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

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	

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

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.

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.

- 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)

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

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

- 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

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

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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MedDRA
QuantiFERON-TB Gold or QuantiFERON-TB Gold Plus
Rituxan

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:
Dixon JS (ed). Second-line agents in the treatment of rheumatic diseases. Informa Health Care, 1991. (456).
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.

Singer M, Webb AR. Oxford Handbook of Critical Care. 2nd ed. New York: Oxford University Press, 2005.

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)

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

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)

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

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)										

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

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.

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).

- 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

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

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.

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).

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

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.

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.

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.

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

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.