, rituximab or SLE continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.11. Appendix 11: American College of Rheumatology (ACR) Criteria for SLE

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

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

12.12. Appendix 12:Country-specific requirements

South Korea Investigational Product Labels

Belimumab

Box

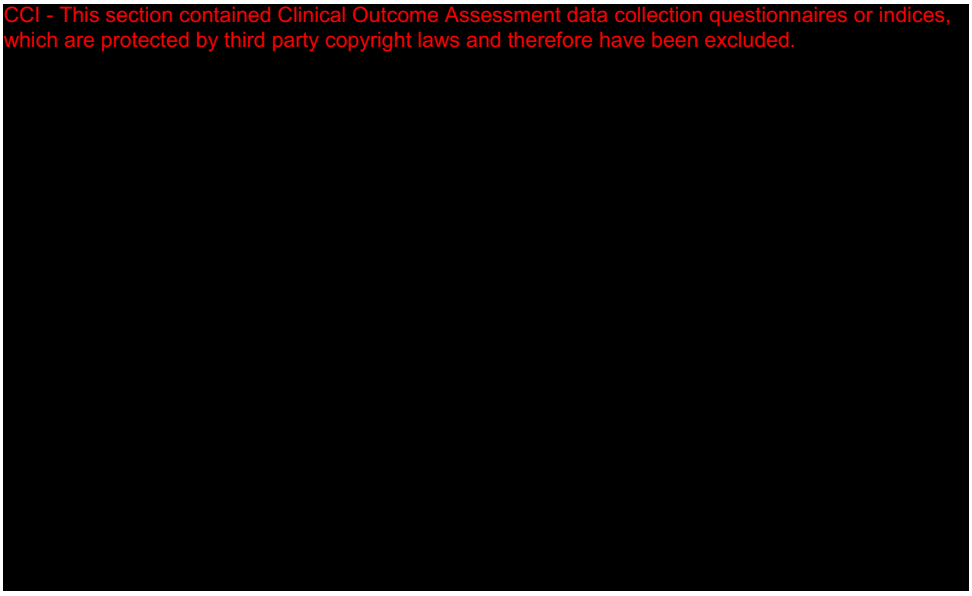
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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.

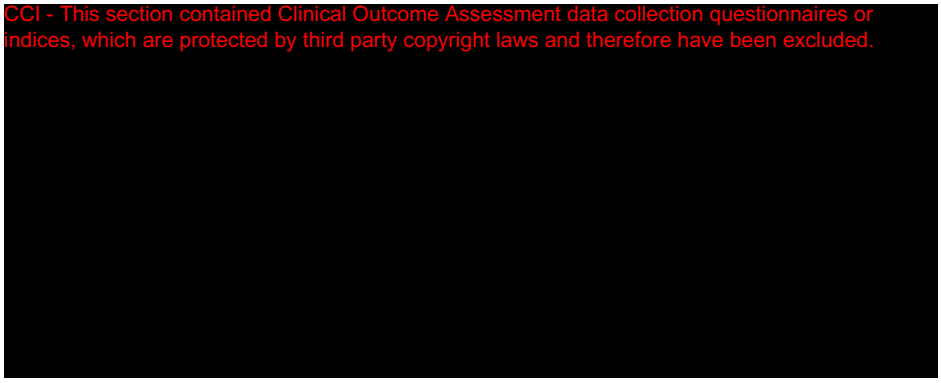
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Rituximab

Box



Vial



Korea Subjects: In regards to Inclusion criteria 1, only adult participants as per local laws at the time of signing the informed consent will be eligible for inclusion in this study.

South Korea:
Amendment 01/KOR-1: see GlaxoSmithKline Document Number 2016N272781_02.

Germany:
Amendment 01/DEU-1: see GlaxoSmithKline Document Number 2016N272781_03.
Amendment 01/DEU-2: see GlaxoSmithKline Document Number 2016N272781_04.

Argentina:
Amendment 01/ARG-1: see GlaxoSmithKline Document Number 2016N272781_05.

12.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 03 (Global) 15-AUG-2019

Overall rationale for the Amendment: 1) To define dosing interruptions based on neutrophil count, 2) Incorporate country-specific changes for S. Korea, Germany and Argentina into Global Amendment 03 protocol, 3) define an MITT population for analysis, and 4) provide clarification of changes and updates on wording related to study conduct.

Section # and Name	Description of Change	Brief Rationale
2: Schedule of Activities (SoA) Table 1, Table 2, Table 3 and Table 4	Listed sample analysis that are for exploratory further research	Add clarity for sites so as not to confuse protocol required samples with further research samples
2: Schedule of Activities (SoA) Table 1 and Table 3	Footnote a – corrected visit week that 7 day window begins Footnote b – corrected early withdrawal only for patient who discontinue study Footnote u (Table 1) and footnote o (Table 3) – indicated samples are optional and for further research purposes from select European centers	Incorrect in previous version Incorrectly indicated this applied to patients discontinuing IP as well in previous version Clarification for sites regarding sample collection for further research
2: Schedule of Activities (SOA), Table 1, Table 2, Table 3, and Table 4	Footnotes n and q (Table 1) and footnotes g and l (Table 2), footnotes j and l (Table 3) and footnotes f and h (Table 4) updated text to “suspected “ SLE flare	Clarification to sites that B-cell samples should be collected any time flare is suspected.
2 SoA Table 2 and Table 4	Footnote d (Table 2) and footnote f (Table 4) Include Argentina specific requirement for monthly pregnancy testing during study year 2 testing Footnote n (Table 2) indicated samples are optional and for further research purposes from	Incorporation of country specific amendments into Amendment 03 Global Protocol Clarification for sites regarding sample collection for further research

Section # and Name	Description of Change	Brief Rationale
	select European centers	
2 Table 2: SoA	Add Further Research collection of B-cell subsets at Year 2 Unschedued Visit	Allow for further research sample collection for patients who restart belimumab in Year 2
3: Benefit/Risk Assessment	Removed text indicating there are no published clinical research data on use of belimumab and rituximab	Published literature is available
3.3.1: Risk Assessment: Infections	Included Germany specific change: for subjects with hypogammaglobulinemia - changed from IgG <250 mg/dL to IgG <400 mg/dL Neutropenia language updated to reflect new value for interrupting belimumab treatment and potential for continued dosing	Incorporation of country specific amendments into Amendment 03 Global Protocol To allow flexibility to continue dosing with belimumab in instances of neutropenia if clinically appropriate
4 and Study Synopsis: Objectives and Endpoints	Added two additional secondary efficacy (Other) endpoints added based on principal investigator assessment of SLEDAI-2K	Changed to aid assessment of difference between the blinded assessor and principal investigator
5.1: Overall Design	Removed text indicating participants who discontinued IP but remained in the study may have to perform unscheduled visit	Corrected error in text
5.3: Participant and Study Completion	Removed text indicating participants who discontinued IP but remained in the study may have to perform unscheduled visit	Corrected error in text
6.1: Inclusion criteria	Included Germany specific change that oral cyclophosphamide is not an allowed medication in the list of concomitant medications	Incorporation of country specific amendments into Amendment 03 Global Protocol
6.2: Exclusion Criteria	Included Germany specific changes:	Incorporation of country specific amendments into Amendment

Section # and Name	Description of Change	Brief Rationale
	exclusion of subjects with hypogammaglobulinemia - changed from IgG <250 mg/dL to IgG <400 mg/dL added to the relevant prior/concomitant therapy exclusion criterion and exclusion of subjects who had oral cyclophosphamide within 60 days of Day 1	03 Global Protocol
7.7.1.4: Other Immunosuppressant Agents	Included Germany specific change: Deleted oral cyclophosphamide, 2.5 mg/kg/day from the list of common allowable maximum doses at baseline and during the study	Incorporation of country specific amendments into Amendment 03 Global Protocol
7.7.2: Prohibited Medications and Non-Drug Therapies	Text added to clarify when medical monitor must be contacted. Included Germany specific change: Added oral cyclophosphamide to list of medications prohibited at any time during the study	Statement added for clarity. Incorporation of country specific amendments into Amendment 03 Global Protocol
7.7.4 Additional SLE Therapy	Added that rescue medications should be documented.	Ensure collection of this information in the source documentation.
8.2: Discontinuation of Study Treatment and 12.3 Appendix 3: Contraception Guidance and Collection of Pregnancy Information	Included Germany specific change: Clarification that women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.	Incorporation of country specific amendments into Amendment 03 Global Protocol
8.3: Temporary Discontinuation and Restart of Belimumab	Language regarding temporary belimumab discontinuation and potential restart due to neutropenia added	To describe action to be taken in instances of neutropenia
9.1: Screening Assessment - Pregnancy Test	Included Argentina specific change: reference to additional pregnancy tests during study year 2.	Incorporation of country specific amendments into Amendment 03 Global Protocol

Section # and Name	Description of Change	Brief Rationale
Laboratory tests	Added text regarding repeat samples.	Statement added for clarity.
9.4: Assessments at Unscheduled Visits	Removed text indicating participants who discontinued IP but remained in the study may have to perform unscheduled visit	Corrected error in text
9.6.1 Patient-Reported Outcomes Assessments – Patient Interviews	Removed reference to the Patient Interview Communication Plan as plan is not implemented by the site.	Corrected text.
9.9.6 Suicidal Risk Monitoring	Added wording to monitoring statement regarding informing families and caregivers	Wording added to address privacy concerns
9.11 Pharmacodynamics	Added text for exploratory research performed on additional blood samples for future B cell research	Added for conduct of future B cell research in newly enrolled participants at selected sites.
9.13 Biomarkers	Added statement on remaining sample use	Aligned with further research intent in ICF
9.13.3: B Cell Receptors	Added “further research”	Highlight these analyses are part of further research
10.3 Populations for Analyses	Modified Intent-to-Treat population added	Additional population excluding subjects for whom their independent blinded assessor was potentially unblinded, to facilitate analysis excluding these subjects.
12.1 Trademarks	Added trademarks.	Added trademarks
12.4 Appendix 4: Study Governance Considerations	Changed wording to clarify the adjudication process	Corrected text.
12.9 Appendix 9: Clinical Laboratory tests	Added wording indicating local labs are required for participants consented into exploratory further B cell research	Inadvertenly not included in previous version.
12.12 Appendix 12: Country-specifc requirements	Korea specific label and enrolment criteria language added	Incorporation of country specific amendments into Amendment 03 Global Protocol
Throughout protocol	Minor editorial revisions	Corrections of typographical errors and minor revisions for

Section # and Name	Description of Change	Brief Rationale
		clarity.

Amendment 02 (KOR-1) 02-FEB-2019

Overall Rationale for the Amendment: To add changes specific for South Korea from previously approved KOR-1 (shown in the table below) to the Global Amendment 02 Protocol.

Section # and Name	Description of Change	Brief Rationale
Appendix 12: Country-Specific requirments, following addition of new appendix in Amendment 02 (Global), the country-specific requirements previously found in Appendix 11 in Amendment 01/KOR-1 are now located in Appendix 12.	Include IP label, additional clarification about the inclusion criteria age as per local regulations, provide details of IPs supplied for South Korea	Country specific requirement for South Korea

Amendment 02 (ARG-1) 11-DEC-2018

Overall Rationale for the Amendment: To add changes specific for Argentina from previously approved ARG-1 (shown in the table below) to the Global Amendment 02 Protocol:

Section # and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activities (SoA), Table 2 and Table 4	Include requirement for monthly pregnancy testing during study year 2.	Country specific requirement for Argentina
Section 9.1: Screening Assessment - Pregnancy Test	Include reference to additional pregnancy tests during study year 2.	Country specific requirement for Argentina

Amendment 02 (DEU-2) 28-NOV-2018

Overall Rationale for the Amendment: To add changes specific for Germany from previously approved DEU-1 and DEU-2 (shown in the table below) to the Global Amendment 02 Protocol:

Section # and Name	Description of Change	Brief Rationale
3.3.1 Risk Assessment, Mitigation Strategy	Exclusion criterion for subjects with hypogammaglobulinemia	Country specific requirement for Germany

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion criteria	changed from IgG <250 mg/dL to IgG <400 mg/dL	
8.2 Discontinuation of Study Treatment Appendix 3, Contraceptive Guidance and Collection of Pregnancy Information	Clarification that women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.	Consistent with recommendation from rituximab EU SmPC
6.1 Inclusion criteria 7.7.1.4 Other Immunosuppresant Agents	Deleted oral cyclosphosphamide as an allowed medication in the list of concomitant medications Deleted oral cyclophosphamide, 2.5 mg/kg/day from the list of common allowable maximum doses at baseline and during the study	Country specific requirement for Germany
6.2 Exclusion criteria	Added oral cyclophosphamide within 60 days of Day 1 to the relevant prior/concomitant therapy exclusion criterion	Country specific requirement for Germany
7.7.2 Prohibited Medications and Non-Drug Therapies	Added oral cyclophosphamide to list of medications prohibited at any time during the study	

Amendment 02 (Global) 17-NOV-2018

Rationale for the Amendment: 1) To change the timing of the initial analysis from Study Week 64 to Study Week 52 to support an earlier submission to regulatory authorities, 2) Recruit additional 80 participants into the study to ensure adequate number of evaluable participants, and 3) provide clarification of changes and updates on wording related to study conduct.

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 1) Objectives and Endpoints; 2) Number of Participants	1) Removed reference to timing of analysis from this section. 2) Changed the number of participants	Changed for consistency.

Section # and Name	Description of Change	Brief Rationale
1, Synopsis; 3.3.1 Risk Management; 5.1 Overall Design; 5.4.1, Selection of Controls; 6.1 Inclusion Criteria IC #5,	Removed reference to “oral” antihistamine	Increase flexibility to administer pre-medication for rituximab/rituximab placebo treatment arms A or B)
2 Schedule of Activities (Table 1-Table 4)	1) Added a new row “Vital Signs” for Screening phase 2) Deleted select sample collection times for “B Cell Receptor” 3) Added new footnote for Dispense Belimumab for weekly dosing (SC)” advising that if Week 4 and 6 belimumab dosing should happen to be scheduled for the day of the rituximab/rituximab placebo infusions, whenever possible, the day of belimumab dosing should be altered within the dosing window to occur on a day other than that of the infusion. 4) Added information to monitor subjects including vital signs during IV Rituximab/ rituximab placebo infusion. 5) Updated footnote for “Urine Pregnancy Test (WCBP)” 6) Added footnote to “SLEDAI-2K: Blinded Assessor” row to 1) clarify the need to perform Symptom-driven physical exam, vital signs same as primary or sub investigator and 2) indicate the need to maintain source documentation for the physical exam and lab report analysis supporting	Added for clarity and consistency with study procedures, added missing information. Rationale for #2: These samples were not part of central lab sample collection procedures. Samples at the deleted time points for B Cell Receptor have not been collected since the sites were informed of this change at study start.

Section # and Name	Description of Change	Brief Rationale
	the S2K scoring. 7) Added clarification to footnotes regarding PBMC blood sample collection and SLE flares 8) Added footnote regarding future B cell research 9) Remove additional text at end of Table 4.	Rationale for #9: This text applies only to GSK early phase/ Pharmacokinetic studies and was not applicable to this study.
4 Objectives and Endpoints	Removed reference to timing of analysis from this section.	Changed for consistency.
5.1 Overall Design, Figure 1	Updated number of participants in study schematic	Changed for consistency.
5.2 Number of Participants	1) Changed number of participants screened: 400 to 560; Changes number of participants randomized: 200 to 280 2) Changed number of added due to dropout/missing data/major protocol deviations: 300 to 320	During the early conduct of the study some participants in Arm C (n=29) were inappropriately identified on the lab report which could have unblinded the independent blinded assessors. Blinding of Arms A and B was not compromised. The increase in the overall sample size from 200 to 280 randomized participants under the same randomization ratio (1:2:1) increases the number of participants enrolled in Arm C from 50 to 70, with 41 of these unaffected by the unblinding issue. The number of participants in Arms A and B are also increased from 50 to 70 and 100 to 140, respectively. This increase allows improved sensitivity to detect treatment effects and assessment of safety. Assumes approx. 10%-15% dropout rate.
6.1 Inclusion criteria	IC #2 - Added minimum number of criteria required for SLE diagnosis (4 or more of	Added for clarity and consistency with study procedures, add missing

Section # and Name	Description of Change	Brief Rationale
	11) IC #3 – Added clarification on presence and scoring of serological activity IC #4 – Removed "key on historical lab report" that explaines positive/negative lab results.	information. Note to IC #4: Use serum antibody threshold described in IC #4 (i.e., ANA titer ≥1:80 and anti-dsDNA ≥30 IU/mL)
6.2 Exclusion Criteria	EC #2 - Revised text EC #2 – Replaced QuantiFERON-TB Gold with QuantiFERON-TB Gold Plus assay EC #4 – Revised text EC #24 – Added examples	Added for clarity and consistency; Qiagen has recently developed an improved version of its Quantiferon-TB Gold assay and as a result this assay is being discontinued. Quantiferon-TB Gold assay is being replaced by "Quantiferon-TB Gold Plus" assay that is more specific and sensitive.
7.3 Method of Treatment Assignment	1) Changed ≥10 mg/day to >10 mg/day 2) Changed the number of participants	1) Corrected information 2) Updated for consistency
7.4 Blinding	Changed timing from Week 64 to Week 52 SAEs will only be unblinded by GCSP for regulatory reporting purposes. Removed text requiring investigator to contact Medical Monitor before unblinding a subject	Change for consistency Added for clarity Removed text as per change to the GSK SOP_54827 for emergency unbliding
7.6 Treatment Compliance	Added information and instruction if any one dose of belimumab is missed. Added information if subject did not administer the full dose of belimumab due to autoinjector malfunction. Revised text on missed	Added for clarity and consistency

Section # and Name	Description of Change	Brief Rationale
	4 doses of belimumab.	
7.7.1.2 Corticosteroids	Added information about corticosteroid dose=0 mg/day at study Day 1	Added for clarity and consistency
8.1 Withdrawal from the Study	Changed 52 weeks to 12 months	Changed for consistency
8.2 Discontinuation of Study Treatment	Changed 52 weeks to 12 months Remove Duplicate pregnancy language	Changed for clarity and consistency
9.3 Assessment of Scheduled Visits	Added “deemed treatment failure”	Added for clarity and consistency
9.6.1 Patient-Reported Outcomes Assessments And Patient Interviews	Added information on timing of PRO assessments Added information on managing SAEs described during “Patient Interview”	Added for clarity and consistency
9.7.6 Pregnancy	Added “e.g., Week 58”	Added for clarity
9.7.7. Medical Device Incidents (Including Malfunctions)	Added “autoinjector” Added cross-reference to Section 7.6 Patient Compliance	Added for clarity and consistency
9.7.7.3 Prompt Reporting of Medical Device Incidents to Sponsor	Added information regarding forms	Added for clarity
9.7.8 Device Malfunction (NEW)	Added a new section for reporting Device Malfunction	Added to align with GSK procedures.
9.9.6 Suicidal Risk Monitoring	Removed “Adverse Event” and changed PSRAE to PSRQ	Changed for consistency
9.11 Pharmacodynamics	Added text for collection of additional blood samples for future B cell research	Added for conduct of future B cell research in newly enrolled participants at selected sites.
10.1.1 Analysis for Marketing Application	Initial database lock (DBL) has been changed to after Week 52.	The first DBL will include the initial 52 week double-blind phase (Primary Endpoint)
10.2 Sample Size Determination	Added text to reflect changes in the sample population	Changed for consistency
11 References	Added references for new	Added new references

Section # and Name	Description of Change	Brief Rationale
	appendix	
12 Appendices	Removed text in Table 7 in Appendix: Recommended Corticosteroid Taper Schedule	Removed text added in error
	Updated timing from Week 64 to Week 52 in Appendix: Study Goverance, Committee Structure	Changed for consistency
	Added ACR Criteria for SLE	Added new appendix for clarity.
	Update appendix for Country-specific Requirements.	Adedd cross-reference for country-specific amendments for Korea, Germany, and Argentina.
Throughtout protocol	Minor editorial and document formatting revisions	Added for clarity

Amendment 01/ARG-1 -02-JUL-2018

Overall Rationale for the Amendment: The purpose of this amendment is to support country-specific requirements and amendments for Argentina.

Section # and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activities (SoA), Table 2 and Table 4	Include requirement for monthly pregnancy testing during study year 2.	Country specific requirement for Argentina
Section 9.1: Screening Assessment - Pregnancy Test	Include reference to additional pregnancy tests during study year 2.	Country specific requirement for Argentina

Amendment 01/DEU-2 27-NOV-2017

Overall Rationale for the Amendment: The purpose of this amendment is to support country-specific requirements for Germany.

Section # and Name	Description of Change	Brief Rationale
6.1 Inclusion criteria	Deleted oral cyclosphosphamide as an allowed medication in the list of concomitant medications	Country specific requirement for Germany
7.7.1.4 Other Immunosuppresant Agents	Deleted oral cyclophosphamide, 2.5 mg/kg/day from the list of common allowable maximum	

Section # and Name	Description of Change	Brief Rationale
	doses at baseline and during the study	
6.2 Exclusion criteria	Added oral cyclophosphamide within 60 days of Day 1 to the relevant prior/concomitant therapy exclusion criterion	Country specific requirement for Germany
7.7.2 Prohibited Medications and Non-Drug Therapies	Added oral cyclophosphamide to list of medications prohibited at any time during the study	

Amendment 01/DEU-1 23-OCT-2017

Overall Rationale for the Amendment: The purpose of this amendment is to support country-specific requirements for Germany.

Section # and Name	Description of Change	Brief Rationale
3.3.1 Risk Assessment, Mitigation Strategy 6.2 Exclusion criteria	Exclusion criterion for subjects with hypogammaglobulinemia changed from IgG <250 mg/dL to IgG <400 mg/dL	Country specific requirement for Germany
8.2 Discontinuation of Study Treatment Appendix 3, Contraceptive Guidance and Collection of Pregnancy Information	Clarification that women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.	Consistent with recommendation from rituximab EU SmPC

Amendment 01/KOR-1 22-JUN-2017

Overall Rationale for the Amendment: The purpose of this amendment is to support country-specific requirements and amendments for South Korea.

Section # and Name	Description of Change	Brief Rationale
Appendix 11	Include IP label, additional clarification about the inclusion criteria age as per local regulations, provide details of IPs supplied for South Korea	Country specific requirement for South Korea

Amendment 01 (Global) 17-APR-2017

Overall Rationale for the Amendment: GSK received additional comments and feedback from EMA and FDA and incorporated the recommendations in Amendment 1. In addition, further changes and updates were identified by the study team and incorporated in Amendment 1.

Section # and Name	Description of Change	Brief Rationale
1 Synopsis Number of Participants 5.2 Number of Participants	Adding language to allow for randomization of additional subjects	Account for early dropout rate and provide sufficient exposure in Arms A and B for safety assessment
6.2 Exclusion Criteria	New criterion: History of anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies	Consistent criteria in subjects receiving biological products
7.4 Blinding	Updated text for unblinding by the Investigator	For consistency with updates to GSK required language
7.4 Blinding 10.1.1 Analysis for Marketing Application	Initial database lock (DBL) has been changed to week 64	Address the data analysis request by EMA. DBL will include the initial 52 week double-blind phase (Primary Endpoint)
8.2 Discontinuation of Study Treatment	Updated the third bullet – Pregnancy will require study treatment withdrawal and requirement for pregnancy testing for rituximab 52 week post last dose.	Clarification
7.7.1.3 Corticosteroids for Reasons Other Than SLE Disease Activity	Change corticosteroid dose from 100 mg/day to 60 mg/day for 2-3 days	FDA recommendation to minimize confounding effects of high dose corticosteroids
2 Schedule of Activities (Table 1-Table 4)	Update definition and organization of the tables	Add clarity and consistency with study procedures, add missing information
9.6.1 Patient-Reported Outcomes Assessments	Update information about the assessment scales.	Add clarifying information regarding the scales
9.13.3 B Cell Receptors	Add more blood sample collection times to match those for the B Cell analysis	Required in order to obtain absolute numbers of B Cell subsets and relative values to all B Cells.
10.4.1 Efficacy Analyses	Definition of Clinical SLEDAI-2K	Clarification

Section # and Name	Description of Change	Brief Rationale
10.4.3 Other Analyses	Reference to Efficacy Analysis (Other)	Add missing information
10.4.4 Interim Analyses	Update safety review timeline and processes	Review processes consistent with other belimumab studies and per changes approved by IDMC
12 Appendices	Common corticosteroid dose and prednisone-equivalent multiplier table	Add supporting information
	Liver safety study treatment restart text updated as per updates to GSK guidelines	Change made as per updates to GSK guidelines
11 Reference	References for new appendix	Add new references
Global changes	Change naming convention of 'Exit' visit to 'Early Withdrawal' visit; Replace rituximab premedication "analgesia" with "acetaminophen or equivalent";	More accurate description